CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-932

***Name*:** Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg

***Sponsor*:** Eon Labs, Inc.

***Approval Date*:** November 25, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-932

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-932

APPROVAL LETTER

ANDA 75-932

NOV 25 2003

Eon Labs, Inc.
Attention: Enna Krivitsky
227-15 North Conduit Avenue
Laurelton, NY 11413

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated July 26, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg.

Reference is made to our Tentative Approval letter dated January 24, 2002 and to your amendments dated July 2, September 8, October 8, October 27, November 3, November 7 and November 20, 2003. We acknowledge receipt of your patent correspondence dated February 19, February 20 and March 19, 2003 related to the approval of this drug product. We also acknowledge receipt of your exclusivity correspondence dated November 24, 2003.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. However, because of an exclusivity issue explained below, we are unable to approve your Bupropion Hydrochloride Extended-release Tablets, 150 mg at this time. **Therefore, only your Bupropion Hydrochloride Extended-release Tablets, 100 mg is approved.** The 150 mg strength is tentatively approved and will not be eligible for final approval until the 180-day generic drug exclusivity issue noted below has been satisfactorily resolved.

The Division of Bioequivalence has determined your Bupropion Hydrochloride Extended-release Tablets, 100 mg, to be bioequivalent and therapeutically equivalent to the listed drug (Wellbutrin SR® Tablets, 100 mg, of GlaxoSmithKline). Your dissolution testing should be

incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

> The dissolution testing is conducted in 900 mL of 0.1 N HCl, pH 1.5, at 37°C using USP26 Apparatus I(basket) at 50 rpm.
>
> Based on the dissolution data submitted for the test product, the following interim tolerances are recommended:
>
> | | |
> |---|---|
> | 1st hour | —— % |
> | 2nd hour | —— % |
> | 4th hour | —— % |
> | 6th hour | NLT —% |
>
> The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a "Special Supplement - Changes Being Effected" when there are no revisions to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The listed drug product referenced in your application, Wellbutrin SR® Tablets, 100 mg, of GlaxoSmithKline, is subject to multiple periods of patent protection. The following United States patents and their expiration dates currently appear in the Agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book":

Patent Number	Expiration Date
5,358,970	August 12, 2013
5,427,798	August 12, 2013
5,731,000	August 12, 2013
5,763,493	August 12, 2013

Your application contains paragraph IV certifications to each of these patents under Section 505(j)(2)(A)(vii)(IV) of the Act stating that none of these patents will be infringed by your manufacture, use, offer for sale, or sale

of Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Eon Labs, Inc. (Eon) for infringement of one or more of the patents which were the subjects of the paragraph IV certifications. This action must be brought against Eon prior to the expiration of forty-five (45) days from the date the notice you provided under paragraph (2)(B)(i) was received by the patent and NDA holder(s). You have informed the Agency that Eon complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for patent infringement was brought against Eon within the statutory forty-five day period, concerning the '970, '000 and '493 patents. You have also informed the Agency that Glaxo Wellcome, Inc. initiated a patent infringement action against Eon in the United States District Court for the Southern District of New York (Glaxo Wellcome, Inc. v. Eon Labs Manufacturing, Inc.), Civil Action No. 00-CIV-9089, concerning the '798 patent and U.S. Patent No. RE33994. We acknowledge receipt of your correspondence dated February 20, 2003, informing the Agency that U.S. Patent No. RE33994 was deleted from the "Orange Book" and that your patent certification to the '994 patent is withdrawn.

The Agency also recognizes that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act, during which time the FDA was precluded from approving your application has expired, concerning the '798 patent.

Under Section 506(A) of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change can be made.

Post-marketing requirements for this ANDA for Bupropion Hydrochloride Extended-release Tablets, 100 mg 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 your Bupropion Hydrochloride Extended-release Tablets, 100 mg.

We request that you submit, in duplicate, any proposed advertising or promotional copy that 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 final printed labeling to the Division of Drug

Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 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 FDA 2253 at the time of their initial use.

Our decision to grant tentative approval to your Bupropion Hydrochloride Extended-release Tablets, 150 mg, is based upon information currently available to the Agency; (i.e., data in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This decision is subject to change on the basis of new information that may come to our attention.

We are unable to grant final approval to your Bupropion Hydrochloride Extended-release Tablets, 150 mg, at this time because an ANDA for the 150 mg strength containing paragraph IV certifications to the patents listed in the Orange Book was submitted to OGD prior to the submission of your application. Accordingly, your Bupropion Hydrochloride Extended-release Tablets, 150 mg, will be eligible for final approval beginning on the date that is one hundred and eighty days after the date the Agency received notice of the first commercial marketing of the 150 mg strength under the previous application, or the date of a court decision described under Section 505(j)(5)(B)(iv), whichever event occurs earlier. For additional information, we refer you to the Agency's guidance document entitled "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1988).

In order to reactivate this application to provide for final approval of the 150 mg strength, you must submit a "Supplemental Application - Expedited Review Requested". This supplemental application should be submitted for prior approval approximately 90 days prior to the date you believe that your Bupropion Hydrochloride Extended-release Tablets, 150 mg, will be eligible for final approval. The supplement should include a detailed explanation of why and when you believe final approval should be granted. It

should also include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This supplemental application should be submitted even if no changes have been made to the application since the date of this tentative approval. Significant changes, as well as an update of the status of the manufacturing and testing facilities' compliance with cGMPs are subject to Agency review before final approval of the supplemental application will be granted. We request that you categorize the changes as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt.

In addition to the supplemental application requested above, the Agency may request at any time prior to the date of final approval that you submit an additional document containing the requested information. Failure to submit either or, if requested, both documents may result in the rescission of the tentative approval status of your application for Bupropion Hydrochloride Extended-release Tablets, 150 mg, or may result in a delay in the issuance of the final approval letter.

Please note that under Section 505 of the Act, your Bupropion Hydrochloride Extended-release Tablets, 150 mg, may not be marketed without final Agency approval. The introduction or delivery for introduction into interstate commerce of your Bupropion Hydrochloride Extended-release Tablets, 150 mg, before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, your Bupropion Hydrochloride Extended-release Tablets, 150 mg will not be deemed approved for marketing under 21 U.S.C. 355, and will not be listed in the "Orange Book".

For further information on the status of this application, or prior to submitting an amendment providing for the final approval of your Bupropion Hydrochloride Extended-release Tablets, 150 mg, please contact Stanley Shepperson, Pharm.D., Project Manager, at (301) 827-5798.

Sincerely yours,

Gary Buehler 11/25/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 75-932
Division File
Field Copy
HFD-600/R.West
HFD-330
HFD-205
HFD-600/Orange Book
HFD-600/D.Hare

Endorsements:

HFD-647/L.Tang/
HFD-647/U.Venkataram/
HFD-617/S.Shepperson/
HFD-613/M.Shin/
HFD-613/L.Golson

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APPROVAL - 100 MG

TENTATIVE APPROVAL - 150 MG

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-932

TENTATIVE APPROVAL LETTER

ANDA 75-932

JAN 24 2002

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 (ANDA) dated July 26, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg.

Reference is also made to your amendments dated December 11, 2000; October 2, November 13, December 5, 2001; and January 2, and January 18, 2002.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved.** This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The listed drug product referenced in your application, Wellbutrin-SR Tablets of Glaxo Wellcome, Inc., is subject to periods of patent protection which expire on August 12, 2013, [U.S. Patent Nos. 5,358,970 (the '970 patent), 5,427,798 (the '798 patent)), 5,731,000 (the '000 patent), 5,763,493 (the '493 patent)]; and August 18, 2004, [U.S. Patent No. RE 33,994 (the '994 patent)]. Your application contains patent certifications under Section 505 (j)(2)(A)(vii)(IV) of the Act stating that these patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of this drug

product. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately unless an action is brought before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is received. You have notified FDA that Eon Labs Manufacturing, Inc. (Eon) has complied with the requirements of Section 505(j)(2)(B) 0f the Act. As a result, litigation is currently underway in the United States District Court for the Southern District of New York involving a challenge to the '798 and '994 patents (Glaxo Wellcome, Inc. v. Eon Labs Manufacturing, Inc., Civil Action No. 00 Civ 9089). Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

   b. the date of a court decision [505(j)(5)(B)(iii)(I), (II), or (III)], or,

   c. the patents have expired, and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

In order to reactivate your application prior to final approval, please submit a MINOR AMENDMENT - FINAL APPROVAL REQUESTED between 60 to 90 days prior to the date you believe your application is eligible for final approval. This amendment should to notify the Agency of the circumstances impacting the final approval date. In addition, Your amendment must provide:

1. A copy of the appropriate court order or judgement, settlement agreement between the parties, licensing agreement between you and the patent holder, or any other relevant information, and

2. a. updated information related to final-printed labeling, chemistry, manufacturing and controls data, or any other significant change in the conditions outlined in this abbreviated application, or

b. a statement that no such changes have been made to the application since the date of this tentative approval.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made.

In addition to, or instead of, the amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

The amendment should be designated as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED in your cover letter. Before you submit the amendment, please contact Stanley Shepperson, Project Manager, at 301-827-5849, for further instructions.

Sincerely yours,

Gary Buehler 1/24/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-932
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-92

Endorsements:
HFD-647/L.Tang/12/12/01
HFD-647/U.Venkataram/12/17/01
HFD-617/S.Shepperson/12/11/01
HFD-613/A.Vezza/
HFD-613/C.Hoppes/

v:\firmsam\eon\ltrs&rev\75932TAF
F/T by rad12/18/01

TENTATIVE APPROVAL

12-18-01
U.V. Venkataram 12/17/01
D. Shepperson 12/14/01
A. Vezza 12/26/01
C/all for / 12/26/01
conc satisfactory
Vilayat Sayeed 12/31/01
Robert West 1/24/2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-932

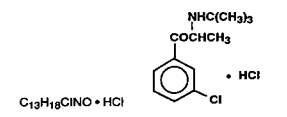
LABELING

Rev. 11/03E
0410

Bupropion Hydrochloride
Extended-Release Tablets
Rx only

DESCRIPTION

Bupropion hydrochloride extended-release, an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, 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 $C_{13}H_{18}ClNO•HCl$. 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:



$C_{13}H_{18}ClNO • HCl$ M.W. 276.2

Each tablet for oral administration contains 100 mg of bupropion hydrochloride and the following inactive ingredients: carnauba wax, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, opadry blue, hypromellose, titanium dioxide, FD & C Blue No. 1 Lake, macrogol PEG 400, and polysorbate 80.

CLINICAL PHARMACOLOGY

Pharmacodynamics: Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine, and does not inhibit monoamine oxidase. While the mechanism of action of bupropion, as with other antidepressants, is unknown, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

Pharmacokinetics: Bupropion is a racemic mixture. The pharmacologic activity and pharmacokinetics of the individual enantiomers have not been studied.

The mean elimination half-life (±SD) of bupropion after chronic dosing is 21 (±9) hours, and steady-state plasma concentrations of bupropion are reached within 8 days.

In a study comparing chronic dosing with bupropion hydrochloride extended-release tablets 150 mg twice daily to the immediate-release formulation of bupropion at 100 mg three times daily, peak plasma concentrations of bupropion at steady state for bupropion hydrochloride extended-release tablets were approximately 85% of those achieved with the immediate-release formulation. There was equivalence for bupropion AUCs, as well as equivalence for both peak plasma concentration and AUCs for all three of the detectable bupropion metabolites. Thus, at steady state, bupropion hydrochloride extended-release tablets, given twice daily, and the immediate-release formulation of bupropion, given three times daily, are essentially bioequivalent for both bupropion and the three quantitatively important metabolites.

Absorption: Following oral administration of bupropion hydrochloride extended-release tablets to healthy volunteers, peak plasma concentrations of bupropion are achieved within 3 hours. Food increased C_{max} and AUC of bupropion by 11% and 17%, respectively, indicating that there is no clinically significant food effect.

Distribution: *In vitro* tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 mcg/mL. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Metabolism: Bupropion is extensively metabolized in humans. Three metabolites have been shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via reduction of the carbonyl group. *In vitro* findings suggest that cytochrome P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. However, it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold less potent than bupropion. This may be of clinical importance because the plasma concentrations of the metabolites are as high or higher than those of bupropion.

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 P450IID6 (CYP2D6), there is the potential for drug-drug interactions when bupropion is co-administered with drugs metabolized by this isoenzyme (see **PRECAUTIONS: Drug Interactions**).

Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur approximately 6 hours after administration of bupropion hydrochloride extended-release tablets. Peak plasma concentrations of hydroxybupropion are approximately 10 times the peak level of the parent drug at steady state. The elimination half-life of hydroxybupropion is approximately 20 (±5) hours, and its AUC at steady state is about 17 times that of bupropion. The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the hydroxybupropion metabolite. However, their elimination half-lives are longer, 33 (±10) and 37 (±13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion, respectively.

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300 to 450 mg/day.

Elimination: Following oral administration of 200 mg of ^{14}C-bupropion in humans, 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 consistent with the extensive metabolism of bupropion.

Population Subgroups: Factors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure [CHF], age, concomitant medications, etc.) or elimination may be expected to influence the degree and extent of accumulation of the active metabolites of bupropion. 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 further metabolism or conjugation in the liver prior to urinary excretion.

Hepatic: The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in 2 single-dose studies, one in patients with alcoholic liver disease and one in patients with mild to severe cirrhosis. The first study showed that the half-life of hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in 8 healthy volunteers (32±14 hours versus 21±5 hours, respectively). Although not statistically significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be greater (by 53% to 57%) in patients with alcoholic liver disease. The differences in half-life for bupropion and the other metabolites in the 2 patient groups were minimal.

The second study showed no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites ($t_{1/2}$) in patients with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean difference: by approximately 70% and 3-fold, respectively) and more variable when compared to values in healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients with severe hepatic cirrhosis vs. 19 hours in healthy subjects). For the metabolite hydroxybupropion, the mean C_{max} was approximately 69% lower. For the combined amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C_{max} was approximately 31% lower. The mean AUC increased by about 1 1/2-fold for hydroxybupropion to about 2 1/2-fold for threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold, respectively, in patients with severe hepatic cirrhosis compared to healthy volunteers (see **WARNINGS, PRECAUTIONS,** and **DOSAGE AND ADMINISTRATION**).

Renal: The effect of renal disease on the pharmacokinetics of bupropion has not been studied. The elimination of the major metabolites of bupropion may be affected by reduced renal function.

Left Ventricular Dysfunction: During a chronic dosing study with bupropion in 14 depressed patients with left ventricular dysfunction (history of CHF or an enlarged heart on x-ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites was revealed, compared to healthy normal volunteers.

Age: 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 risk for accumulation of bupropion and its metabolites (see **PRECAUTIONS: Geriatric Use**).

Gender: A single-dose study involving 12 healthy male and 12 healthy female volunteers revealed no sex-related differences in the pharmacokinetic parameters of bupropion.

Smokers: The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were nonsmokers. Following oral administration of a single 150-mg dose of bupropion, there was no statistically significant difference in C_{max}, half-life, t_{max}, AUC, or clearance of bupropion or its active metabolites between smokers and nonsmokers.

CLINICAL TRIALS

The efficacy of the immediate-release formulation of bupropion as a treatment for depression was established in two 4-week, placebo-controlled trials in adult inpatients with depression and in one 6-week, placebo-controlled trial in adult outpatients with depression. In the first study, patients were titrated in a bupropion dose range of 300 to 600 mg/day on a three times daily schedule; 78% of patients received maximum doses of 450 mg/day or less. This trial demonstrated the effectiveness of the immediate-release formulation of bupropion on the Hamilton Depression Rating Scale (HDRS) total score, the depressed mood item (item 1) from that scale, and the Clinical Global Impressions (CGI) severity score. A second study included two fixed doses of the immediate-release formulation of bupropion (300 and 450 mg/day) and placebo. This trial demonstrated the effectiveness of the immediate-release formulation of bupropion, but only at the 450-mg/day dose; the results were positive for the HDRS total score and the CGI severity score, but not for HDRS item 1. In the third study, outpatients received 300 mg/day of the immediate-release formulation of bupropion. This study demonstrated the effectiveness of the immediate-release formulation of bupropion on the HDRS total score, HDRS item 1, the Montgomery-Asberg Depression Rating Scale, the CGI severity score, and the CGI improvement score.

Although there are not as yet independent trials demonstrating the antidepressant effectiveness of the extended-release formulation of bupropion, studies have demonstrated the bioequivalence of the immediate-release and extended-release forms of bupropion under steady-state conditions, i.e., bupropion extended-release 150 mg twice daily was shown to be bioequivalent to 100 mg three times daily of the immediate-release formulation of bupropion, with regard to both rate and extent of absorption, for parent drug and metabolites.

INDICATIONS AND USAGE

Bupropion hydrochloride extended-release tablets are indicated for the treatment of depression.

The efficacy of bupropion in the treatment of depression was established in two 4-week controlled trials of depressed inpatients and in one 6-week controlled trial of depressed outpatients whose diagnoses corresponded most closely to the Major Depression category of the APA Diagnostic and Statistical Manual (DSM) (see **CLINICAL PHARMACOLOGY**).

A major depressive episode (DSM-IV) implies the presence of 1) depressed mood or 2) loss of interest or pleasure; in addition, at least five of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The physician who elects to use bupropion hydrochloride extended-release tablets for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Bupropion hydrochloride extended-release tablets are contraindicated in patients with a seizure disorder.

Bupropion hydrochloride extended-release tablets are contraindicated in patients treated with ZYBAN® (bupropion hydrochloride) Sustained-Release Tablets, or any other medications that contain bupropion because the incidence of seizure is dose dependent.

Bupropion hydrochloride extended-release tablets are contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion. Bupropion hydrochloride extended-release tablets are contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines).

The concurrent administration of bupropion hydrochloride extended-release tablets and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with bupropion hydrochloride extended-release tablets.

Bupropion hydrochloride extended-release tablets are contraindicated in patients who have shown an allergic response to bupropion or the other ingredients that make up bupropion hydrochloride extended-release tablets.

WARNINGS

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

Seizures: Bupropion is associated with a dose-related risk of seizures. The risk of seizures is also related to patient factors, clinical situations, and concomitant medications, which must be considered in selection of patients for therapy with bupropion hydrochloride extended-release tablets. Bupropion hydrochloride extended-release tablets should be discontinued and not restarted in patients who experience a seizure while on treatment.

- **Dose: At doses of bupropion hydrochloride extended-release tablets up to a dose of 300 mg/day, the incidence of seizure is approximately 0.1% (1/1000) and increases to approximately 0.4% (4/1000) at the maximum recommended dose of 400 mg/day.**

  Data for the immediate-release formulation of bupropion revealed a seizure incidence of approximately 0.4% (i.e., 13 of 3200 patients followed prospectively) in patients treated at doses in a range of 300 to 450 mg/day. The 450 mg/day upper limit of this dose range is close to the currently recommended maximum dose of 400 mg/day for bupropion hydrochloride extended-release tablets. This seizure incidence (0.4%) may exceed that of other marketed antidepressants and bupropion hydrochloride extended-release tablets up to 300 mg/day by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted.

  Additional data accumulated for the immediate-release formulation of bupropion suggested that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day, which is twice the usual adult dose and one and one-half the maximum recommended daily dose (400 mg) of bupropion hydrochloride extended-release tablets. This disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

  Data for bupropion hydrochloride extended-release tablets revealed a seizure incidence of approximately 0.1% (i.e., 3 of 3100 patients followed prospectively) in patients treated at doses in a range of 100 to 300 mg/day. It is not possible to know if the lower seizure incidence observed in this study involving the extended-release formulation of bupropion resulted from the different formulation or the lower dose used. However, as noted above, the immediate-release and extended-release formulations are bioequivalent with regard to both rate and extent of absorption during steady state (the most pertinent condition to estimating seizure incidence), since most observed seizure occur under steady-state conditions.
- **Patient factors: Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, central nervous system (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications that lower seizure threshold.**
- **Clinical Situations: Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives (including benzodiazepines); 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) are known to lower seizure threshold.**

Recommendations for Reducing the Risk of Seizure: **Retrospective analysis of clinical experience gained during the development of bupropion suggests that the risk of seizure may be minimized if**

- **the total daily dose of bupropion hydrochloride extended-release tablets does *not* exceed 400 mg,**
- **the daily dose is administered twice daily, and**
- **the rate of incrementation of dose is gradual.**
- **No single dose should exceed 200 mg to avoid high peak concentrations of bupropion and/or its metabolites.**
- **Bupropion hydrochloride extended-release tablets should be administered with extreme caution to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or patients treated with other agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold.**

Hepatic Impairment: Bupropion hydrochloride extended-release should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required, as peak bupropion, as well as AUC levels are substantially increased and accumulation is likely to occur in such patients to a greater extent than usual. The dose should not exceed 100 mg every day or 150 mg every other day in these patients (see **CLINICAL PHARMACOLOGY, PRECAUTIONS,** and **DOSAGE AND ADMINISTRATION**).

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:*** Patients in placebo-controlled trials with bupropion hydrochloride extended-release tablets experienced agitation, anxiety, and insomnia as shown in Table 1.

Table 1: Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled trials

Adverse Event Term	Bupropion Hydrochloride Extended-Release Tablets 300 mg/day (n = 376)	Bupropion Hydrochloride Extended-Release Tablets 400 mg/day (n = 114)	Placebo (n = 385)
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Insomnia	11%	16%	6%

In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs.

Symptoms were sufficiently severe to require discontinuation of treatment in 1% and 2.6% of patients treated with 300 and 400 mg/day, respectively, of bupropion hydrochloride extended-release tablets and 0.8% of patients treated with placebo.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Depressed patients treated with an immediate-release formulation of bupropion or with bupropion hydrochloride extended-release tablets have been reported to show a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in bipolar disorder patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Bupropion hydrochloride extended-release tablets are expected to pose similar risks.

Altered Appetite and Weight: In placebo-controlled studies, patients experienced weight gain or weight loss as shown in Table 2.

Table 2: Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials

Weight Change	Bupropion Hydrochloride Extended-Release Tablets 300 mg/day (n = 339)	Bupropion Hydrochloride Extended-Release Tablets 400 mg/day (n = 112)	Placebo (n = 347)
Gained >5 lbs	3%	2%	4%
Lost >5 lbs	14%	19%	6%

In studies conducted with the immediate-release formulation of bupropion, 35% of patients receiving tricyclic antidepressants gained weight, compared to 9% of patients treated with the immediate-release formulation of bupropion. If weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight-reducing potential of bupropion hydrochloride extended-release tablets 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 hydrochloride extended-release tablets 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 hydrochloride extended-release tablets 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 extended-release formulation of bupropion (Zyban® Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of extended-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 extended-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of extended-release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with extended-release bupropion, NTS, and placebo, respectively. The majority of these patients had evidence of preexisting hypertension. Three patients (1.2%) treated with the combination of Zyban and NTS and one patient (0.4%) treated with NTS had study medication discontinued due to hypertension compared to none of the patients treated with Zyban or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

There is no clinical experience establishing the safety of bupropion hydrochloride extended-release tablets in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Bupropion was well tolerated in depressed patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in two patients for exacerbation of baseline hypertension.

Hepatic Impairment: Bupropion hydrochloride extended-release should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients, a reduced frequency and/or dose is required. Bupropion hydrochloride extended-release should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis.

All patients with hepatic impairment should be closely monitored for possible adverse effects that could indicate high drug and metabolite levels (see **CLINICAL PHARMACOLOGY, WARNINGS,** and **DOSAGE AND ADMINISTRATION**).

Renal Impairment: No studies have been conducted in patients with renal impairment. Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and subsequently excreted by the kidneys. Bupropion hydrochloride extended-release should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered as bupropion and its metabolites may accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible adverse effects that could indicate high drug or metabolite levels.

Information for Patients: Patients should be made aware that bupropion hydrochloride extended-release tablets contains the same active ingredient found in ZYBAN, used as an aid to smoking cessation treatment, and that bupropion hydrochloride extended-release tablets 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:

As dose is increased during initial titration to doses above 150 mg/day, patients should be instructed to take bupropion hydrochloride extended-release tablets in two divided doses, preferably with at least 8 hours between successive doses, to minimize the risk of seizures. Patients should be told that bupropion hydrochloride extended-release tablets should be discontinued and not restarted if they experience a seizure while on treatment.

Patients should be told that any CNS-active drug like bupropion hydrochloride extended-release tablets may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until *they are reasonably certain that bupropion* hydrochloride extended-release tablets do not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.

Patients should be told that the excessive use or abrupt discontinuation of alcohol or sedatives (including benzodiazepines) may alter the seizure threshold. Some patients have reported lower alcohol tolerance during treatment with bupropion hydrochloride extended-release tablets. Patients should be advised that the consumption of alcohol should be minimized or avoided.

Patients should be advised to inform their physicians if they are taking or plan to take any prescription or over-the-counter drugs. Concern is warranted because bupropion hydrochloride extended-release tablets and other drugs may affect each other's metabolism.

Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy.

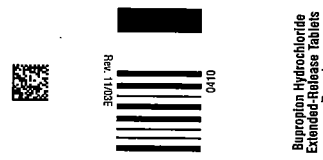
Patients should be advised to swallow bupropion hydrochloride extended-release tablets whole so that the release rate is not altered. Do not chew, divide, or crush tablets.

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions: Few systemic data have been collected on the metabolism of bupropion hydrochloride extended-release tablets following concomitant administration with other drugs or, alternatively, the effect of concomitant administration of bupropion hydrochloride extended-release tablets on the metabolism of other drugs.

Because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. *In vitro* studies indicate that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug interaction between bupropion hydrochloride extended-release tablets and drugs that affect the CYP2B6 isoenzyme (e.g., orphenadrine and cyclophosphamide). The threohydrobupropion metabolite of bupropion does not appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy young male volunteers. Following oral administration of two 150 mg bupropion hydrochloride extended-release tablets with and without 800 mg of cimetidine, the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and C_{max}, respectively, of the combined moieties of threohydrobupropion and erythrohydrobupropion.

While not systematically studied, certain drugs may induce the metabolism of bupropion (e.g., carbamazepine, phenobarbital, phenytoin).



Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in humans. In one study, following chronic administration of bupropion, 100 mg three times daily to eight healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism. Nevertheless, there may be the potential for clinically important alterations of blood levels of coadministered drugs.

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 hydroxybupropion are inhibitors of 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**).

Levodopa and Amantadine: Limited clinical data suggest a higher incidence or adverse experiences in patients receiving bupropion concurrently with either levodopa or amantadine. Administration of bupropion hydrochloride extended-release tablets to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, using small initial doses and gradual dose increases.

Drugs that Lower Seizure Threshold: Concurrent administration of bupropion hydrochloride extended-release tablets and agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold should be undertaken only with extreme caution (see **WARNINGS**). Low initial dosing and gradual dose increases should be employed.

Nicotine Transdermal System: (see **PRECAUTIONS: Cardiovascular Effects**)

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg per day, respectively. These doses are approximately seven and two times the maximum recommended human dose (MRHD), respectively, on a mg/m^2 basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg per day (approximately two to seven times the MRHD on a mg/m^2 basis); 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 positive response (two to three times control mutation rate) in two of five strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in one of three *in vivo* rat bone marrow cytogenetic studies.

A fertility study in rats at doses up to 300 mg/kg revealed no evidence of impaired fertility.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B. Teratology studies have been performed at doses up to 450 mg/kg in rats, and at doses up to 150 mg/kg in rabbits (approximately 7 to 11 and 7 times the MRHD, respectively, on a mg/m^2 basis), and have revealed no evidence of harm to the fetus due to bupropion. 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 hydrochloride extended-release tablets 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 hydrochloride extended-release tablets, 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 hydrochloride extended-release tablets in pediatric patients below 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 extended-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 is extensively metabolized in the liver to active metabolites, which are further metaboized and excreted by the kidneys. 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 **PRECAUTIONS: Renal Impairment** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

(See also **WARNINGS** and **PRECAUTIONS**)

The information included under the Incidence in Controlled Trials subsection of ADVERSE REACTIONS is based primarily on data from controlled clinical trials with bupropion hydrochloride extended-release tablets. Information on additional adverse events associated with the extended-release formulation of bupropion in smoking cessation trials, as well as the immediate-release formulation of bupropion, is included in a separate section (see Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion).

Incidence in Controlled Trials With bupropion hydrochloride extended-release tablets: ***Adverse Events Associated With Discontinuation of Treatment Among Patients Treated With Bupropion Hydrochloride Extended-Release Tablets:*** In placebo-controlled clinical trials, 9% and 11% of patients treated with 300 and 400 mg/day, respectively, of bupropion hydrochloride extended-release tablets and 4% of patients treated with placebo discontinued treatment due to adverse events. The specific adverse events in these trials that led to discontinuation in at least 1% of patients treated with either 300 or 400 mg/day of bupropion hydrochloride extended-release tablets and at a rate at least twice the placebo rate are listed in Table 3.

Table 3: Treatment Discontinuation Due to Adverse Events in Placebo-Controlled Trials

Adverse Event Term	Bupropion Hydrochloride Extended-Release Tablets 300 mg/day (n = 376)	Bupropion Hydrochloride Extended-Release Tablets 400 mg/day (n = 114)	Placebo (n = 385)
Rash	2.4%	0.9%	0.0%
Nausea	0.8%	1.8%	0.3%
Agitation	0.3%	1.8%	0.3%
Migraine	0.0%	1.8%	0.3%

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated With Bupropion Hydrochloride Extended-Release Tablets: Table 4 enumerates treatment-emergent adverse events that occurred among patients treated with 300 and 400 mg/day of bupropion hydrochloride extended-release tablets and with placebo in placebo-controlled trials. Events that occurred in either the 300 or 400 mg/day group at an incidence of 1% or more and were more frequent than in the placebo group are included. Reported adverse events were classified using a COSTART-based Dictionary.

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. 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 differ from those that prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

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

Table 4: Treatment-Emergent Adverse Events in Placebo-Controlled Trials*

Body System/ Adverse Event	Bupropion Hydrochloride Extended-Release Tablets 300 mg/day (n = 376)	Bupropion Hydrochloride Extended-Release Tablets 400 mg/day (n = 114)	Placebo (n = 385)
Body (General)			
Headache	26%	25%	23%
Infection	8%	9%	6%
Abdominal pain	3%	9%	2%
Asthenia	2%	4%	2%
Chest pain	3%	4%	1%
Pain	2%	3%	2%
Fever	1%	2%	–
Cardiovascular			
Palpitation	2%	6%	2%
Flushing	1%	4%	–
Migraine	1%	4%	1%
Hot flashes	1%	3%	1%
Digestive			
Dry mouth	17%	24%	7%
Nausea	13%	18%	8%
Constipation	10%	5%	7%
Diarrhea	5%	7%	6%
Anorexia	5%	3%	2%
Vomiting	4%	2%	2%
Dysphagia	0%	2%	0%
Musculoskeletal			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	0%	2%	0%
Twitch	1%	2%	–
Nervous system			
Insomnia	11%	16%	6%
Dizziness	7%	11%	5%
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Tremor	6%	3%	1%
Nervousness	5%	3%	3%
Somnolence	2%	3%	2%
Irritability	3%	2%	2%
Memory decreased	–	3%	1%
Paresthesia	1%	2%	1%
Central nervous system stimulation	2%	1%	1%
Respiratory			
Pharyngitis	3%	11%	2%
Sinusitis	3%	1%	2%
Increased cough	1%	2%	1%
Skin			
Sweating	6%	5%	2%
Rash	5%	4%	1%
Pruritus	2%	4%	2%
Urticaria	2%	1%	0%
Special senses			
Tinnitus	6%	6%	2%
Taste perversion	2%	4%	–
Amblyopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	–	2%	0%
Vaginal hemorrhage †	0%	2%	–
Urinary tract infection	1%	0%	–

*Adverse events that occurred in at least 1% of patients treated with either 300 or 400 mg/day of bupropion hydrochloride extended-release tablets, but equally or more frequently in the placebo group, were: abnormal dreams, accidental injury, acne, appetite increased, back pain, bronchitis, dysmenorrhea, dyspepsia, flatulence, flu syndrome, hypertension, neck pain, respiratory disorder, rhinitis, and tooth disorder.
† Incidence based on the number of female patients.
– Hyphen denotes adverse events occurring in greater than 0 but less than 0.5% of patients.

Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials: Adverse events from Table 4 occurring in at least 5% of patients treated with bupropion hydrochloride extended-release tablets and at a rate at least twice the placebo rate are listed below for the 300- and 400-mg/day dose groups.

Bupropion hydrochloride extended-release tablets 300 mg/day: Anorexia, dry mouth, rash, sweating, tinnitus, and tremor.

Bupropion hydrochloride extended-release tablets 400 mg/day: Abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary frequency.

Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion: In addition to the adverse events noted above, the following events have been reported in clinical trials and postmarketing experience with the extended-release formulation of bupropion in depressed patients and in nondepressed smokers, as well as in clinical trials and postmarketing clinical experience with the immediate-release formulation of bupropion.

Adverse events for which frequencies are provided below occurred in clinical trials with the extended-release formulation of bupropion. The frequencies represent the proportion of patients who experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled studies for depression (n = 987) or smoking cessation (n = 1013), or patients who experienced an adverse event requiring discontinuation of treatment in an open-label surveillance study with bupropion hydrochloride extended-release tablets (n = 3100). All treatment-emergent adverse events are included except those listed in Tables 1 through 4, those events listed in other safety-related sections, those adverse events subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, those events not reasonably associated with the use of the drug, and those events that were not serious and occurred in fewer than two patients. Events of major clinical importance are described in the **WARNINGS** and **PRECAUTIONS** sections of the labeling.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: 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.

Adverse events for which frequencies are not provided occurred in clinical trials or postmarketing experience with bupropion. Only those adverse events not previously listed for extended-release bupropion are included. The extent to which these events may be associated with bupropion hydrochloride extended-release tablets are unknown.

Body (General): Infrequent were chills, facial edema, musculoskeletal chest pain, and photosensitivity. Rare was malaise. Also observed were arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness (see **PRECAUTIONS**).

Cardiovascular: Infrequent were postural hypotension, stroke, tachycardia, and vasodilation. Rare was syncope. Also observed were complete atrioventricular block, extrasystoles, hypotension, hypertension (in some cases severe, see **PRECAUTIONS**), myocardial infarction, phlebitis, and pulmonary embolism.

Digestive: Infrequent were abnormal liver function, bruxism, gastric reflux, gingivitis, glossitis, increased salivation, jaundice, mouth ulcers, stomatitis, and thirst. Rare was edema of tongue. Also observed were colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, intestinal perforation, liver damage, pancreatitis, and stomach ulcer.

Endocrine: Also observed were hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone.

Hemic and Lymphatic: Infrequent was ecchymosis. Also observed were anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministrated with warfarin.

Metabolic and Nutritional: Infrequent were edema and peripheral edema. Also observed was glycosuria.

Musculoskeletal: Infrequent were leg cramps. Also observed were muscle rigidity/fever/rhabdomyolysis and muscle weakness.

Nervous System: Infrequent were abnormal coordination, decreased libido, depersonalization, dysphoria, emotional lability, hallucinations, hostility, hyperkinesia, hypertonia, hypesthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also observed were abnormal electroencephalogram (EEG), akinesia, aphasia, coma, delirium, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid reaction, and unmasking tardive dyskinesia.

Respiratory: Rare was bronchospasm. Also observed was pneumonia.

Skin: Rare was maculopapular rash. Also observed were alopecia, angioedema, exfoliative dermatitis, and hirsutism.

Special Senses: Infrequent were accommodation abnormality and dry eye. Also observed were deafness, diplopia, and mydriasis.

Urogenital: Infrequent were impotence, polyuria, and prostate disorder. Also observed were abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Bupropion is not a controlled substance.

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

In a population of individuals experienced with drugs of abuse, a single dose of 400 mg of bupropion produced mild amphetamine-like activity as compared to placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI), and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug desirability.

Findings in clinical trials, however, are not known to reliably predict the abuse potential of drugs. 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 that could not be tested because of the risk of seizure might be modestly attractive to those who abuse stimulant drugs.

Animals: Studies in rodents and primates have shown that bupropion exhibits some pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase locomotor activity, elicit a mild stereotyped behavioral response, and increase rates of responding in several schedule-controlled behavior paradigms. In primate models to assess the positive reinforcing effects of psychoactive drugs, bupropion was self-administered intravenously. In rats, bupropion produced amphetamine-like and cocaine-like discriminative stimulus effects in drug discrimination paradigms used to characterize the subjective effects of psychoactive drugs.

OVERDOSAGE

Human Overdose Experience: There has been very limited experience with overdosage of bupropion hydrochloride extended-release tablets; three cases were reported during clinical trials. One patient ingested 3000 mg of bupropion hydrochloride extended-release tablets and vomited quickly after the overdose; the patient experienced blurred vision and lightheadedness. A second patient ingested a "handful" of bupropion hydrochloride extended-release tablets and experienced confusion, lethargy, nausea, jitteriness, and seizure. A third patient ingested 3600 mg of bupropion hydrochloride extended-release tablets and a bottle of wine; the patient experienced nausea, visual hallucinations, and "grogginess". None of the patients experienced further sequelae.

There has been extensive experience with overdosage of the immediate-release formulation of bupropion. 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 the immediate-release formulation of bupropion and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

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

Although most patients recovered without sequelae, death associated with overdoses of the immediate-release formulation of bupropion alone have been reported rarely in patients ingesting massive doses of the drug. 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 hydrochloride extended-release, 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 extended-release tablets in a manner most likely to minimize the risk of seizure (see **WARNINGS**). 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. Bupropion hydrochloride extended-release tablets should be swallowed whole and not crushed, divided, or chewed.

Initial Treatment: The usual adult target dose for bupropion hydrochloride extended-release tablets is 300 mg/day, given as 150 mg twice daily. Dosing with bupropion hydrochloride extended-release tablets should begin at 150-mg/day given as a single daily dose in the morning. If the 150-mg initial dose is adequately tolerated, an increase to the 300-mg/day target dose, given as 150 mg twice daily, may be made as early as day 4 of dosing. There should be an interval of at least 8 hours between successive doses.

Increasing the Dosage Above 300 mg/day: As with other antidepressants, the full antidepressant effect of bupropion hydrochloride extended-release tablets may not be evident until 4 weeks of treatment or longer. An increase in dosage to the maximum of 400 mg/day, given as 200 mg twice daily, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day.

Maintenance: It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacological therapy. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Dosage Adjustment for Patients with Impaired Hepatic Function: Bupropion hydrochloride extended-release should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed 100 mg every day or 150 mg every other day in these patients. Bupropion hydrochloride extended-release should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis (see **CLINICAL PHARMACOLOGY, WARNINGS**, and **PRECAUTIONS**).

Dosage Adjustment for Patients with Impaired Renal Function: Bupropion hydrochloride extended-release should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

HOW SUPPLIED: Bupropion hydrochloride extended-release tablets, 100 mg, are round, biconvex, aquamarine, film coated tablets imprinted "Æ" over "410" on one side and plain on the other side in bottles of 60, 100, and 500 tablets.

Store at controlled room temperature 15°-30°C (59°-86°F)[see USP]. Store in a dry place. Keep tightly closed. Protect from light.

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

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

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, Inc
Laurelton, NY 11413

Rev. 11/03E
MF0410REV11/03E
OS7652
MG #18239

Information for the Patient
Bupropion Hydrochloride Extended-Release Tablets

Read this information completely before you start taking bupropion hydrochloride extended-release tablets. Read the information each time you get more medicine. There may be something new. This leaflet provides a summary about bupropion hydrochloride extended-release tablets. It does not include everything there is to know about your medicine. This information should not take the place of discussions with your doctor about your medical condition or bupropion hydrochloride extended-release tablets.

What is the most important information I should know about bupropion hydrochloride extended-release tablets?

- At a dose of up to 300 mg each day, there is a chance that approximately 1 out of every 1,000 people taking bupropion hydrochloride, the active ingredient in bupropion hydrochloride extended-release tablets, will have a seizure. The chance of seizures further increases with doses above 300 mg a day. Seizures are also called convulsions. They can cause you to fall with uncontrolled shaking.
- **You may have an increased risk of seizures while taking bupropion hydrochloride extended-release tablets if you have certain medical problems.** Be sure to tell your doctor about all of your medical problems.
- **You may have an increased risk of seizures while taking bupropion hydrochloride extended-release tablets if you take certain medicines.** Be sure to tell your doctor about all the medicines you take, including non-prescription medicines and herbal or natural supplements.

For more information, see the section "Who should not take bupropion hydrochloride extended-release tablets?"

If you have a seizure while taking bupropion hydrochloride extended-release tablets, stop taking the tablets and call your doctor right away. Do not take bupropion hydrochloride extended-release tablets again if you have a seizure.

What are bupropion hydrochloride extended-release tablets?

Bupropion hydrochloride extended-release tablets are a prescription medicine used to treat depression. Bupropion hydrochloride extended-release tablets are thought to treat depression by correcting an imbalance of certain chemicals in your brain.

Who should not take bupropion hydrochloride extended-release tablets?

Do not take bupropion hydrochloride extended-release tablets if you

- have or have ever had a seizure disorder such as epilepsy.
- are taking ZYBAN (used to help people stop smoking) or any other medicines that contain bupropion hydrochloride, the active ingredient in bupropion hydrochloride extended-release tablets.
- are abruptly discontinuing use of alcohol or sedatives (including benzodiazepines).
- have taken within the last 14 days one of the medicines for depression known as a monoamine oxidase inhibitor (MAOI), such as NARDIL® (phenelzine sulfate), PARNATE® (tranylcypromine sulfate), or MARPLAN® (isocarboxazid).
- have or have ever had an eating disorder such as anorexia nervosa or bulimia.
- are allergic to the active ingredient, bupropion, or to any of the inactive ingredients. Your doctor and pharmacist have a list of the inactive ingredients.

What should I tell my doctor before using bupropion hydrochloride extended-release tablets?

- **Tell your doctor about your medical conditions.** Tell your doctor if you
  - are pregnant or plan to become pregnant. It is not known if bupropion hydrochloride extended-release tablets can harm the unborn baby.
  - are breastfeeding.
    Bupropion hydrochloride extended-release tablets pass through your milk. It is not known whether bupropion hydrochloride extended-release tablets in breast milk can harm the baby.
  - have liver or kidney problems.
  - have an eating disorder such as anorexia nervosa or bulimia.
  - have had a head injury.
  - have had a seizure.
  - have a tumor in your nervous system.
  - recently had a heart attack, have heart problems, or have high blood pressure.
  - are a diabetic taking insulin or other medicines to control your blood sugar.
  - are a heavy drinker of alcoholic beverages.
  - use tranquilizers or sedatives frequently.
- **Tell your doctor about all the medicines you take,** including non-prescription medicines and herbal or natural remedies. Some may increase your chance of getting seizures or other side effects if you take bupropion hydrochloride extended-release tablets.

How should I take bupropion hydrochloride extended-release tablets?

- Take bupropion hydrochloride extended-release tablets at the same time each day exactly as prescribed by your doctor. You may take bupropion hydrochloride extended-release tablets with or without food.
- It may take 4 weeks or more for you to feel that bupropion hydrochloride extended-release tablets are working. Once you feel better, it is important to keep taking bupropion hydrochloride extended-release tablets as directed by your doctor.
- Take your doses at least 8 hours apart.
- If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and take your next tablet the regular time. It is important so you do not increase your chance of having a seizure.
- It is important to swallow bupropion hydrochloride extended-release tablets whole. Do not chew, divide, or crush tablets.

What should I avoid while taking bupropion hydrochloride extended-release tablets?

- Limit the amount of alcohol you drink while taking bupropion hydrochloride extended-release tablets. If you usually drink a lot of alcohol, talk with your doctor before suddenly stopping. If you suddenly stop drinking alcohol, you may increase your risk of seizures.
- Do not drive a car or use heavy machinery until you know if bupropion hydrochloride extended-release tablets affect your ability to perform these tasks.

What are possible side effects of bupropion hydrochloride extended-release tablets?

- **Seizures.** Some patients get seizures while taking bupropion hydrochloride extended-release tablets. **If you have a seizure while taking bupropion hydrochloride extended-release tablets, stop taking the tablets and call your doctor right away.** Do not take bupropion hydrochloride extended-release tablets again if you have a seizure.
- **Hypertension (high blood pressure).** Some patients get high blood pressure, sometimes severe, while taking bupropion hydrochloride extended-release tablets. The chance of high blood pressure may be increased if you also use nicotine replacement therapy (for example a nicotine patch) to help you stop smoking.

Call your doctor right away if you get a rash, itching, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, swelling of the lips or tongue, or have trouble breathing. These could be signs of a serious allergic reaction.

The most common side effects of bupropion hydrochloride extended-release tablets are loss of appetite, dry mouth, skin rash, sweating, ringing in the ears, shakiness, stomach pain, agitation, anxiety, dizziness, difficulty sleeping, muscle pain, nausea, rapid heart beat, sore throat, and urinating more often.

If you have nausea, you may want to take your medicine with food. If you have difficulty sleeping, avoid taking your medicine too close to bedtime.

These are not all the side effects of bupropion hydrochloride extended-release tablets. For a complete list, ask your doctor or pharmacist. Tell your doctor right away about any side effects that bother you. Do not change your dose or stop taking bupropion hydrochloride extended-release tablets without talking with your doctor first.

General information about bupropion hydrochloride extended-release tablets.

- Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use bupropion hydrochloride extended-release tablets for a condition for which it was not prescribed. Do not give bupropion hydrochloride extended-release tablets to other people, even if they have the same symptoms you have, it may harm them. Keep bupropion hydrochloride extended-release tablets out of the reach of children.
- Store bupropion hydrochloride extended-release tablets at room temperature, out of direct sunlight. Keep bupropion hydrochloride extended-release tablets in a tightly closed container.
- Bupropion hydrochloride extended-release tablets may have a characteristic odor. If present, this odor is normal.

This leaflet summarizes the most important information about bupropion hydrochloride extended-release tablets. For more information, talk with your doctor or pharmacist. They can give you information about bupropion hydrochloride extended-release tablets that is written for health professionals.

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

Issued 10/03C
OS8058
MG #18290

75-932

Final Printed Labeling
Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg

Exp. Date:

Lot No.:

NOV 25 2003

USUAL DOSAGE: See accompanying literature for complete prescribing information.

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

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

Issued 01/03
L6082

NDC 0185-0410-60

Bupropion Hydrochloride Extended-Release Tablets

100 mg

NOV 25 2003

Rx only

60 Tablets

Eon Labs

Each extended-release 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, Inc.
Laurelton, NY 11413

APPROVED

3 0185-0410-60 6

Exp. Date:

Lot No.:

NOV 25 2003

USUAL DOSAGE: See accompanying literature for complete prescribing information.

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

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

Issued 01/03
L6068

NDC 0185-0410-01

Bupropion Hydrochloride Extended-Release Tablets

100 mg

25 2003

Rx only

100 Tablets

Eon Labs

Each extended-release 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, Inc.
Laurelton, NY 11413

3 0185-0410-01 9

Exp. Date:

Lot No.:

NOV 25 2003

USUAL DOSAGE: See accompanying literature for complete prescribing information.

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

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

Issued 01/03
L6075

NDC 0185-0410-05

Bupropion Hydrochloride Extended-Release Tablets

100 mg

Rx only

500 Tablets

Eon Labs

Each extended-release 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, Inc.
Laurelton, NY 11413

APPROVED

3 0185-0410-05 7

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-932

LABELING REVIEWS

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

ANDA Number: **75-932** Date of Submission: **July 26, 2000**

Applicant's Name: **Eon Labs Manufacturing, Inc.**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg**

Labeling Deficiencies:

1. GENERAL COMMENTS:

   a. Please revise your storage temperature recommendations throughout your labels and labeling as follows:

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

   b. "Zyban®" and "ZYBAN®" rather than "Zyban", "ZYBAN", "Zyban™", and "ZYBAN™"

2. CONTAINER 60s, 100s, and 500s

   See GENERAL COMMENTS above.

3. PHYSICIAN INSERT

   a. GENERAL COMMENTS

      i. "in vitro" and "in vivo" (italics) throughout the insert labeling

      ii. Delete the hyphen between the number and the units when expressing a dose (e.g., "150 mg" rather than "150-mg").

      iii. Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert

      iv. Replace "Bupropion ER" with "bupropion hydrochloride extended-release tablets" throughout the insert labeling.

   b. CLINICAL PHARMACOLOGY

      i. Pharmacokinetics, seventh paragraph, last sentence

         A). "coadministered" (delete hyphen)

         B). "(see PRECAUTIONS: Drug Interactions)" (plural)

      ii. Population Subgroups

         A). The title is plural.

B). Age, last sentence - "... 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).

C). Gender - "pharmacokinetic" (singular)

c. CLINICAL TRIALS

i. The title is plural.

ii. First paragraph, third sentence - "... Clinical ..."

d. INDICATIONS AND USAGE

The title is plural.

e. WARNINGS

i. The title is plural.

ii. Paragraph beginning "Data for ...", last sentence - "conditions" (plural)

f. PRECAUTIONS

i. General

A). Allergic Reactions, add the following text as the last paragraph:

... 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.

B). Replace the "[redacted] subsection with the following sub-subsections:

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 extended-release formulation of bupropion (Zyban™ Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of extended-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 extended-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of extended-release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with extended-release bupropion, NTS, and placebo, respectively. The majority of these patients had evidence of preexisting hypertension. Three patients (1.2%) treated with the combination of Zyban and NTS and one patient (0.4%) treated with NTS had study

medication discontinued due to hypertension compared to none of the patients treated with Zyban or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

There is no clinical experience establishing the safety of bupropion hydrochloride extended-release in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Bupropion was well tolerated in depressed patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine blood pressure in the study of patients with 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 a greater extent than usual. The patient should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.

ii. Information for Patients, fourth paragraph - "seizures" (plural)

iii. Drug Interactions

A). The title is plural.

B). Second paragraph, sixth sentence - "tablets" rather than "Ttablets"

C). Drugs Metabolized By Cytochrome P450IID6 ..., second paragraph, first sentence - "coadministration" (delete hyphen)

D). Nicotine Transdermal System - Delete the text of this sub-subsection and replace with "(see PRECAUTIONS: Cardiovascular Effects)."

iv. Geriatric Use

A). Second paragraph - "... 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 PRECAUTIONS: Geriatric Use)."

B). Last sentence - Delete "[redacted]".

g. ADVERSE REACTIONS

i. First sentence - "ADVERSE REACTIONS" (plural)

ii. Incidence in Controlled Trials With Bupropion Hydrochloride Extended-release, Adverse Events Occurring at an Incidence of 1% or More ...

A). First paragraph, last sentence - "COSTART" (spelling)

B). Second paragraph, second sentence - "judgments" (plural)

iii. Other Events Observed During the Clinical Development ...

A). Second paragraph, third sentence - "Tables" (plural)

B). Third paragraph, first sentence - "1/100" rather than "1/1000"

C). Body (General) - Add the following as the last two sentences:

... malaise. Also observed were arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness (see PRECAUTIONS).

D). Cardiovascular - ... hypotension, hypertension (in some cases severe, see PRECAUTIONS), myocardial ...

h. DRUG ABUSE AND DEPENDENCE

i. Humans

A). First paragraph - "subjects" (plural)

B). Third paragraph, first sentence - "findings" (plural)

ii. Animals, last sentence - "amphetamine-like and cocaine-like" (add hyphens)

i. OVERDOSAGE

Replace the "Management of Overdose" subsection with the following text:

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 hydrochloride extended-release, 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).

j. HOW SUPPLIED

i. See GENERAL COMMENTS (1)(a).

ii. "Dispense contents with a child-resistant closure ..." ("with" rather than "in" to be in accord with your container labels)

4. PATIENT PACKAGE INSERT

a. GENERAL COMMENTS

i. Please submit the patient package insert as a separate labeling piece as well as it currently appears in conjunction with your physician insert.

ii. How and how many PPI's will be provided with each container size?

iii. See GENERAL COMMENTS (1)(b).

iv. See comments (3)(a)(iii) and (3)(a)(iv).

b. Item 7, penultimate paragraph - "... taking 400 mg/day gained more than 5 lbs., and 4 out of 100 people taking placebo (a sugar pill) lost more than 5 lbs."

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels: 60s, 100s, 500s (100 mg and 150 mg)

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Wellbutrin SR®

NDA Number: 20-358

NDA Drug Name: Wellbutrin SR® (bupropion hydrochloride extended-release) Tablets

NDA Firm: Glaxo Wellcome

Date of Approval of NDA Insert and supplement #: April 10, 2000 (S-015)

Has this been verified by the MIS system for the NDA? YES

Was this approval based upon an OGD labeling guidance? NO

Basis of Approval for the Container Labels: side-by-sides

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	

Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? ANDA IN HDPE CONTAINERS	??		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List			

Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. This review was based on the labeling for Wellbutrin SR (Glaxo Wellcome; Approved 4-10-00; Revised 9-99) NDA 20-358/S-015. Supplement 16 had nothing to do with labeling.

2. The inactive ingredients are listed accurately in the DESCRIPTION section (pp 152, 153 v 1.1).

3. Eon Labs is the manufacturer (p 289 v 1.2).

4. The RLD is available in 100 mg and 150 mg strengths - both in 60s. The ANDA will be available in 100 mg and 150 mg strengths in container sizes of 60s, 100s and 500s. All containers have CRC lids and are made of HDPE (p 620 v 1.3).

5. The tablet descriptions are okay as seen in the HOW SUPPLIED section (pp 816, 818 v 1.3).

6. There are 5 patents (no exclusivities) for this drug product:

5,358,970	8-12-13
5,427,798	8-12-13
RE33994	8-18-04
5,763,493	8-12-13
5,731,000	8-12-13

The firm has filed under Paragraph IV to each of the above patents.

7. Per memo from Kim Dettelbach, we will not require generic bupropions to reference a Pregnancy Registry.

8. Storage/dispensing recommendations:

RLD - Store at controlled room temperature 20°-25°C (68°-77°F)(see USP). Dispense in a tight, light-resistant container as defined in the USP.

ANDA - [containers] Store at controlled room temperature 15°-30°C (59°-86°F). Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP.
[insert] Store at controlled room temperature 15°-30°C (59°-86°F). Dispense contents in a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP.

USP - not USP

I have asked the firm to revise the labels and labeling to "Store at controlled room temperature 15°-30°C (59°-86°F)(see USP)."

9. Both the RLD and the ANDA are unscored.

Date of Review: 10-18-00 **Date of Submission:** 7-26-00

Primary Reviewer: Adolph Vezza **Date:** 10/30/00

Team Leader: Charlie Hoppes **Date:** 10/30/00

cc:

ANDA: 75-932
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/10/18/00|V:\FIRMSAM\EON\LTRS&REV\75932na1.l
Review

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: **75-932** Date of Submission: **January 31, 2001**

Applicant's Name: **Eon Labs Manufacturing, Inc.**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg**

Labeling Deficiencies:

1. CONTAINER 100s (100 mg)

   Add "(see USP)" to the storage temperature recommendations.

2. PHYSICIAN INSERT

   a. PRECAUTIONS

      i. Cardiovascular Effects

         A). Second paragraph

            1). First sentence - "Zyban®" rather than "Zyban™"

            2). The sentence beginning "There is no ..." begins a new paragraph (the third).

         B). Third paragraph

            1). Third sentence - "... had previously developed orthostatic ..."

            2). Last sentence - "bupropion" rather than "bupropine"

      ii. Geriatric Use, last sentence - Add a period to the end of the sentence.

   b. ADVERSE REACTIONS

      Cardiovascular - "... see PRECAUTIONS), myocardial ..."

   c. DRUG ABUSE AND DEPENDENCE

      Animals, last sentence - "amphetamine-like" (add hyphen)

   d. OVERDOSAGE

      Overdosage Management

      i. Revise the subsection title as seen above.

      ii. Second sentence - "... vital signs. EEG monitoring ..."

3. PATIENT PACKAGE INSERT

Item 7

a. Paragraph beginning "For people who lost weight ..." - " ... and 6 out of 100 people taking placebo ..." rather than "4 out of 100"

b. Paragraph beginning "For people who gained weight ..." - "... taking 400 mg/day gained more than 5 lbs., and 4 out of 100 people taking placebo (a sugar pill) lost more than 5 lbs."

Please revise your container labels and physician and patient package insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels: 60s, 100s, 500s (100 mg and 150 mg)
All satisfactory in printer's proof except for 100 mg 100s [left out "(see USP)"]

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Wellbutrin SR®

NDA Number: 20-358

NDA Drug Name: Wellbutrin SR® (bupropion hydrochloride extended-release) Tablets

NDA Firm: Glaxo Wellcome

Date of Approval of NDA Insert and supplement #: April 10, 2000 (S-015)

Has this been verified by the MIS system for the NDA? YES

Was this approval based upon an OGD labeling guidance? NO

Basis of Approval for the Container Labels: side-by-sides

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	

Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? ANDA IN HDPE CONTAINERS	??		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	

Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling for Wellbutrin SR (Glaxo Wellcome; Approved 4-10-00; Revised 9-99) NDA 20-358/S-015. Supplement 16 had nothing to do with labeling.

2. The inactive ingredients are listed accurately in the DESCRIPTION section (pp 152, 153 v 1.1).

3. Eon Labs is the manufacturer (p 289 v 1.2).

4. The RLD is available in 100 mg and 150 mg strengths - both in 60s. The ANDA will be available in 100 mg and 150 mg strengths in container sizes of 60s, 100s and 500s. All containers have CRC lids and are made of HDPE (p 620 v 1.3).

   PPIs - ___ per each ____ of 60s and 100s – ___ per each ____ of 500s

5. The tablet descriptions are okay as seen in the HOW SUPPLIED section (pp 816, 818 v 1.3).

6. There are 5 patents (no exclusivities) for this drug product:

5,358,970	8-12-13
5,427,798	8-12-13
RE33994	8-18-04
5,763,493	8-12-13
5,731,000	8-12-13

   The firm has filed under Paragraph IV to each of the above patents.

7. Per memo from Kim Dettelbach, we will not require generic bupropions to reference a Pregnancy Registry.

8. Storage/dispensing recommendations:

   RLD - Store at controlled room temperature 20°-25°C (68°-77°F)(see USP). Dispense in a tight, light-resistant container as defined in the USP.

   ANDA - [containers] Store at controlled room temperature 15°-30°C (59°-86°F)(see USP). Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP.
   [insert] Store at controlled room temperature 15°-30°C (59°-86°F)(see USP). Dispense contents in a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP.

   USP - not USP

   The firm has failed to add "(see USP)" to the 100 mg 100s container size.

9. Both the RLD and the ANDA are unscored.

Date of Review: 2-5-01 Date of Submission: 1-31-01

Primary Reviewer: Adolph Vezza A. Vezza Date: 2/6/01

Team Leader: Charlie Hoppes Date:

Charlie Hoppes 2/6/01

TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-932** Date of Submission: **July 17, 2001**

Applicant's Name: **Eon Labs Manufacturing, Inc.**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? No – Tentative Approval

Container Labels: 60s, 100s, 500s (100 mg and 150 mg)
All satisfactory in printer's proof except for 100 mg 100s [left out "(see USP)"] as of the January 31, 2001 submission.
100s (100 mg) – *Satisfactory in printers proof as of the July 17, 2001 submission.*

Professional Package Insert Labeling:
Satisfactory in draft as of the July 31, 2001 submission.

Patient Package Insert Labeling:
Satisfactory in draft as of the July 31, 2001 submission.

Revisions needed post-approval:
CONTAINER LABELS – (1) BuPROPion – when listing the established name (2) "medicines that contain" or "medicine that contains" FIRM TO BE NOTIFIED BY PHONE WHEN READY FOR TA SO THAT THEY CAN SUBMIT REVISED CONTAINER LABELS WHEN THEY SUBMIT FPL. FIRM ALSO TO BE NOTIFIED AT THAT TIME THAT THE LATEST APPROVED LABELING FOR THE RLD (NDA 20-358/S-019) APPROVED JUNE 11, 2001 HAS GOTTEN 3 YEARS OF EXCLUSIVITY AND THEY HAVE TO CERTIFY TO THAT. SINCE IT IS NOT YET LISTED IN THE ORANGE BOOK WE WILL NOT ASK THEM TO DO IT AT THIS TIME.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Wellbutrin SR®

NDA Number: 20-358

NDA Drug Name: Wellbutrin SR® (bupropion hydrochloride extended-release) Tablets

NDA Firm: Glaxo Wellcome

Date of Approval of NDA Insert and supplement #: April 10, 2000 (S-015)

Has this been verified by the MIS system for the NDA? YES

Was this approval based upon an OGD labeling guidance? NO

Basis of Approval for the Container Labels: side-by-sides

Other Comments: As mentioned above NDA 20-358/S-019 was the latest labeling supplement approved but it is going to get 3 years of exclusivity (PER Mary Ann Holovak – 7-31-01).

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	

Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? ANDA IN HDPE CONTAINERS	??		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. This review was based on the labeling for Wellbutrin SR (Glaxo Wellcome; Approved 4-10-00; Revised 9-99) NDA 20-358/S-015. Supplement 16 had nothing to do with labeling and Supplement 19 (for the use of the drug in maintaining an antidepressant effect when dosed up to one year) will be getting 3 years exclusivity.* (see following page)

2. The inactive ingredients are listed accurately in the DESCRIPTION section (pp 152, 153 v 1.1).

3. Eon Labs is the manufacturer (p 289 v 1.2).

4. The RLD is available in 100 mg and 150 mg strengths - both in 60s. The ANDA will be available in 100 mg and 150 mg strengths in container sizes of 60s, 100s and 500s. All containers have CRC lids and are made of HDPE (p 620 v 1.3).

   PPIs - — per each —— of 60s and 100s -- — per each —— of 500s

5. The tablet descriptions are okay as seen in the HOW SUPPLIED section (pp 816, 818 v 1.3).

6. There are 5 patents (no exclusivities) for this drug product:

5,358,970	8-12-13
5,427,798	8-12-13
RE33994	8-18-04
5,763,493	8-12-13
5,731,000	8-12-13

   The firm has filed under Paragraph IV to each of the above patents.

   See # 1 above for exclusivity information.

7. Per memo from Kim Dettelbach, we will not require generic bupropions to reference a Pregnancy Registry.

8. Storage/dispensing recommendations:

RLD - Store at controlled room temperature 20°-25°C (68°-77°F)(see USP). Dispense in a tight, light-resistant container as defined in the USP.

ANDA - [containers] Store at controlled room temperature 15°-30°C (59°-86°F)(see USP). Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP.
[insert] Store at controlled room temperature 15°-30°C (59°-86°F)(see USP). Dispense contents in a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP.

USP - not USP

9. Both the RLD and the ANDA are unscored.

Date of Review: 7-31-01 **Date of Submission:** 7-17-01

Primary Reviewer: Adolph Vezza **Date:** 8/1/01

A. Vezza

Team Leader: Charlie Hoppes **Date:** 8/1/01

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cc:

ANDA: 75-932
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/7/31/01|V:\FIRMSAM\EON\LTRS&REV\75932TAP.L
Review

* The exclusivity shows that the drug is effective for depression up to 44 wks. The old labeling says there have been no studies done showing effectiveness for more than 6 weeks. At this time we will allow the generics to use the old labeling - but this issue will be discussed with the New Drug Project Manager for their input.

A. Vezza 1/18/02

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

ANDA Number: **75-932** Date of Submission: **July 2, 2003**

Applicant's Name: **Eon Labs Manufacturing, Inc.**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg**

Labeling Deficiencies:

- **GENERAL**

  a. You noted in your submission that all necessary revisions were made in accordance with the most recently approved labeling for the reference listed drug Wellbutrin SR, however, it appears that the most current labeling of Wellbutrin SR® approved October 22, 2002 was not used as a model. Please revise your labeling accordingly.

  b. Please revise your storage temperature statement as follows:

  "Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Store in a dry place and dispense in a child-resistant closure in a tight, light-resistant container as defined in the USP"

  c. For your larger package sizes, please describe how you plan to provide patient information sheets to the patients and indicate how many will be provided with each container size.

  d. Please note that USAN (United States Adopted Names) names (i.e., bupropion hydrochloride extended-release tablets) are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert.

- **CONTAINER:** 60s, 100s, and 500s (100 mg & 150 mg)

  a. See comment (b) under **GENERAL**

  b. Delete "This is a bulk package"

- **PHYSICIAN INSERT**

  1. CLINICAL PHARMACOLOGY

     a. Hepatic

     Please make the following revisions to the second paragraph starting with "The second study showed..... (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION)"

OLD	New
The mean AUC increased by — for hydroxybupropion and — for threo/erythrohydrobupropion.	Change — to "about 1 ½ -fold" Change — to "about 2 ½ -fold"
The median..... and — hours later for threo/erythrohydrobupropion.	Change — hours to "31 hours"

The mean half-lives... [redacted] ... Change [redacted] to "5- and 2-fold" administration).

2. CONTRAINDICATIONS

Add the following statement to the end of the third paragraph starting with, "Bupropion hydrochloride ..... immediate-release formulation of bupropion."

"Bupropion hydrochloride extended-release tablets are contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines)."

3. WARNINGS

a. To the end of the second paragraph starting with "Seizures: Bupropion ..... for therapy with Bupropion hydrochloride extended-release tablets.", add the following sentence.

"Bupropion hydrochloride extended-release tablets should be discontinued and not restarted in patients who experience a seizure while on treatment."

b. Revise the "• Clinical Situations" section as follows:

"Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives (including benzodiazepines); addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin.

c. Revise the "• Concomitant medication" section as follows:

"Many medications (e.g., antipsychotics, antidepressants, theophylline, systemic steroids) are known to lower seizure threshold."

d. Under "• Bupropion Hydrochloride extended-release should be administered... seizure threshold." section, delete the following sentence:

[redacted]

4. PRECAUTIONS

a. "Information for Patients" subsection

i. Add the following sentence next to "As dose is increased during ..... minimize the risk of seizures."

"Patients should be told that bupropion hydrochloride extended-release tablets should be discontinued and not restarted if they experience a seizure while on treatment."

ii. Replace the following statement as follows:

Old	New
[redacted]	Patients should be told that the excessive use or abrupt discontinuation of alcohol or sedatives (including benzodiazepines) may alter the seizure threshold. Some patients have reported lower alcohol tolerance during treatment with bupropion hydrochloride extended-release tablets. Patients should be advised that the consumption of alcohol should be minimized or avoided.

b. Replace the following subsection as follows:

Old	New
[redacted]	**Levodopa and Amantadine:** Limited clinical data suggest a higher incidence of adverse experiences in patients receiving bupropion Concurrently with either levodopa or amantadine Administration of bupropion hydrochloride extended-release tablets to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, using small Initial doses and gradual dose increases.

c. Under "Drugs that Lower Seizure Threshold" subsection, please delete the following sentence:

[redacted]

5. ADVERSE REACTIONS

a. Under "Hemic and Lymphatic" section, add the following sentence at the end:

"Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.

b. Under "Nervous Systems" section, add term "hallucinations".

6. DOSAGE AND ADMINISTRATION

Under "General Dosing Considerations" section, add the following sentence to the end of the paragraph:

"Bupropion hydrochloride extended-release tablets should be swallowed whole and not crushed, divided, or chewed."

7. HOW SUPPLIED

See comment (b) under **GENERAL**

- **PATIENT PACKAGE INSERT**

Please revise the patient package insert to be the same as the attached reference listed drug's patient package insert, approved October 22, 2002. Replace Wellbutrin SR by "Bupropion hydrochloride extended-release tablets"

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

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes.

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment

APPEARS THIS WAY
ON ORIGINAL

Copy of Reference Listed Drug
Patient Insert Labeling removed.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	

Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? ANDA IN HDPE CONTAINERS	??		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. GENERAL

The tentative approval letter was issued on January 24, 2002, and the sponsor submitted this minor amendment requesting final approval of the application. However, the sponsor failed to use the most currently approved labeling as a model and needs to make requested revisions prior to approval. The sponsor submitted this application with the patent certification IV (the court has not made any final decision yet on all patents) and the 30-month stay period expired on April 18, 2003. RLD also has exclusivity that expires on June 11, 2004 and the sponsor indicated in their January 18, 2002 letter that they are not planning to market their product until the exclusivity is expired. Therefore, the labeling will be same as the last approved RLD labeling not the OGD model labeling with the carve outs.

2. MODEL LABELING

This review was based on the labeling for Wellbutrin SR (Glaxo Wellcome; Approved 10-22-02) NDA 20-358/S-029. The sponsor stated in their cover letter that they used the most currently approved Wellbutrin SR labeling, however, there was no information regarding the labeling that was used as a model. According to the COMIS, SLR-029 was the most current labeling, and it was noted that this labeling was not used as a model, especially the patient package insert. I have asked the sponsor to revise the whole patient package insert to be the same as the attached RLD PPI in addition to the requested revisions to the physician package insert.

3. DESCRIPTION

The inactive ingredients are listed accurately in the DESCRIPTION section (Vol. 1.1 Page 152-153)

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Eon Labs Manufacturing, Inc.
227-15 North Conduit Avenue
Laurelton, New York 11413

(Vol. 1.2. Page 289).

5. PACKAGING CONFIGURATIONS

RLD: 100 mg and 150 mg strengths - both in 60s.

ANDA: 100 mg and 150 mg strengths in container sizes of 60s, 100s and 500s.

Package Size	Bottle Size/Shape	Resin	Filler	Closure Size/Type	Innerseal/Liner
100 mg					
60 count	100 cc round	HDPE	Cotton	38 mm CRC	
100 count	100 cc round	HDPE	Cotton	38 mm CRC	
500 count	300 cc round	HDPE	Cotton	45 mm CRC	
150 mg					
60 count	100 cc round	HDPE	Cotton	38 mm CRC	
100 count	100 cc round	HDPE	Cotton	38 mm CRC	
500 count	400 cc round	HDPE	Cotton	53 mm CRC	

(Vol. 1.3. Page 621).

6. TABLET IMPRINT

The tablet imprintings have been accurately described in the HOW SUPPLIED section of the Insert according to the sponsor's "Quality Control Finished Tablet Specification & Report Form".

100 mg Tablets: Round, biconvex, aquamarine, film-coated tablets imprinted "E" over "410" on one side and plain on the other side in bottles of 60, 100, and 500 tablets.

150 mg Tablets: Round, biconvex, plum, film-coated tablets imprinted "E" over "415" on one side and plain on the other side in bottles of 60, 100, and 500 tablets.

(Vol. 1.3. Page 816 – 818)

7. PATENT/EXCLUSIVITY STATEMENT

Patent Data

Patent Number	**Patent Expiration**	**How Filed**	**Labeling Impact**
5358970	August 12, 2013	IV	None
5427798	August 12, 2013	IV	None
5731000	August 12, 2013	IV	None

5763493	August 12, 2013	IV	None

Exclusivity Data

Exclusivity Code	Reference	Expiration	Labeling Impact
M-10	INFORMATION REGARDING MAINTENANCE OF AN ANTIDEPRESSANT EFFECT UP TO 1 YEAR OF DOSING	June 11, 2004	None (This product will not be marketed until the exclusivity is expired per 1/18/02 GC)

8. Per memo from Kim Dettelbach, we will not require generic bupropions to reference a Pregnancy Registry.

9. Storage/dispensing recommendations:

RLD - Store at controlled room temperature 20°-25°C (68°-77°F) [see USP]. Dispense in a tight, light-resistant container as defined in the USP.

ANDA - [containers] Store at controlled room temperature 15°-30°C (59°-86°F) [see USP]. This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP.

[insert] Store at controlled room temperature 15°-30°C (59°-86°F) [see USP]. Store in a dry place Keep tightly closed. Protect from light. Dispense contents in a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP.

***I have asked the sponsor to revise the statement as follows:**

"Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Store in a dry place and dispense in a child-resistant closure in a tight, light-resistant container as defined in the USP"

Date of Review: September 17, 2003

Date of Submission: July 2, 2003

Primary Reviewer: Melaine Shin

10-16-03
Date:

Team Leader: Lillie Golson

10/16/03
Date

cc:

ANDA: 75-932
DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)
V:Firmsam\Eon\Ltr&Rev\75932NA2.Labeling Review

TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-932** Date of Submissions: **10/27/03, 11/03/03, & 11/07/03**

Applicant's Name: **Eon Labs Manufacturing, Inc.**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg**

NOTE: WE ARE FULLY APPROVING THE 100 MG ONLY AT THIS TIME, THEREFORE, THE 150 MG EXTENDED-RELEASE TABLETS WITH COMBINED LABELING IS TENTATIVELY APPROVED UNTIL THE GENERIC EXCLUSIVITY IS EXPIRED OR BECOMES INVALID.

APPROVAL SUMMARY (List the package size, strengths(s), and date of submission for approval)

Do you have 12 Final Printed Labels and Labeling?

Yes, however, the new Final Printed Labeling & Labels will be submitted post approval incorporating a new storage legend and other revisions.

CONTAINER LABELS – 100 mg (60s, 100s, and 500s)

Satisfactory in FPL as of July 2, 2003 submission (vol. 4.1). Post approval changes will be made at the next reprint.

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in FPL as of October 27, 2003 submission (Rev. 10/03, MG#18239) [vol. 4.1]. Post approval changes will be made at the next reprint.

PATIENT INFORMATION LEAFLET

Satisfactory in FPL as of November 7, 2003 submission (vol. 4.1).

REVISIONS NEEDED POST-APPROVAL

1. GENERAL

The sponsor indicated that they have completed the packaging and labeling with the container labels bearing the old USP storage legend of 15-30°C, and changing container labels at this time would a burdensome task. The sponsor stated in their October 27, 2003 submission that the changes will be incorporated at the next reprint and FPLs for labels and labeling will be submitted as a Special Supplement – Changes Being Effected – 0 Day, and it is acceptable.

- The revised storage temperature statement will read "Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Store in a dry place and dispense in a child-resistant closure in a tight, light-resistant container as defined in the USP".

- "This is a bulk package" will be deleted from the container labels.

BASIS OF APPROVAL

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Wellbutrin SR

NDA Number: 20-358

NDA Drug Name: Wellbutrin SR ® Tablets.

NDA Firm: Glaxo Wellcome

Date of Approval of NDA Insert and supplement #: October 22, 2002 / S-029

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			

Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? ANDA IN HDPE CONTAINERS	x		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. GENERAL

The tentative approval letter was issued on January 24, 2002, and the sponsor submitted a minor amendment requesting final approval of the application. However, the sponsor failed to use the most currently approved labeling as a model and needs to make requested revisions prior to approval. The sponsor submitted this application with the patent certification IV (the court has not made any final decision yet on all patents) and the 30-month stay period expired on April 18, 2003. RLD also has exclusivity that expires on June 11, 2004 and the sponsor indicated in their January 18, 2002 letter that they are not planning to market their product until the exclusivity is expired. Therefore, the labeling will be same as the last approved RLD labeling not the OGD model labeling with the carve outs.

During a teleconference call on October 24, 2003 in response to the deficiency letter faxed on October 23, 2003, the sponsor indicated that they have completed the packaging and labeling with the container labels bearing the old USP storage legend of 15-30°C, and changing container labels at this time would a burdensome task. As discussed, the sponsor stated in their October 27, 2003 submission that the changes will be incorporated at the next reprint and FPLs for labels and labeling will be submitted as a Special Supplement – Changes Being Effected – 0 Day, and it is acceptable.

On October 30, 2003, the sponsor was notified that the Patient Package Insert was not revised as instructed in the deficiency letter and the sponsor submitted the revised version on October 31, 2003 which was found to be acceptable.

On November 3, 2003, the sponsor submitted the revised PPI which the dosage form "tablets" was added to "bupropion hydrochloride extended-release" after notified by the labeling reviewer.

On November 6, 2003, the labeling review team became aware that we are only fully approving 100 mg strength of bupropion hydrochloride extended-release tablets and the sponsor was notified by the Division Director, Peter Rickman, to submit a separate labeling for bupropion hydrochloride extended-release 100 mg tablets since the sponsor's labeling was a combined labeling with 150 mg tablets.

Until the generic exclusivity is expired or becomes invalid, we are approving the 100 mg strength and tentatively approve 150 mg strength with the combined labeling.

2. MODEL LABELING

This review was based on the labeling for Wellbutrin SR (Glaxo Wellcome; Approved 10-22-02) NDA 20-358/S-029. The sponsor stated in their cover letter that they used the most currently approved Wellbutrin SR labeling, however, there was no information regarding the labeling that was used as a model. According to the COMIS, SLR-029 was the most current labeling, and it was noted that this labeling was not used as a model, especially the patient package insert. I have asked the sponsor to revise the whole patient package insert to be the same as the attached RLD PPI in addition to the requested revisions to the physician package insert.

3. DESCRIPTION

The inactive ingredients are listed accurately in the DESCRIPTION section (Vol. 1.1 Page 152-153)

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Eon Labs Manufacturing, Inc.
227-15 North Conduit Avenue
Laurelton, New York 11413

(Vol. 1.2. Page 289).

5. PACKAGING CONFIGURATIONS

RLD: 100 mg and 150 mg strengths - both in 60s.

ANDA: 100 mg and 150 mg strengths in container sizes of 60s, 100s and 500s.

Package Size	Bottle Size/Shape	Resin	Filler	Closure Size/Type	Innerseal/Liner
100 mg					
60 count	100 cc round	HDPE	Cotton	38 mm CRC	
100 count	100 cc round	HDPE	Cotton	38 mm CRC	
500 count	300 cc round	HDPE	Cotton	45 mm CRC	
150 mg					
60 count	100 cc round	HDPE	Cotton	38 mm CRC	
100 count	100 cc round	HDPE	Cotton	38 mm CRC	
500 count	400 cc round	HDPE	Cotton	53 mm CRC	

(Vol. 1.3. Page 621).

6. TABLET IMPRINT

The tablet imprintings have been accurately described in the HOW SUPPLIED section of the Insert according to the sponsor's "Quality Control Finished Tablet Specification & Report Form".

100 mg Tablets: Round, biconvex, aquamarine, film-coated tablets imprinted "E" over "410" on one side and plain on the other side in bottles of 60, 100, and 500 tablets.

150 mg Tablets: Round, biconvex, plum, film-coated tablets imprinted "E" over "415" on one side and plain on the other side in bottles of 60, 100, and 500 tablets.

(Vol. 1.3. Page 816 – 818)

7. PATENT/EXCLUSIVITY STATEMENT

Patent Data

Patent Number	**Patent Expiration**	**How Filed**	**Labeling Impact**
5358970	August 12, 2013	IV	None
5427798	August 12, 2013	IV	None
5731000	August 12, 2013	IV	None
5763493	August 12, 2013	IV	None

Exclusivity Data

Exclusivity Code	**Reference**	**Expiration**	**Labeling Impact**

M-10	INFORMATION REGARDING MAINTENANCE OF AN ANTIDEPRESSANT EFFECT UP TO 1 YEAR OF DOSING	June 11, 2004	None (This product will not be marketed until the exclusivity is expired per 1/18/02 GC)

8. Per memo from Kim Dettelbach, we will not require generic bupropions to reference a Pregnancy Registry.

9. Storage/dispensing recommendations:

RLD - Store at controlled room temperature 20°-25°C (68°-77°F) [see USP]. Dispense in a tight, light-resistant container as defined in the USP.

ANDA - [containers] Store at controlled room temperature 15°-30°C (59°-86°F) [see USP]. This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP.

[insert] Store at controlled room temperature 15°-30°C (59°-86°F) [see USP]. Store in a dry place Keep tightly closed. Protect from light. Dispense contents in a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP.

***I have asked the sponsor to revise the statement as follows:**

"Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Store in a dry place and dispense in a child-resistant closure in a tight, light-resistant container as defined in the USP"

Date of Review: November 7, 2003 Date of Submissions: 10/27/03, ~~10/31/03~~, 11/3/03, & 11/7/03

Primary Reviewer: Melaine Shin Date: 11/13/03

Team Leader: Lillie Golson Date 11/13/03

cc:

ANDA: 75-932
DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)
V:Firmsam\Eon\Ltr&Rev\75932AP1.Labeling Review

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

ANDA Number: **75-932** Date of Submissions: ~~**10/27/03**~~, ~~**10/31/03**~~, ~~**11/03/03**~~, ~~**11/07/03**~~ **& 11/20/03**

Applicant's Name: **Eon Labs Manufacturing, Inc.**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg**

NOTE: We are only fully approving the 100 mg strength and tentatively approve the 150 mg strength.

APPROVAL SUMMARY (List the package size, strengths(s), and date of submission for approval)

Do you have 12 Final Printed Labels and Labeling?

Yes, however, the new Final Printed Labeling & Labels will be submitted post approval incorporating a new storage legend and other revisions.

CONTAINER LABELS – 100 mg (60s, 100s, and 500s)

Satisfactory in FPL as of July 2, 2003 submission (vol. 4.1). Post approval changes will be made at the next reprint.

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in FPL as of November 21, 2003 submission. Post approval changes will be made at the next reprint.

PATIENT INFORMATION LEAFLET

Satisfactory in FPL as of November 7, 2003 submission.

REVISIONS NEEDED POST-APPROVAL

1. GENERAL

The sponsor indicated that they have completed the packaging and labeling with the container labels bearing the old USP storage legend of 15-30°C, and changing container labels at this time would a burdensome task. The sponsor stated in their October 27, 2003 submission that the changes will be incorporated at the next reprint and FPLs for labels and labeling will be submitted as a Special Supplement – Changes Being Effected – 0 Day, and it is acceptable.

- The revised storage temperature statement will read "Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Store in a dry place and dispense in a child-resistant closure in a tight, light-resistant container as defined in the USP".

- "This is a bulk package" will be deleted from the container labels.

BASIS OF APPROVAL

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Wellbutrin SR

NDA Number: 20-358

NDA Drug Name: Wellbutrin SR ® Tablets.

NDA Firm: Glaxo Wellcome

Date of Approval of NDA Insert and supplement #: October 22, 2002 / S-029

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			

Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? ANDA IN HDPE CONTAINERS	x		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. GENERAL

The tentative approval letter was issued on January 24, 2002, and the sponsor submitted this minor amendment requesting final approval of the application. However, the sponsor failed to use the most currently approved labeling as a model and needs to make requested revisions prior to approval. The sponsor submitted this application with the patent certification IV (the court has not made any final decision yet on all patents) and the 30-month stay period expired on April 18, 2003. RLD also has exclusivity that expires on June 11, 2004 and the sponsor indicated in their January 18, 2002 letter that they are not planning to market their product until the exclusivity is expired. Therefore, the labeling will be same as the last approved RLD labeling not the OGD model labeling with the carve outs.

During a teleconference call on October 24, 2003 in response to the deficiency letter faxed on October 23, 2003, the sponsor indicated that they have completed the packaging and labeling with the container labels bearing the old USP storage legend of 15-30°C, and changing container labels at this time would a burdensome task. As discussed, the sponsor stated in their October 27, 2003 submission that the changes will be incorporated at the next reprint and FPLs for labels and labeling will be submitted as a Special Supplement – Changes Being Effected – 0 Day, and it is acceptable.

On October 30, 2003, the sponsor was notified that the Patient Package Insert was not revised as instructed in the deficiency letter and the sponsor submitted the revised version on October 31, 2003 which was found to be acceptable.

On November 3, 2003, the sponsor submitted the revised PPI which the dosage form "tablets" was added to "bupropion hydrochloride extended-release" after notified by the labeling reviewer.

On November 6, 2003, the labeling review team became aware that we are only fully approving 100 mg strength of bupropion hydrochloride extended-release tablets and the sponsor was notified by the Division Director, Peter Rickman, to submit a separate labeling for bupropion hydrochloride extended-release 100 mg tablets since the sponsor's labeling was a combined labeling with 150 mg tablets.

On November 19, 2003, the firm was notified that if they wish to market 100 mg tablets before M-10 exclusivity expires on June 11, 2004, in contrast to what they certified on January 18, 2002, they need to revise the labeling and carve out the relevant wording. The firm was provided with the instruction as to which sections to be modified from the FPL for 100 mg tablets that was submitted on November 7, 2003.

2. MODEL LABELING

This review was based on the labeling for Wellbutrin SR (Glaxo Wellcome; Approved 10-22-02) NDA 20-358/S-029. The sponsor stated in their cover letter that they used the most currently approved Wellbutrin SR labeling, however, there was no information regarding the labeling that was used as a model. According to the COMIS, SLR-029 was the most current labeling, and it was noted that this labeling was not used as a model, especially the patient package insert. I have asked the sponsor to revise the whole patient package insert to be the same as the attached RLD PPI in addition to the requested revisions to the physician package insert.

3. DESCRIPTION

The inactive ingredients are listed accurately in the DESCRIPTION section (Vol. 1.1 Page 152-153)

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Eon Labs Manufacturing, Inc.
227-15 North Conduit Avenue
Laurelton, New York 11413

(Vol. 1.2. Page 289).

5. PACKAGING CONFIGURATIONS

RLD: 100 mg and 150 mg strengths - both in 60s.

ANDA: 100 mg and 150 mg strengths in container sizes of 60s, 100s and 500s.

Package Size	Bottle Size/Shape	Resin	Filler	Closure Size/Type	Innerseal/Liner
100 mg					
60 count	100 cc round	HDPE	Cotton	38 mm CRC	
100 count	100 cc round	HDPE	Cotton	38 mm CRC	
500 count	300 cc round	HDPE	Cotton	45 mm CRC	
150 mg					
60 count	100 cc round	HDPE	Cotton	38 mm CRC	
100 count	100 cc round	HDPE	Cotton	38 mm CRC	
500 count	400 cc round	HDPE	Cotton	53 mm CRC	

(Vol. 1.3. Page 621).

6. TABLET IMPRINT

The tablet imprintings have been accurately described in the HOW SUPPLIED section of the Insert according to the sponsor's "Quality Control Finished Tablet Specification & Report Form".

100 mg Tablets: Round, biconvex, aquamarine, film-coated tablets imprinted "E" over "410" on one side and plain on the other side in bottles of 60, 100, and 500 tablets.

150 mg Tablets: Round, biconvex, plum, film-coated tablets imprinted "E" over "415" on one side and plain on the other side in bottles of 60, 100, and 500 tablets.

(Vol. 1.3. Page 816 – 818)

7. PATENT/EXCLUSIVITY STATEMENT

Patent Data

Patent Number	**Patent Expiration**	**How Filed**	**Labeling Impact**
5358970	August 12, 2013	IV	None
5427798	August 12, 2013	IV	None
5731000	August 12, 2013	IV	None
5763493	August 12, 2013	IV	None

Exclusivity Data

Exclusivity Code	Reference	Expiration	Labeling Impact
M-10	INFORMATION REGARDING MAINTENANCE OF AN ANTIDEPRESSANT EFFECT UP TO 1 YEAR OF DOSING	June 11, 2004	Carved out

8. Per memo from Kim Dettelbach, we will not require generic bupropions to reference a Pregnancy Registry.

9. Storage/dispensing recommendations:

RLD - Store at controlled room temperature 20°-25°C (68°-77°F) [see USP]. Dispense in a tight, light-resistant container as defined in the USP.

ANDA - [containers] Store at controlled room temperature 15°-30°C (59°-86°F) [see USP]. This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP.

[insert] Store at controlled room temperature 15°-30°C (59°-86°F) [see USP]. Store in a dry place Keep tightly closed. Protect from light. Dispense contents in a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP.

***I have asked the sponsor to revise the statement as follows:**

"Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Store in a dry place and dispense in a child-resistant closure in a tight, light-resistant container as defined in the USP"

Date of Review: November 7, 2003 Date of Submissions: 10/27/03, 10/31/03, 11/3/03, 11/7/03, 11/20/03

Primary Reviewer: Melaine Shin Date: 11-20-03.

Team Leader: Lillie Golson Date 11/21/03

cc:

ANDA: 75-932
DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)
V:Firmsam\Eon\Ltr&Rev\75932AP1.Labeling Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-932

CHEMISTRY REVIEWS

OFFICE OF GENERIC DRUGS

DIVISION OF CHEMISTRY II

ANDA REVIEW

1. CHEMISTRY REVIEW NO.1

2. ANDA #

75-932

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

Innovator Product: Wellbutrin SR®
Innovator Company: Glaxo Wellcome
Patent Expiration: 8/12/2013

On pages 7 - 9 the applicant includes Patent Certifications and Exclusivity Statement.

There is no exclusivity for the referenced drug product.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME

Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR

N/A

9. AMENDMENTS AND OTHER DATES

Firm:

7-26-2000: Original submission.
8-24-2000: New Correspondence.

FDA:

9-14-2000: Acknowledgment.

10. PHARMACOLOGICAL CATEGORY

Antidepressant

11. R_x or OTC

R_x

12. RELATED IND/NDA/DMF(s)

NDA 18-644 Wellbutrin® (Burroughs Wellcome)
DMF [redacted]

13. DOSAGE FORM

Extended-release Tablets

14. POTENCIES

100 mg and 150 mg

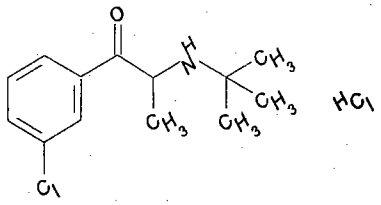
15. CHEMICAL NAME AND STRUCTURE

Bupropion Hydrochloride:

Chemical name:
1-Propanone, 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-, hydrochloride (±)-

Chemical Formula	Molecular Weight	Cas Number
$C_{18}H_{18}ClNO \bullet HCl$	276.21	31677-93-7

Structure:



16. RECORDS AND REPORTS

N/A

17. COMMENTS

Status:

APPEARS THIS WAY
ON ORIGINAL

a. EER status: Pending

EER was requested for [redacted] and Eon Laboratories by Tim Ames on September 13, 1999 and is pending.

b. Method Validation status: Pending

Not compendial.

Method validation for samples of the active ingredient and finished product will be sent to Northeast Regional Laboratory when the NA letter is ready.

c. Bio-review status: Satisfactory,

Satisfactory per H Nguyen reviewed on 10-18-2000.

d. Labeling review status: Not Satisfactory

Not Satisfactory per A. Vezza reviewed on 10-18-2000.

e. DMF [redacted] Satisfactory

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

18. CONCLUSIONS AND RECOMMENDATIONS

This application is Not approvable

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 12-6-2000, Revised 12-12-2000

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confidential commercial

information from

CHEMISTRY REVIEW #1

3. A satisfactory compliance evaluation for the firms referenced in the ANDA is required for approval.

Sincerely yours,

12/21/00

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

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 75-932
ANDA DUP
Division File
FIELD COPY

Endorsements:

HFD-647/LTang/12-6-2000, revised 12-12-2000 U.V. Venkataram for

HFD-647/UVenkataram/12-9-00; 12-13-00 U.V. Venkataram

HFD-647/BMcNeal/12-20-00 B. McNeal 12/21/00 12/21/2000

HFD-641/FFang

F/T by pah/12-21-00
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NOT APPROVABLE - Major

OFFICE OF GENERIC DRUGS

DIVISION OF CHEMISTRY II

ANDA REVIEW

1. CHEMISTRY REVIEW NO.2

2. ANDA #

   75-932

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

   Innovator Product: Wellbutrin SR®
   Innovator Company: Glaxo Wellcome
   Patent Expiration: 8/12/2013

   On pages 7 - 9 the applicant includes Patent Certifications and Exclusivity Statement.

   There is no exclusivity for the referenced drug product.

5. SUPPLEMENT(s)

   N/A

6. PROPRIETARY NAME
   N/A

7. NONPROPRIETARY NAME

   Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR

   N/A

9. AMENDMENTS AND OTHER DATES

   Firm:

7-26-2000: Original submission.
8-24-2000: Amendment
1-31-2001: Amendment

FDA:

9-14-2000: Acknowledgment.
1-02-2001: 1st 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)
DMF

13. DOSAGE FORM

Extended-release Tablets

14. POTENCIES

100 mg and 150 mg

15. CHEMICAL NAME AND STRUCTURE

Bupropion Hydrochloride:

Chemical name:
1-Propanone, 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-, hydrochloride (±)-

Chemical Formula	Molecular Weight	Cas Number
$C_{18}H_{18}ClNO \bullet HCl$	276.21	31677-93-7

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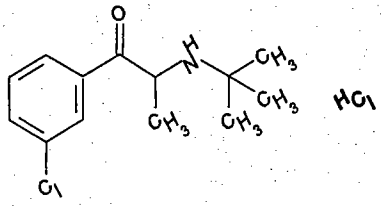

16. RECORDS AND REPORTS

N/A

17. COMMENTS

A. Chemistry Deficiencies:
1. Regarding the composition of the drug product:

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confidential commercial

information from

CHEMISTRY REVIEW #2 (PP. 3-6)

a. EER status: Acceptable

EER was requested for [redacted] and Eon Laboratories by Tim Ames on September 13, 1999 and found Acceptable on 4-19-01.

b. Method Validation status: Acceptable with comments

Not compendial.

Method validation for samples of the active ingredient and finished product has been sent to Northeast Regional Laboratory on 1-8-2001 and found acceptable with comments.

c. Bio-review status: Satisfactory,

Satisfactory per H Nguyen reviewed on 10-18-2000.

d. Labeling review status: Not Satisfactory

Not Satisfactory per A. Vezza reviewed on 2-6-2001.

e. DMF [redacted]: Satisfactory

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

18. CONCLUSIONS AND RECOMMENDATIONS

This application is not approvable - minor

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 6-11-2001, revised 6-15-01

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information from

CHEMISTRY REVIEW #2 (pp. 8-25)

cc: ANDA 75-932
DIV FILE
Field Copy

Endorsements:

HFD-647/Ltang/6-11-2001, revised 6-15-01 6-27-01

HFD-647/UVenkataram/6-15-2001/6/18/01 U.V. Venkataram

HFD-647/BMcNeal/6-21-2001 Concur for B.M. 6/26/01.
6/27/01

HFD-600/FFang/

F/T by: DJ 6/25/01

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Not Approvable- Minor

OFFICE OF GENERIC DRUGS

DIVISION OF CHEMISTRY II

ANDA REVIEW

1. CHEMISTRY REVIEW NO.3

2. ANDA #

   75-932

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

   Innovator Product: Wellbutrin SR®
   Innovator Company: Glaxo Wellcome
   Patent Expiration: 8/12/2013

   On pages 7 - 9 the applicant includes Patent Certifications and Exclusivity Statement.

   There is no exclusivity for the referenced drug product.

5. SUPPLEMENT(s)

   N/A

6. PROPRIETARY NAME
   N/A

7. NONPROPRIETARY NAME

   Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR

   N/A

9. AMENDMENTS AND OTHER DATES

   Firm:

7-26-2000: Original submission.
8-24-2000: Amendment
1-31-2001: Amendment
7-17-2001: Aamendment

FDA:

9-14-2000: Acknowledgment.
1-02-2001: 1st NA letter
6-28-2001: 2nd 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)
DMF

13. DOSAGE FORM

Extended-release Tablets

14. POTENCIES

100 mg and 150 mg

15. CHEMICAL NAME AND STRUCTURE

Bupropion Hydrochloride:

Chemical name:
1-Propanone, 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-, hydrochloride (±)-

Chemical Formula	Molecular Weight	Cas Number
$C_{18}H_{18}ClNO \bullet HCl$	276.21	31677-93-7

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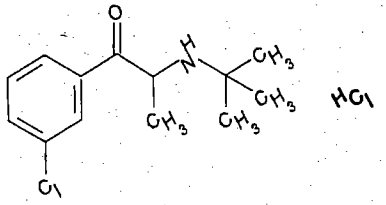

16. RECORDS AND REPORTS

N/A

17. COMMENTS

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CHEMISTRY REVIEW #3 (PP. 3-5)

Satisfactory per A. Vezza reviewed on 8-1-2001.

e. DMF [redacted]: Satisfactory

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

18. CONCLUSIONS AND RECOMMENDATIONS

This application is not approvable - minor

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 8-14-2001

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CHEMISTRY REVIEW #3 (PP. 7-23)

cc: ANDA 75-932
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Endorsements:

HFD-647/LTang/8/14/2001, revised 8/24/01 8-29-01

HFD-647/UVenkataram/8/23/2001 Bita M. Azam for U.V. 08/29/01.

HFD-647/BMcNeal/88/27/01

HFD-600/FFang

F/T by rad8/28/01

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Not Approvable- Minor

OFFICE OF GENERIC DRUGS

DIVISION OF CHEMISTRY II

ANDA REVIEW

1. CHEMISTRY REVIEW NO.4

2. ANDA #

   75-932

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

   Innovator Product: Wellbutrin SR®
   Innovator Company: Glaxo Wellcome
   Patent Expiration: 8/12/2013

   On pages 7 - 9 the applicant includes Patent Certifications and Exclusivity Statement.

   There is no exclusivity for the referenced drug product.

5. SUPPLEMENT(s)

   N/A

6. PROPRIETARY NAME
   N/A

7. NONPROPRIETARY NAME

   Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR

   N/A

9. AMENDMENTS AND OTHER DATES

   Firm:

7-26-2000: Original submission.
8-24-2000: Amendment
1-31-2001: Amendment
7-17-2001: ~~Aamendment~~ Amendment
10-2-2001: Amendment
11-13-2001: Telephone amendment

FDA:

9-14-2000: Acknowledgment.
1-02-2001: 1st NA letter
6-28-2001: 2nd NA letter
8-31-2001: 3rd NA letter
11-13-2001: Tel Con

10. PHARMACOLOGICAL CATEGORY

Antidepressant

11. R_x or OTC

R_x

12. RELATED IND/NDA/DMF(s)

NDA 18-644 Wellbutrin® (Burroughs Wellcome)
DMF

13. DOSAGE FORM

Extended-release Tablets

14. POTENCIES

100 mg and 150 mg

15. CHEMICAL NAME AND STRUCTURE

Bupropion Hydrochloride:

Chemical name:
1-Propanone, 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-, hydrochloride (±)-

Chemical Formula	Molecular Weight	Cas Number
$C_{18}H_{18}ClNO \bullet HCl$	276.21	31677-93-7

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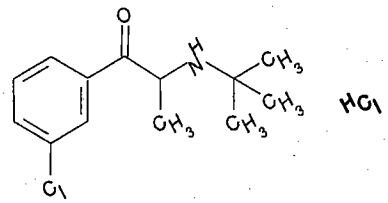

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CHEMISTRY REVIEW #4 (P. 3)

A: OK (see respose 5 and Attachments 5 & 6 of 10-2-2001 amendment).

Status:

a. EER status: Acceptable

EER was requested for [redacted] and Eon Laboratories by Tim Ames on September 13, 1999 and found Acceptable on 4-19-01.

b. Method Validation status: Acceptable

Not compendial.

Method validation for samples of the active ingredient and finished product has been sent to Northeast Regional Laboratory on 1-8-2001 and found acceptable on 8-14-01.

c. Bio-review status: Satisfactory,

Satisfactory per H Nguyen reviewed on 10-18-2000.

d. Labeling review status: Satisfactory

Satisfactory per A. Vezza reviewed on 8-1-2001.

e. DMF [redacted]: 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 11-9-2001

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CHEMISTRY REVIEW #4 (PP. 5-19)

cc: ANDA 75-932
DIV FILE
Field Copy

Endorsements:

HFD-647/Ltang/11-09-01, revised 11-14-01 12-18-01

HFD-647/UVenkataram/12/4/01 U.V. Venkataram 12/18/01.

HFD-647/SShepperson/12/6/01

HFD-600/FFang/

F/T by rad12/18/01

75932N04.RLT/disk LCT approval#13

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Approval

OFFICE OF GENERIC DRUGS

DIVISION OF CHEMISTRY II

ANDA REVIEW

1. CHEMISTRY REVIEW NO.5

2. ANDA # 75-932

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

Innovator Product: Wellbutrin SR7
Innovator Company: Glaxo Wellcome
Patent Expiration: 8/12/2013

On pages 7 - 9 of the original submission, applicant includes Patent Certifications and Exclusivity Statement.

There is no exclusivity for the referenced drug product.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR

N/A

9. AMENDMENTS AND OTHER DATES

Firm:

7-26-2000:	Original submission.
8-24-2000:	Amendment
1-31-2001:	Amendment
7-17-2001:	Amendment
10-2-2001:	Amendment
07-2-2003:	Minor amendment for final approval request
9-08-2003:	Telecom amendment
10-08-2003:	Telecom amendment
10-27-2001:	Labeling amendment
11-03-2003:	Labeling amendment
11-07-2003:	Labeling amendment
11-2--2003:	Labeling amendment

FDA:

9-14-2000:	Acknowledgment.
1-02-2001:	1st NA letter
6-28-2001:	2nd NA letter
8-31-2001:	3rd NA letter
1-24-2002:	4th tentative approval
9-08-2003:	Telecom request
9-26-2003:	Telecom request

10. PHARMACOLOGICAL CATEGORY

Antidepressant

11. R_x or OTC

R_x

12. RELATED IND/NDA/DMF(s)

NDA 18-644 Wellbutrin[7] (Burroughs Wellcome)
DMF [redacted]

13. DOSAGE FORM

Extended-release Tablets

14. POTENCIES

100 mg and 150 mg

15. CHEMICAL NAME AND STRUCTURE

Bupropion Hydrochloride:

Chemical name:
1-Propanone, 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-, hydrochloride (∀)-

Chemical Formula	Molecular Weight	Cas Number
$C_{18}H_{18}ClNO!HCl$	276.21	31677-93-7

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confidential commercial

information from

CHEMISTRY REVIEW #5 (PP. 3-5)

12-10-01.

b. Method Validation status: Acceptable

Not compendial.

Method validation for samples of the active ingredient and finished product has been sent to Northeast Regional Laboratory on 1-8-2001 and found acceptable on 8-14-01.

Now the drug substance and the drug product are compendial items.

c. Bio-review status: Satisfactory,

Satisfactory per H Nguyen reviewed on 10-18-2000.

d. Labeling review status: *Acceptable for full approval of 100 mg strength and tentative approval of 150 mg strength*

Acceptable per M. Shin reviewed on 11-13-2003 and 11-21-2003.

e. DMF [redacted]: Satisfactory

Satisfactory per L. Tang reviewed on 10-15-2003.

18. CONCLUSIONS AND RECOMMENDATIONS

This application was tentative approved on 1-24-02.
It is acceptable for final approval of the 100 mg strength and tentative approval of the 150 mg strength.

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 10-15-2003, revised 11-24-03

cc: ANDA 75-932
DIV FILE
Field Copy

Endorsements:

HFD-647/LTang/10-15-03, revised 11-24-03 11-24-03

HFD-647/UVenkataram/10-16-03 11/25/2003

HFD-647/SShepperson/11-24-03 11/25/03

HFD-600/FFang

F/T by SMS/11-24-2003

75932N05.RLT/disk LCT D#2

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Approval

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-932

BIOEQUIVALENCE REVIEW

BUPROPION HCL EXTENDED-RELEASE TABLETS, 100 mg & 150 mg
ANDA 75-932
Reviewer: Hoainhon Nguyen
File: W#75932sdw.700

Eon Labs Manufacturing, Inc
Laurelton, NY

Submission Date: 07/26/00

Review of Bioequivalence Studies, Dissolution Data and Waiver Requests (Electronic Submission)

Introduction

Indication: for treatment of depression
RLD: Wellbutrin SR® Tablets
Recommended Dose: 300 mg/day, given as 150 mg twice daily

Background

Bupropion is a racemic mixture. Following oral administration of Wellbutrin SR tablets to healthy volunteers, peak plasma concentrations of bupropion occur within 3 hours. Food increased CMAX and AUC of bupropion by 11% and 17%, respectively. In vitro tests show that bupropion is 84% bound to human plasma proteins. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Following oral administration of 200 mg of ^{14}C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. The fraction of the oral dose of bupropion excreted unchanged was only 0.5%, a finding consistent with the extensive metabolism of bupropion. The mean elimination half-life of bupropion after chronic dosing is 21±9 hours.

Three metabolites have been shown to be active: hydroxybupropion and amino-alcohol isomers threohydroxybupropion and erythrohydrobupropion. These metabolites may be clinically important because their plasma concentrations are higher than those of bupropion. Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur approximately 6 hours after administration of Wellbutrin SR tablets. The elimination half-life of hydroxybupropion is approximately 20±5 hours. TMAX for erythro- and threohydrobupropion are similar to that of the hydroxybupropion. However, their elimination half-lives are longer, 33±10 and 37±13 hours, respectively. Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300 to 450 mg/day.

Adverse effects associated with bupropion include seizure, agitation, anxiety, insomnia, weight loss, suicide, rash and nausea.

This submission contains a single-dose, fasting bio study, a multiple-dose fasting bio study, and a food effect bio study for the 150 mg, and a single-dose, fasting bio study for the 100 mg strength. The submission also contains the dissolution data of the test and RLD product, comparative formulations of the test product and a waiver request for the 100 mg strength.

Financial Disclosure: yes (p.2961)

Protocol No.: B-01059, A SINGLE-DOSE, RELATIVE BIOAVAILABILITY STUDY OF BUPROPION HCl 150 MG SUSTAINED-RELEASE TABLETS UNDER FASTING CONDITIONS

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Medical Director:	[redacted], M.D.
Scientific Director:	[redacted] PH.D.
Clinical Study Dates:	09/11/99 to 10/10/99
Analytical Facility	[redacted]
Principal Investigator:	[redacted] M.S.
Analytical Study Dates:	10/13/99 to 11/19/99
Storage Period:	69 days

TREATMENT INFORMATION

Treatment ID:	1	2
Test or Reference:	T	R
Product Name:	Bupropion Hydrochloride Tablets, Extended Release, 150mg	WELLBUTRIN SR Tablets, 150 mg
Manufacturer:	EON LABS MANUFACTURING, INC.	CATALYTICA PHARMACEUTICALS, INC. FOR GLAXO WELLCOME INC.
Manufacture Date:	8/12/99	N/A
Expiration Date:	N/A	5/2000
ANDA Batch Size:	[redacted]	
Full Batch Size:	[redacted]	
Batch/Lot Number:	990707	8I1890
Potency:	102.9%	103.1%
Strength:	150 mg	150 mg
Dosage Form:	TABLET	TABLET
Dose Administered:	150 mg	150 mg
Study Condition:	fasting	fasting
Length of Fasting:	14 hours	14 hours

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	21 DAYS

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 ML	**No. of Subjects Enrolled:**	28
Route of Administration:	ORAL	**No. of Subjects Completing:**	25
Dosing Interval:	N/A	**No. of Subjects Plasma Analyzed:**	24
Number of Doses:	N/A	**No. of Dropouts:**	3*
Loading Dose:	N/A	**Sex(es) Included:**	Male
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**Mean age:** 28 yrs (18-43)	
		Mean height: 70 in.	
		Mean weight: 166 lbs.	

Confinement:	10 hours pre-dose until 24 hours post-dose
Dietary Restrictions:	No alcohol, grapefruit products, caffeine, or zanthine-containing food or drink 48 hours prior to and during the study
Activity Restrictions:	Only non-strenuous activity permitted. Subjects were not permitted lie down or sleep during first 4 hours after dosing.
Drug Restrictions:	No prescriptions medication within 14 days of dosing No OTC medication within 7 days prior to dosing until the last study sample collection
Blood Sampling:	Predose, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 24, 36, 48, 60, 72, 96, 120, 144, 168 and 192 hours post-dose

Study Results

1) Clinical
Adverse Events:
None serious event was reported. Four and two mild drug-related adverse events were reported during the test and reference treatments, respectively. They were fever blister, headache, RBC's in urine and elevaled bilirubin.

Protocol Deviations: None is significant.
Dropouts:

SUBJECT NO.:	7	8	9
REASON:	dropped prior to Period II as he did not report for Period II check-in	dropped prior to Period II as he did not report for Period II check-in	repeated missed blood samples

2) Analytical (Not to be Released Under FOI)

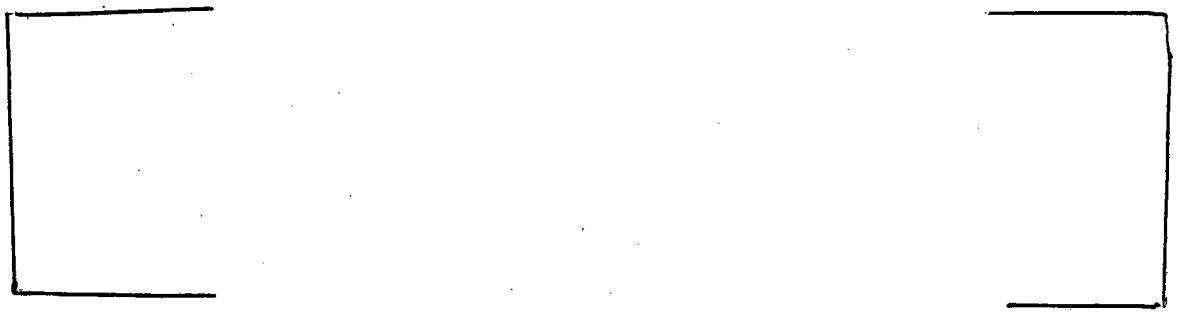
Assay procedure for bupropion, hydroxybupropion, threo/erthroamino-Alcohol Bupropion:

Bupropion:

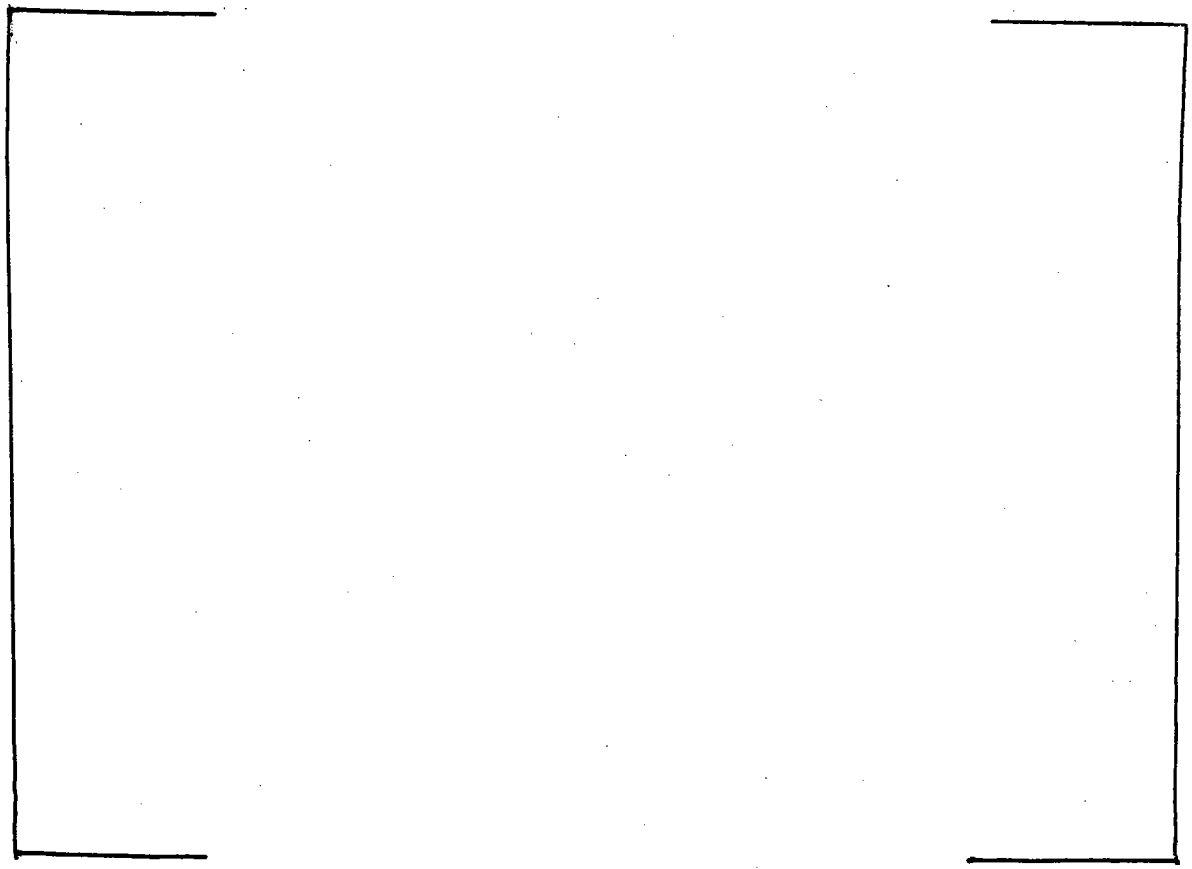
[redacted]

Hydroxybupropion:

[redacted]



Threo/Erythroamino-Alcohol Bupropion:



3) Pharmacokinetic:

PARAMETER	**PROGRAM USED**	**CALCULATION METHOD**
TMAX	SAS 6.12 FOR WINDOWS	INSPECTION
KELM	SAS 6.12 FOR WINDOWS	LEAST SQUARES REGRESSION
THALF	SAS 6.12 FOR WINDOWS	0.693/KELM
AUCTLQC	SAS 6.12 FOR WINDOWS	LINEAR TRAPEZOIDAL RULE
AUCINF	SAS 6.12 FOR WINDOWS	AUCTLQC + Ct/KELM
CMAX	SAS 6.12 FOR WINDOWS	INSPECTION

Table 1 - B-01059 Arithmetic Means, LSMeans & 90% CI of PK Parameters:

Bupropion

BUPROPION HCl 150 MG SR TABLET FASTING STUDY
EON B-01059
BUPROPION DATA
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTLQC	713.0204	781.1244	91.3
AUCINF	739.9284	836.6611	88.4
CMAX	96.46136	91.57008	105
TMAX	3.17803	3.265152	97.3
KELM	0.065766	0.068142	96.5
THALF	12.55336	13.35835	94

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTLQC	(83.3;99.2)	0.98235	0.0730
AUCINF	(77.0;99.8)	0.82139	0.0954
CMAX	(95.7; 115)	0.92521	0.3505
TMAX	(81.8; 113)	0.55400	0.7703
KELM	(85.0; 108)	0.81018	0.6092
THALF	(87.7; 100)	0.99878	0.1109

SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTLQC	6.556096	6.620907	703.520	750.626
AUCINF	6.593081	6.676337	730.027	793.407
CMAX	4.546411	4.486151	94.293	88.779

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTLQC	93.7	(87.3; 101)	0.99400	0.1325
AUCINF	92.0	(84.4; 100)	0.96368	0.1133
CMAX	106	(97.5; 116)	0.96740	0.2387

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

Table 2 - B-01059 Arithmetic Means, LSMeans & 90% CI of PK Parameters:

Hydroxybupropion

BUPROPION HCl 150 MG SR TABLET FASTING STUDY
EON B-01059
HYDROXYBUPROPION DATA
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTLQC	9143.003	9793.825	93.4
AUCINF	9271.629	9930.035	93.4
CMAX	255.2557	260.3545	98
TMAX	6.098485	6.689394	91.2
KELM	0.031425	0.032357	97.1
THALF	26.97342	23.09174	117

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTLQC	(85.7; 101)	0.98798	0.1487
AUCINF	(85.9; 101)	0.99069	0.1397
CMAX	(90.0; 106)	0.98070	0.6789
TMAX	(79.0; 103)	0.76974	0.2249
KELM	(87.6; 107)	0.92796	0.6097
THALF	(94.6; 139)	0.30184	0.2060

SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTLQC	9.004025	9.043705	8135.76	8465.08
AUCINF	9.020894	9.062912	8274.17	8629.24
CMAX	5.428012	5.436404	227.70	229.61

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTLQC	96.1	(89.7; 103)	0.99597	0.3318
AUCINF	95.9	(89.7; 102)	0.99733	0.2883
CMAX	99.2	(92.4; 106)	0.99427	0.8407

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

Table 3 - B-01059 Arithmetic Means, LSMeans & 90% CI of PK Parameters:

Threo/Erythroamino-Alcohol Bupropion

BUPROPION HCl 150 MG SR TABLET FASTING STUDY
EON B-01059
THREO/ERYTHROAMINO-ALCOHOL BUPROPION DATA
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTLQC	5612.017	5842.484	96.1
AUCINF	6112.71	6364.395	96
CMAX	125.0356	126.4723	98.9
TMAX	5.609848	6.117424	91.7
KELM	0.014236	0.014347	99.2
THALF	51.90829	52.01469	99.8

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTLQC	(90.7; 101)	0.99987	0.2164
AUCINF	(90.7; 101)	0.99985	0.2195
CMAX	(92.4; 105)	0.99809	0.7650
TMAX	(84.8;98.6)	0.99555	0.0521
KELM	(93.4; 105)	0.99946	0.8220
THALF	(92.8; 107)	0.99502	0.9604

SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTLQC	8.588713	8.618147	5370.69	5531.13
AUCINF	8.669973	8.697848	5825.34	5990.01
CMAX	4.770822	4.778794	118.02	118.96

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTLQC	97.1	(92.1; 102)	0.99990	0.3447
AUCINF	97.3	(92.3; 102)	0.99991	0.3668
CMAX	99.2	(93.4; 105)	0.99919	0.8226

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

Table 4 - B-01059 Arithmetic Mean Plasma Concentrations (ng/mL): Bupropion

Time	Test Treatment A	(CV%)	Reference Treatment B	(CV%)	Ratio (A/B)
0.00 HR	0.000	.	0.000	.	0.000
0.50 HR	4.186	185.839	5.910	130.390	0.708
1.00 HR	36.576	50.845	41.113	48.079	0.890
2.00 HR	80.922	32.123	77.439	26.864	1.045
3.00 HR	91.926	19.231	84.652	29.430	1.086
4.00 HR	80.983	19.922	82.757	28.219	0.979
5.00 HR	70.826	16.021	77.600	26.991	0.913
6.00 HR	52.365	19.114	55.352	23.461	0.946
7.00 HR	39.543	19.772	45.017	22.427	0.878
8.00 HR	31.191	21.341	35.891	20.928	0.869
10.0 HR	20.483	21.713	22.826	21.099	0.897
12.0 HR	13.639	23.066	15.826	24.988	0.862
14.0 HR	10.379	30.057	11.887	26.482	0.873
24.0 HR	4.490	34.875	4.967	45.272	0.904
36.0 HR	2.403	58.018	2.682	60.019	0.896
48.0 HR	1.148	95.292	1.338	82.152	0.858
60.0 HR	0.403	175.537	0.533	164.591	0.756
72.0 HR	0.175	253.725	0.325	196.262	0.538
96.0 HR	0.000	.	0.000	.	.
120 HR	0.000	.	0.000	.	.
144 HR	0.000	.	0.000	.	.
168 HR	0.000	.	0.000	.	.
192 HR	0.000	.	1.639	479.583	0.000

Table 5 - B-01059 Arithmetic Mean Plasma Concentrations (ng/mL): Hydroxybupropion

Time	Test Treatment A	(CV%)	Reference Treatment B	(CV%)	Ratio (A/B)
0.00 HR	0.000	.	0.000	.	0.000
0.50 HR	9.341	130.332	11.370	114.970	0.822
1.00 HR	56.510	56.565	57.778	60.922	0.978
2.00 HR	143.474	49.680	136.430	50.729	1.052
3.00 HR	202.035	50.406	188.252	52.412	1.073
4.00 HR	230.330	46.913	227.352	51.114	1.013
5.00 HR	243.796	50.016	239.417	49.716	1.018
6.00 HR	232.891	49.155	237.448	49.958	0.981
7.00 HR	238.383	48.491	244.817	48.719	0.974
8.00 HR	232.057	47.366	244.461	49.896	0.949
10.0 HR	221.826	45.147	228.104	46.246	0.972
12.0 HR	189.922	46.137	204.413	49.403	0.929
14.0 HR	178.657	44.543	188.965	49.394	0.945
24.0 HR	157.452	41.663	173.265	49.465	0.909
36.0 HR	101.796	50.107	109.939	53.985	0.926
48.0 HR	71.374	52.364	75.452	54.981	0.946
60.0 HR	44.957	64.026	47.939	62.577	0.938
72.0 HR	32.429	66.534	35.846	65.889	0.905
96.0 HR	13.993	72.263	16.807	80.347	0.833
120 HR	6.799	91.098	7.653	102.267	0.888
144 HR	2.893	106.444	3.840	124.691	0.753
168 HR	1.106	174.736	1.560	163.648	0.709
192 HR	0.428	259.948	0.951	219.234	0.450

Table 6 - B-01059 Arithmetic Mean Plasma Concentrations (ng/mL): Threo/Erythroamino-Alcohol Bupropion

Time	Test Treatment A	(CV%)	Reference Treatment B	(CV%)	Ratio (A/B)
0.00 HR	0.000	.	0.000	.	0.000
0.50 HR	0.461	479.583	0.861	222.136	0.535
1.00 HR	13.282	97.764	15.095	91.738	0.880
2.00 HR	56.613	45.149	53.109	41.730	1.066
3.00 HR	90.843	38.525	83.400	41.419	1.089
4.00 HR	104.804	35.726	102.135	39.592	1.026
5.00 HR	121.352	37.446	122.670	39.085	0.989
6.00 HR	116.378	35.304	118.517	40.962	0.982
7.00 HR	112.309	36.261	116.065	35.860	0.968
8.00 HR	108.861	36.512	114.709	39.859	0.949
10.0 HR	96.170	35.466	101.509	36.866	0.947
12.0 HR	84.357	35.624	90.517	41.555	0.932
14.0 HR	79.626	34.125	82.217	35.590	0.968
24.0 HR	63.261	33.282	67.091	38.704	0.943
36.0 HR	48.183	27.965	50.535	34.494	0.953
48.0 HR	39.083	27.717	40.996	35.724	0.953
60.0 HR	31.604	27.347	33.617	35.720	0.940
72.0 HR	28.186	34.506	29.025	36.599	0.971
96.0 HR	19.635	39.176	20.332	39.074	0.966
120 HR	14.828	43.648	14.620	46.785	1.014
144 HR	10.413	48.864	11.348	46.992	0.918
168 HR	8.140	49.861	8.118	51.844	1.003
192 HR	6.115	51.783	6.038	61.679	1.013

4) Statistical Analysis: Per protocol, the plasma samples from the first 24 subjects were assayed by the analytical laboratory. With the dropout of Subjects #7, 8 and 9, samples from Subjects #1 through 27 were assayed. The plasma samples from Subject #25 could not be quantitated due to interference from endogeneous peaks. Therefore, there are a total of 23 sets of data used in the statistical analysis for this study.

There was no statistically significant difference (alpha=0.05) between treatment for LAUC(0-T), LAUC(0-Inf) or LCMAX for bupropion, hydroxybupropion or threo/erythroamino alcohol bupropion.

5) Conclusion: The study is acceptable.

Figure 1 - B-01059 Plasma Concentrations (ng/mL) vs. Time: Bupropion

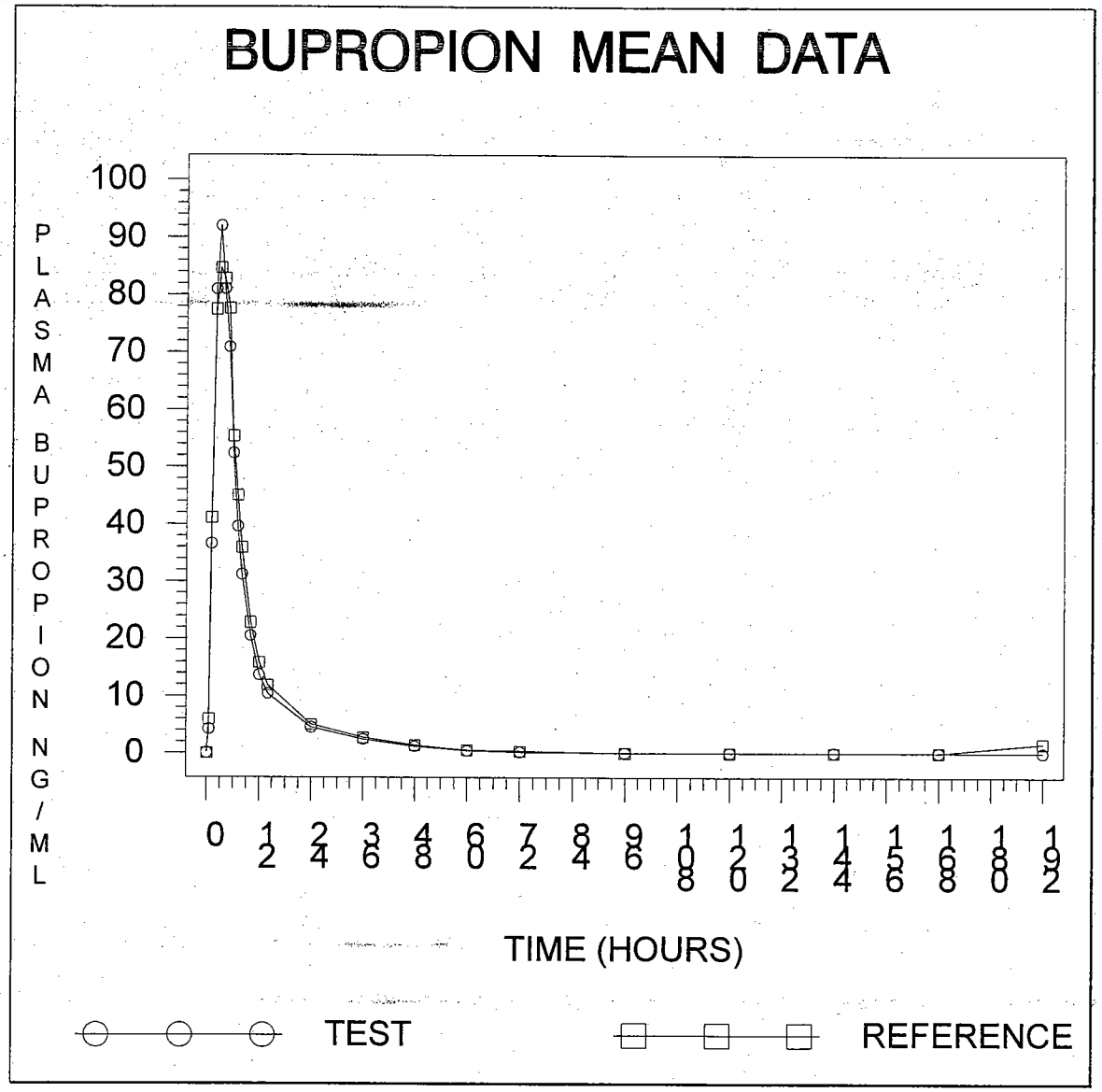


Figure 2 - B-01059 Plasma Concentrations (ng/mL) vs. Time: Hydroxybupropion

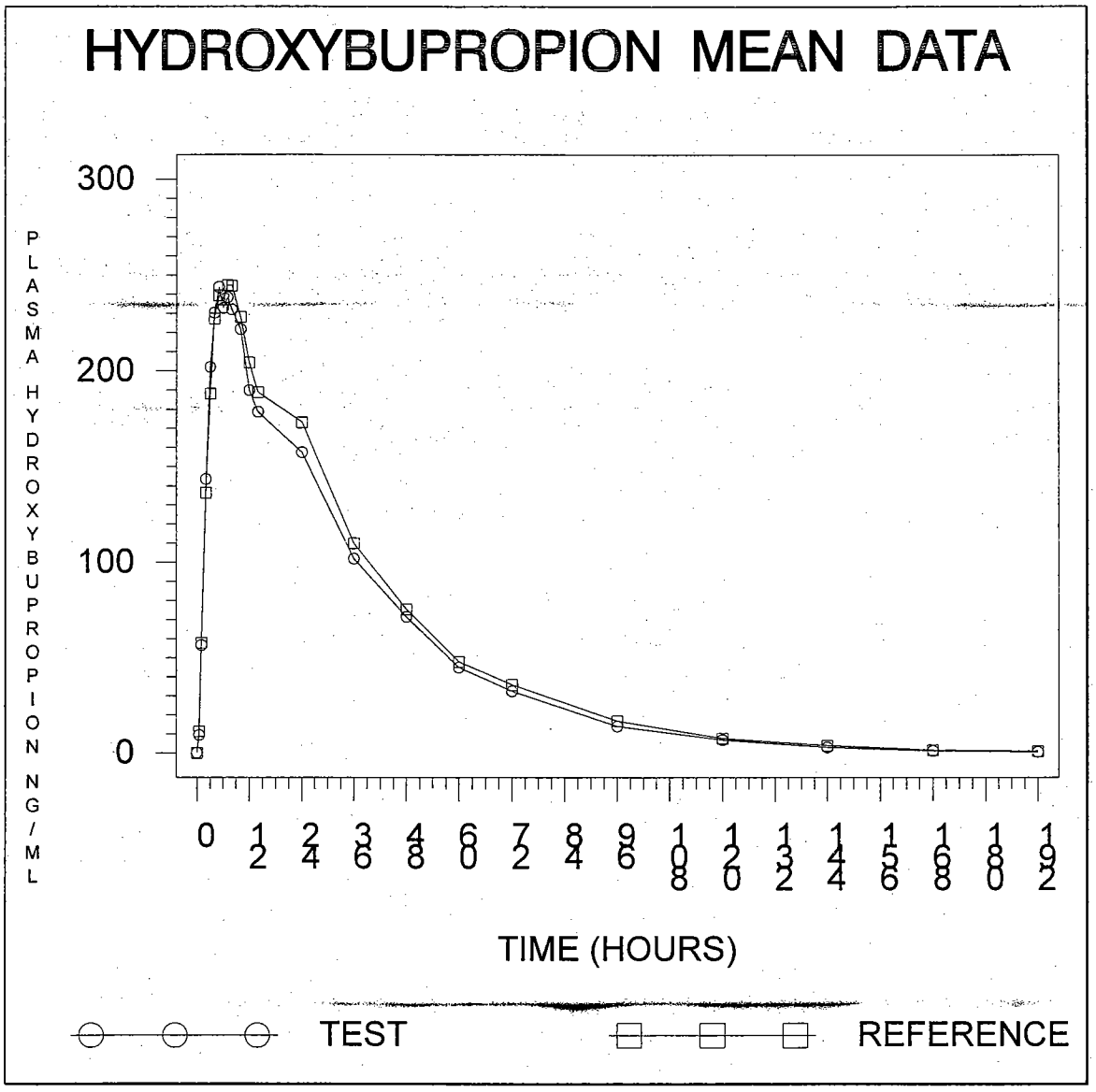
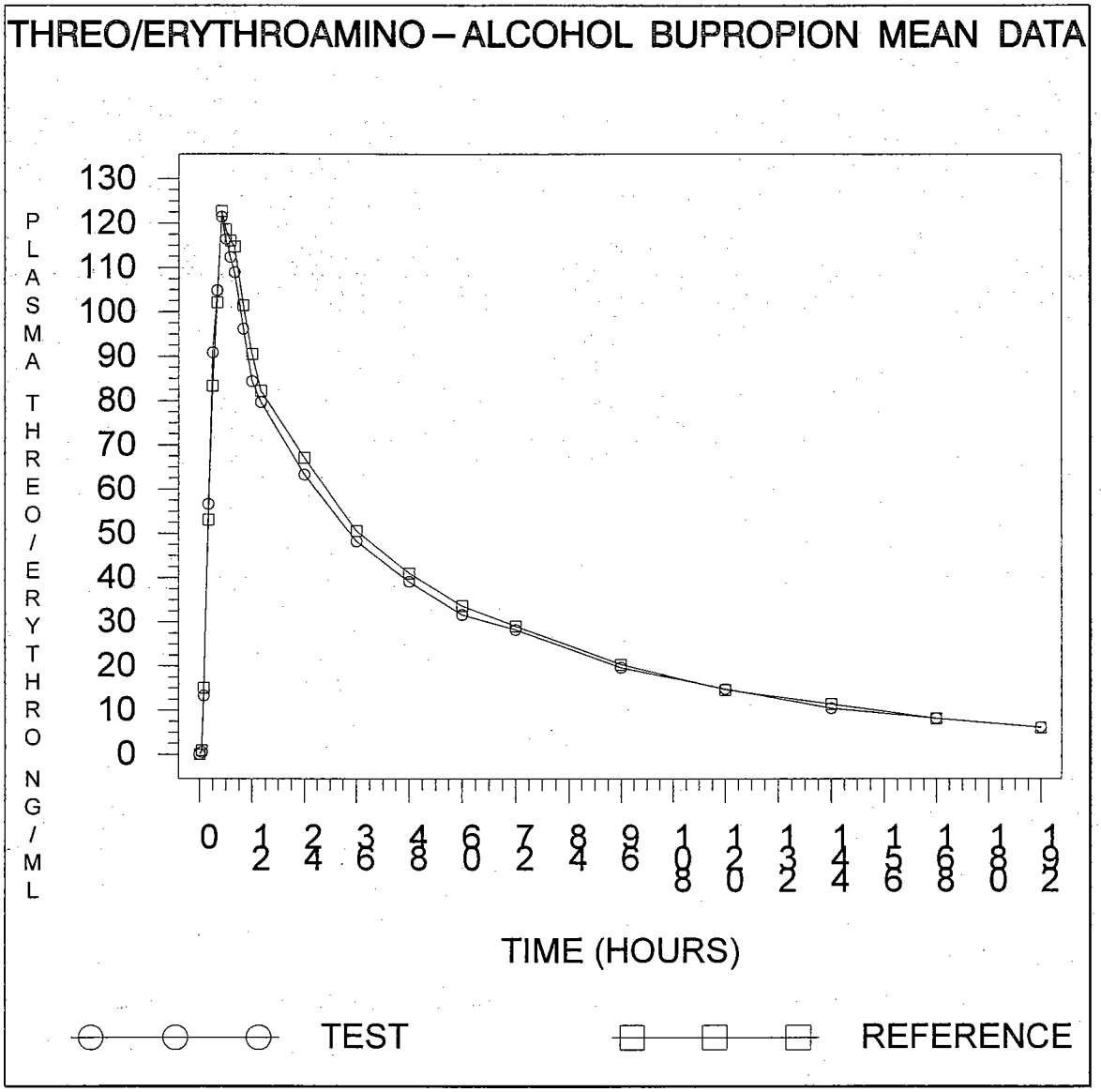


Figure 3 - B-01059 Plasma Concentrations (ng/mL) vs. Time: Threo/Erythroamino-Alcohol Bupropion



Protocol No.: B-04209, A RELATIVE BIOAVAILABILITY MULTIPLE DOSE STUDY OF BUPROPION HCl 150 MG SUSTAINED-RELEASE TABLETS

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Medical Director:	[redacted], M.D.
Scientific Director:	[redacted] PH.D.
Clinical Study Dates:	11/05/99 to 12/24/99
Analytical Facility	[redacted]
Principal Investigator:	[redacted] M.S.
Analytical Study Dates:	01/08/00 to 01/31/00
Storage Period:	87 days

TREATMENT INFORMATION Same as the single-dose, fasting study above except :

Dose Administered:	150 mg every 12 hr (27 doses)	150 mg every 12 hour(27 doses)
Study Condition:	Fasting	fasting
Length of Fasting:	14 hours @ 27th dose*	14 hours @ 27th dose*

***NOTE:** For earlier doses, length of fasting was 10 hours @ AM doses and 4 hours @ PM doses.

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	22 DAYS

DOSING		SUBJECTS	
Single or Multiple Dose:	multiple	**IRB Approval:**	Y
Steady State:	Y	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 ML	**No. of Subjects Enrolled:**	30
Route of Administration:	ORAL	**No. of Subjects Completing:**	25
Dosing Interval:	12 hr	**No. of Subjects Plasma Analyzed:**	24
Number of Doses:	27	**No. of Dropouts:**	5
Loading Dose:	N/A	**Sex(es) Included:**	male
Steady State Dose Time:	312	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**Mean age:** 33 yrs (20-44)	
		Mean height: 70 in.	
		Mean weight: 164 lbs.	

Dietary/Activity/Drug Restrictions: Same as in the B-01059 Study above.

Confinement: 10 hours pre-dose until 324 hours post-dose
Blood sampling: predose of Dose 1, 2, 21, 23, 25, 27, and at 312.5, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322 and 324 hours.

Study Results

1) Clinical
Adverse Events: No serious event was reported. Forty-four and 47 mild, possibly drug-related adverse events were reported during the test and reference treatments, respectively. These were headache, elevated blood pressure, itchiness, sweatiness, hoarse voice, ringing in ears, decreased blood pressure, swollen lymph glands, groin tenderness, dry mouth, rash, euphoria, sleeplessness, runny nose, stomach cramps, eye redness, nasal congestion, nausea, diarrhea and hand scaling.

Protocol Deviations: None is significant.
Dropouts:

SUBJECT NO.:	14	15	24	26
REASON:	DID NOT RETURN FOR PERIOD II CHECK-IN	ELEVATED BLOOD PRESSURE	ELEVATED BLOOD PRESSURE	ELEVATED BLOOD PRESSURE
PERIOD:	1	1	1	2
REPLACEMENT:	Y	Y	Y	N

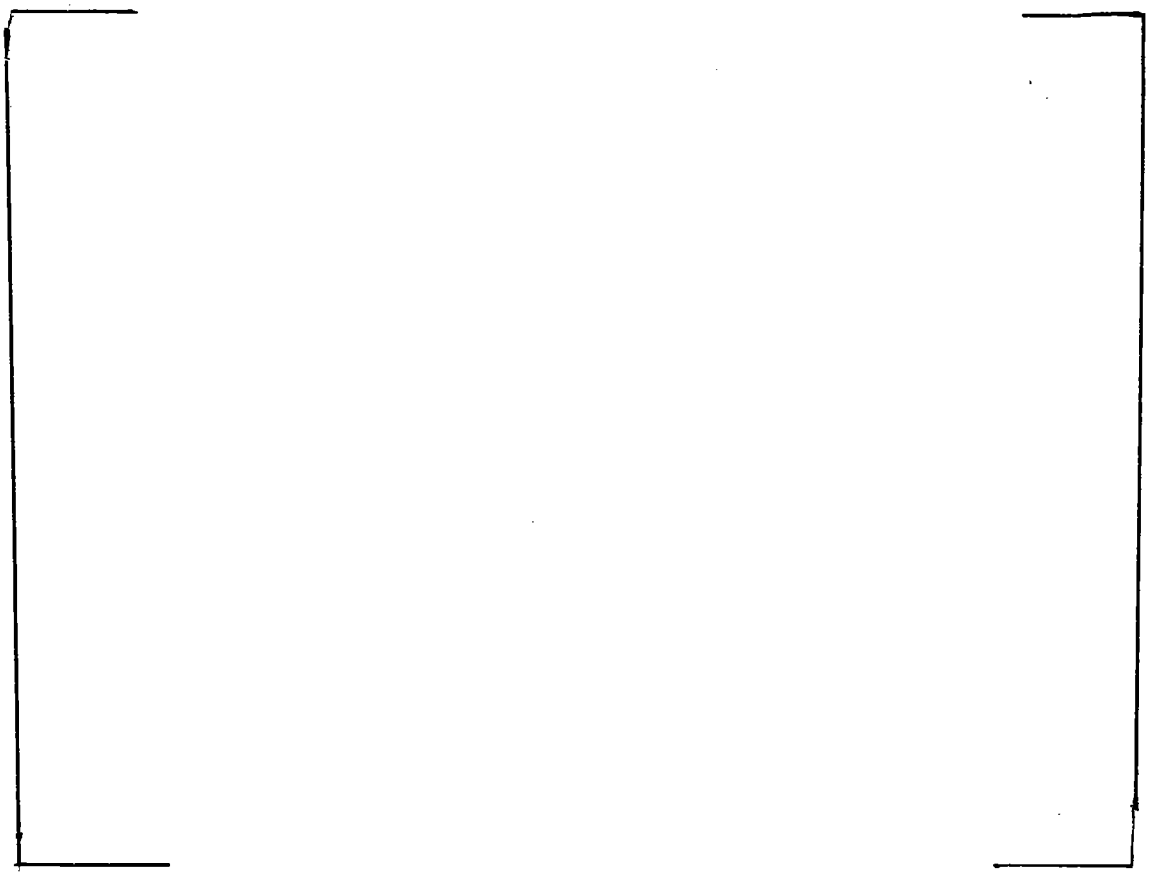
SUBJECT NO.:	30
REASON:	ELEVATED BLOOD PRESSURE
PERIOD:	I
REPLACEMENT:	N

2) Analytical (Not to be Released Under FOI) Assay procedure for bupropion, hydroxybupropion, threo- and erthroamino-alcohol bupropion: [redacted]

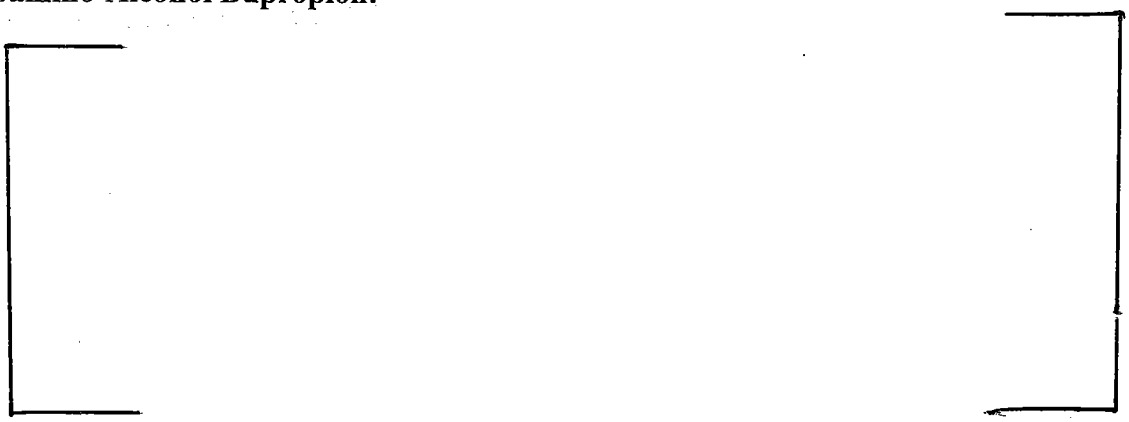
Bupropion:

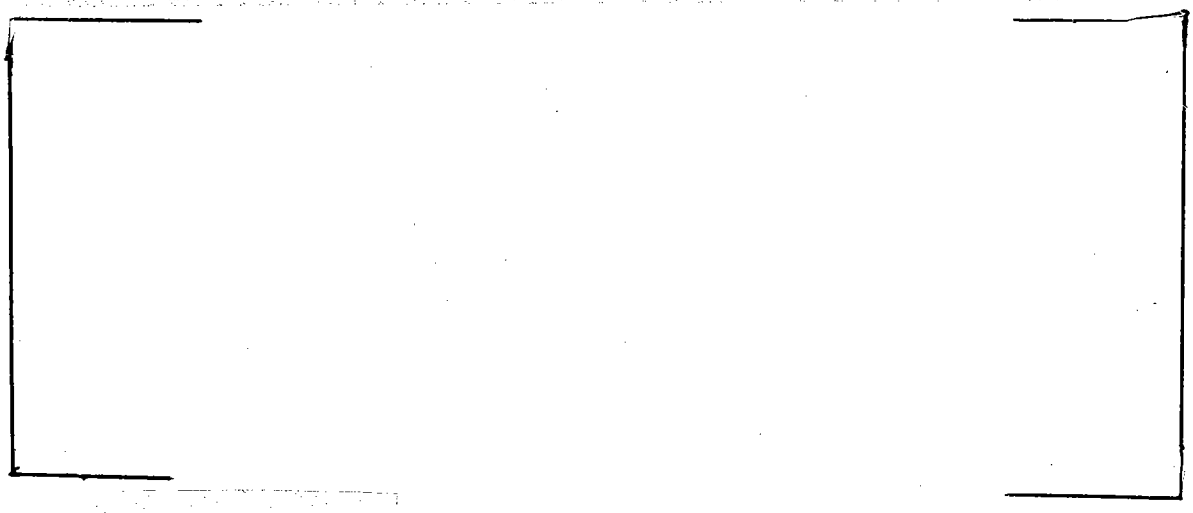
[redacted]

Hydroxybupropion:

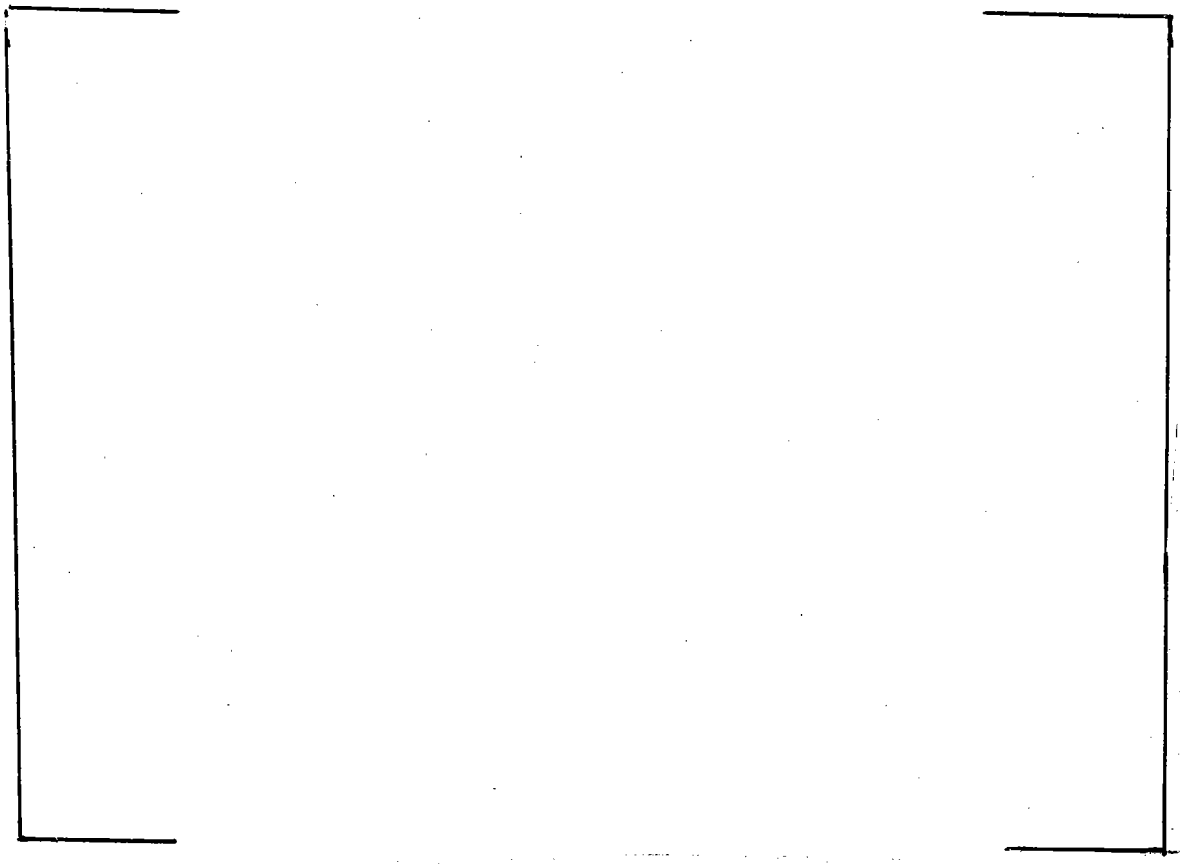


Erythroamino-Alcohol Bupropion:





Threoamino-Alcohol Bupropion:



3) Pharmacokinetic:

PARAMETER	**PROGRAM USED**	**CALCULATION METHOD**
CMAX, TMAX, CMIN	SAS 6.12 FOR WINDOWS	INSPECTION
CAV	SAS 6.12 FOR WINDOWS	AUCTAU/12
PF	SAS 6.12 FOR WINDOWS	[100 X (CMAX-CMIN)/CAV]
AUCTAU	SAS 6.12 FOR WINDOWS	LINEAR TRAPEZOIDAL RULE

Table 7 - B-04209 Arithmetic Means, LSMeans & 90% CI of PK Parameters:

Bupropion

BUPROPION HCl 150 MG SR TABLET MULTIPLE DOSE STUDY
EON B-04209
BUPROPION DATA
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTAU	724.6219	709.2781	102
CMAX	107.3917	98.54167	109
TMAX	2.916667	3.125000	93.3
CMIN	30.12917	29.95833	101
CAV	60.38516	59.10651	102
PF	126.9612	115.8561	110

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTAU	(98.5; 106)	>0.99999	0.3193
CMAX	(102; 116)	0.99380	0.0424
TMAX	(82.8; 104)	0.87302	0.2911
CMIN	(95.8; 105)	0.99998	0.8395
CAV	(98.5; 106)	>0.99999	0.3193
PF	(103; 117)	0.99513	0.0281

SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTAU	6.556626	6.544792	703.893	695.612
CMAX	4.637508	4.566618	103.287	96.218
CAV	4.071719	4.059885	58.658	57.968

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTAU	101	(97.8; 105)	>0.99999	0.5610
CMAX	107	(101; 114)	0.99877	0.0645
CAV	101	(97.8; 105)	>0.99999	0.5610

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

Table 8 - B-04209 Arithmetic Means, LSMeans & 90% CI of PK Parameters:

Hydroxybupropion

BUPROPION HCl 150 MG SR TABLET MULTIPLE DOSE STUDY
EON B-04209
HYDROXYBUPROPION DATA
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTAU	11422.82	11036.65	103
CMAX	1093.042	1055.875	104
TMAX	3.875000	4.125000	93.9
CMIN	824.875	802.375	103
CAV	951.9019	919.7205	103
PF	28.78136	30.06916	95.7

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTAU	(99.1; 108)	>0.99999	0.1878
CMAX	(96.4; 111)	0.99442	0.4031
TMAX	(77.6; 110)	0.51280	0.5299
CMIN	(97.7; 108)	0.99995	0.3516
CAV	(99.1; 108)	>0.99999	0.1878
PF	(72.0; 119)	0.26896	0.7594

SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTAU	9.282234	9.234393	10745.41	10243.45
CMAX	6.937246	6.893909	1029.93	986.25
CAV	6.797328	6.749487	895.45	853.62

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTAU	105	(101; 109)	>0.99999	0.0544
CMAX	104	(97.5; 112)	0.99622	0.2890
CAV	105	(101; 109)	>0.99999	0.0544

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

Table 9 - B-04209 Arithmetic Means, LSMeans & 90% CI of PK Parameters:

Erythroamino-Alcohol Bupropion

BUPROPION HCl 150 MG SR TABLET MULTIPLE DOSE STUDY
EON B-04209
ERYTHROAMINO-ALCOHOL BUPROPION DATA
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTAU	1181.444	1159.092	102
CMAX	112.2458	109.5708	102
TMAX	6.062500	5.041667	120
CMIN	87.09583	86.2875	101
CAV	98.45365	96.59097	102
PF	26.20635	26.11264	100

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTAU	(97.5; 106)	>0.99999	0.4604
CMAX	(95.9; 109)	0.99781	0.5283
TMAX	(99.5; 141)	0.33895	0.1084
CMIN	(95.9; 106)	0.99994	0.7546
CAV	(97.5; 106)	>0.99999	0.4604
PF	(76.0; 125)	0.25753	0.9800

SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTAU	7.032244	7.009607	1132.57	1107.22
CMAX	4.677881	4.654044	107.54	105.01
CAV	4.547337	4.524700	94.38	92.27

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTAU	102	(98.4; 106)	>0.99999	0.3261
CMAX	102	(96.2; 109)	0.99882	0.5181
CAV	102	(98.4; 106)	>0.99999	0.3261

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

Table 10 - B-04209 Arithmetic Means, LSMeans & 90% CI of PK Parameters:

Threoamino-Alcohol Bupropion

BUPROPION HCl 150 MG SR TABLET MULTIPLE DOSE STUDY
EON B-04209
THREOAMINO-ALCOHOL BUPROPION DATA
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTAU	6151.823	6044.281	102
CMAX	585.6667	590.2500	99.2
TMAX	5.041667	5.041667	100
CMIN	434.625	435.7917	99.7
CAV	512.6519	503.6901	102
PF	30.96474	34.92436	88.7

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTAU	(97.5; 106)	>0.99999	0.4787
CMAX	(90.6; 108)	0.96440	0.8789
TMAX	(86.0; 114)	0.64280	1.0000
CMIN	(94.4; 105)	0.99988	0.9319
CAV	(97.5; 106)	>0.99999	0.4787
PF	(55.3; 122)	0.15379	0.5655

SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTAU	8.662017	8.644683	5779.18	5679.87
CMAX	6.313402	6.321389	551.92	556.35
CAV	6.17711	6.159777	481.60	473.32

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTAU	102	(97.8; 106)	>0.99999	0.4614
CMAX	99.2	(91.2; 108)	0.97066	0.8724
CAV	102	(97.8; 106)	>0.99999	0.4614

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

Table 11 - B-04209 Arithmetic Mean Plasma Concentrations (ng/mL): Bupropion

Time	Test Treatment A	(CV%)	Reference Treatment B	(CV%)	Ratio (A/B)
0.00 HR	0.000	.	0.000	.	0.000
24.00 HR	24.525	30.390	24.583	23.530	0.998
240.0 HR	29.617	24.212	30.371	25.332	0.975
264.0 HR	30.950	25.348	30.063	21.831	1.030
288.0 HR	29.775	28.436	29.254	25.161	1.018
312.0 HR	30.129	26.341	29.958	23.094	1.006
312.5 HR	34.613	27.173	33.317	26.006	1.039
313.0 HR	63.800	28.725	62.829	23.701	1.015
314.0 HR	93.713	34.761	85.838	21.268	1.092
315.0 HR	103.088	27.480	95.492	23.110	1.080
316.0 HR	92.229	30.327	90.283	24.040	1.022
317.0 HR	79.650	27.133	81.029	24.240	0.983
318.0 HR	64.700	24.235	65.617	23.884	0.986
319.0 HR	53.275	25.452	55.846	21.654	0.954
320.0 HR	45.367	24.953	45.738	23.075	0.992
321.0 HR	39.521	25.636	39.113	24.829	1.010
322.0 HR	35.508	27.465	34.792	23.567	1.021
324.0 HR	27.129	27.156	26.867	22.981	1.010

Table 12 - B-04209 Arithmetic Mean Plasma Concentrations (ng/mL):

Hydroxybupropion

Time	Test Treatment A	(CV%)	Reference Treatment B	(CV%)	Ratio (A/B)
0.00 HR	0.000	.	0.000	.	0.000
24.00 HR	415.000	37.785	412.167	37.687	1.007
240.0 HR	840.667	35.871	795.750	51.728	1.056
264.0 HR	869.417	36.168	826.042	47.906	1.053
288.0 HR	814.958	38.339	821.083	43.033	0.993
312.0 HR	824.875	35.110	802.375	43.474	1.028
312.5 HR	850.792	35.650	806.208	41.144	1.055
313.0 HR	900.000	35.667	883.458	40.610	1.019
314.0 HR	979.542	34.467	943.292	39.710	1.038
315.0 HR	1041.125	33.382	1003.458	39.283	1.038
316.0 HR	1054.125	34.500	1023.125	38.707	1.030
317.0 HR	1014.583	33.468	984.125	38.305	1.031
318.0 HR	980.833	33.533	945.083	38.641	1.038
319.0 HR	990.083	34.485	925.125	38.827	1.070
320.0 HR	952.500	35.038	927.208	40.043	1.027
321.0 HR	922.500	35.622	888.458	41.306	1.038
322.0 HR	914.083	35.084	886.458	40.956	1.031
324.0 HR	809.792	36.554	800.792	45.585	1.011

Table 13 - B-04209 Arithmetic Mean Plasma Concentrations (ng/mL):

Erythroamino-Alcohol Bupropion

Time	Test Treatment A	(CV%)	Reference Treatment B	(CV%)	Ratio (A/B)
0.00 HR	0.000	.	0.000	.	0.000
24.00 HR	31.621	28.400	31.508	27.091	1.004
240.0 HR	90.113	29.016	87.629	32.442	1.028
264.0 HR	93.950	28.805	92.121	31.556	1.020
288.0 HR	84.992	30.876	86.117	35.690	0.987
312.0 HR	87.096	29.843	86.287	34.822	1.009
312.5 HR	86.742	30.188	85.350	36.120	1.016
313.0 HR	88.896	29.224	91.371	36.204	0.973
314.0 HR	95.917	28.544	95.267	31.169	1.007
315.0 HR	102.113	28.553	101.158	30.755	1.009
316.0 HR	101.475	27.671	101.917	28.045	0.996
317.0 HR	102.842	26.310	103.267	29.512	0.996
318.0 HR	103.925	27.719	99.004	28.950	1.050
319.0 HR	105.517	28.795	97.192	25.499	1.086
320.0 HR	103.563	26.592	101.146	29.432	1.024
321.0 HR	100.329	28.069	97.804	31.345	1.026
322.0 HR	96.971	29.905	94.858	33.457	1.022
324.0 HR	88.492	30.672	87.275	33.866	1.014

Table 14 - B-04209 Arithmetic Mean Plasma Concentrations (ng/mL):

Threoamino-Alcohol Bupropion

Time	Test Treatment A	(CV%)	Reference Treatment B	(CV%)	Ratio (A/B)
0.00 HR	0.000	.	0.000	.	0.000
24.00 HR	157.679	36.617	155.629	41.797	1.013
240.0 HR	455.958	38.737	447.583	40.469	1.019
264.0 HR	462.596	43.661	466.250	41.324	0.992
288.0 HR	423.083	39.702	444.583	44.663	0.952
312.0 HR	434.625	39.511	435.792	44.753	0.997
312.5 HR	431.875	39.595	428.792	45.186	1.007
313.0 HR	451.583	38.256	463.667	46.090	0.974
314.0 HR	502.167	36.581	494.667	38.082	1.015
315.0 HR	543.500	34.718	532.292	35.311	1.021
316.0 HR	549.917	34.575	538.417	31.998	1.021
317.0 HR	560.917	34.089	554.833	34.946	1.011
318.0 HR	551.500	36.516	533.125	34.233	1.034
319.0 HR	553.625	36.025	524.917	35.417	1.055
320.0 HR	535.583	33.943	532.417	37.593	1.006
321.0 HR	513.708	36.838	502.208	38.921	1.023
322.0 HR	490.167	39.153	482.292	40.212	1.016
324.0 HR	442.375	40.248	436.875	42.274	1.013

Figure 4- B-04209 Plasma Concentrations (ng/mL) vs. Time: Bupropion

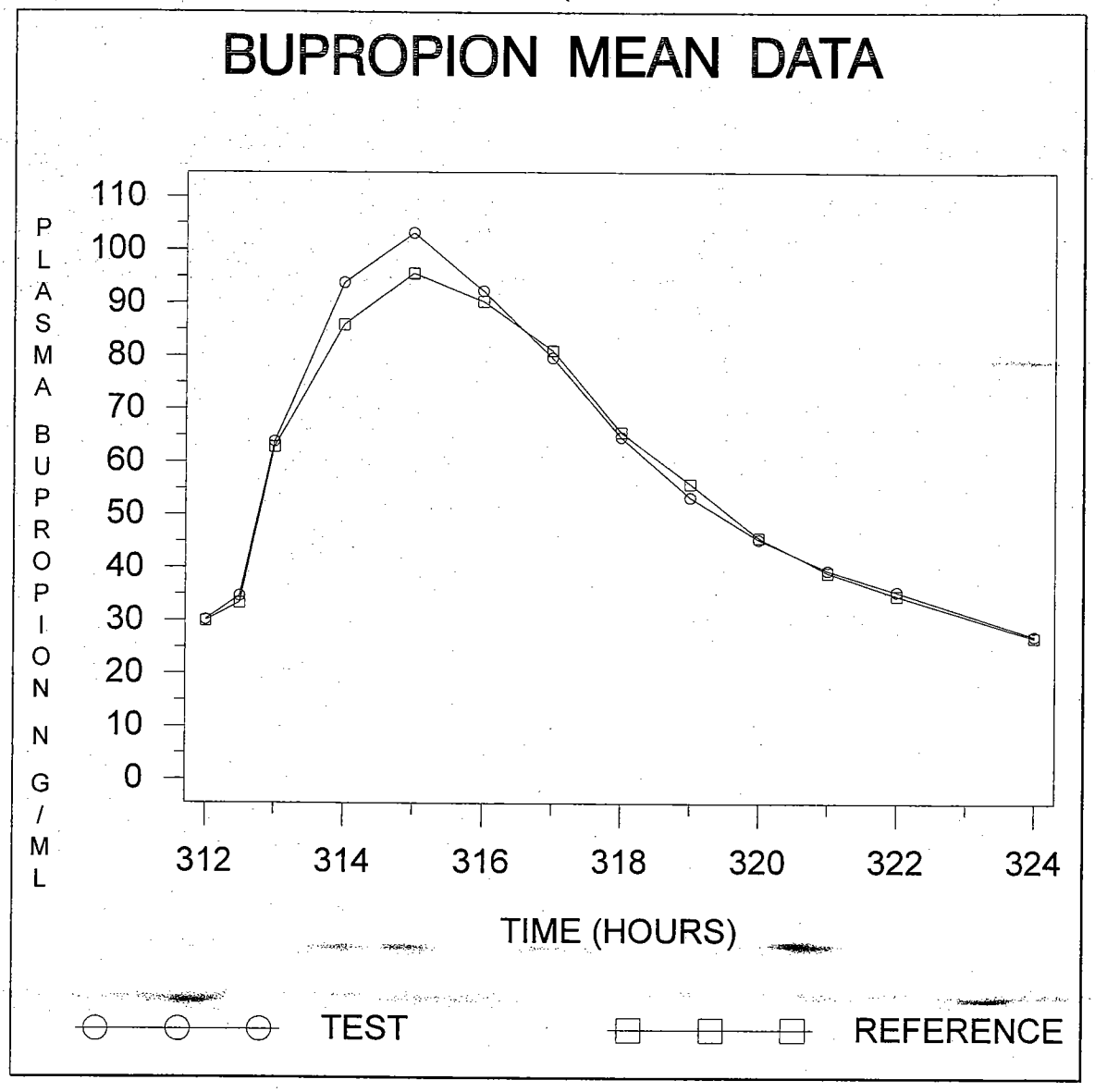


Figure 5 - B-04209 Plasma Concentrations (ng/mL) vs. Time: Hydroxybupropion

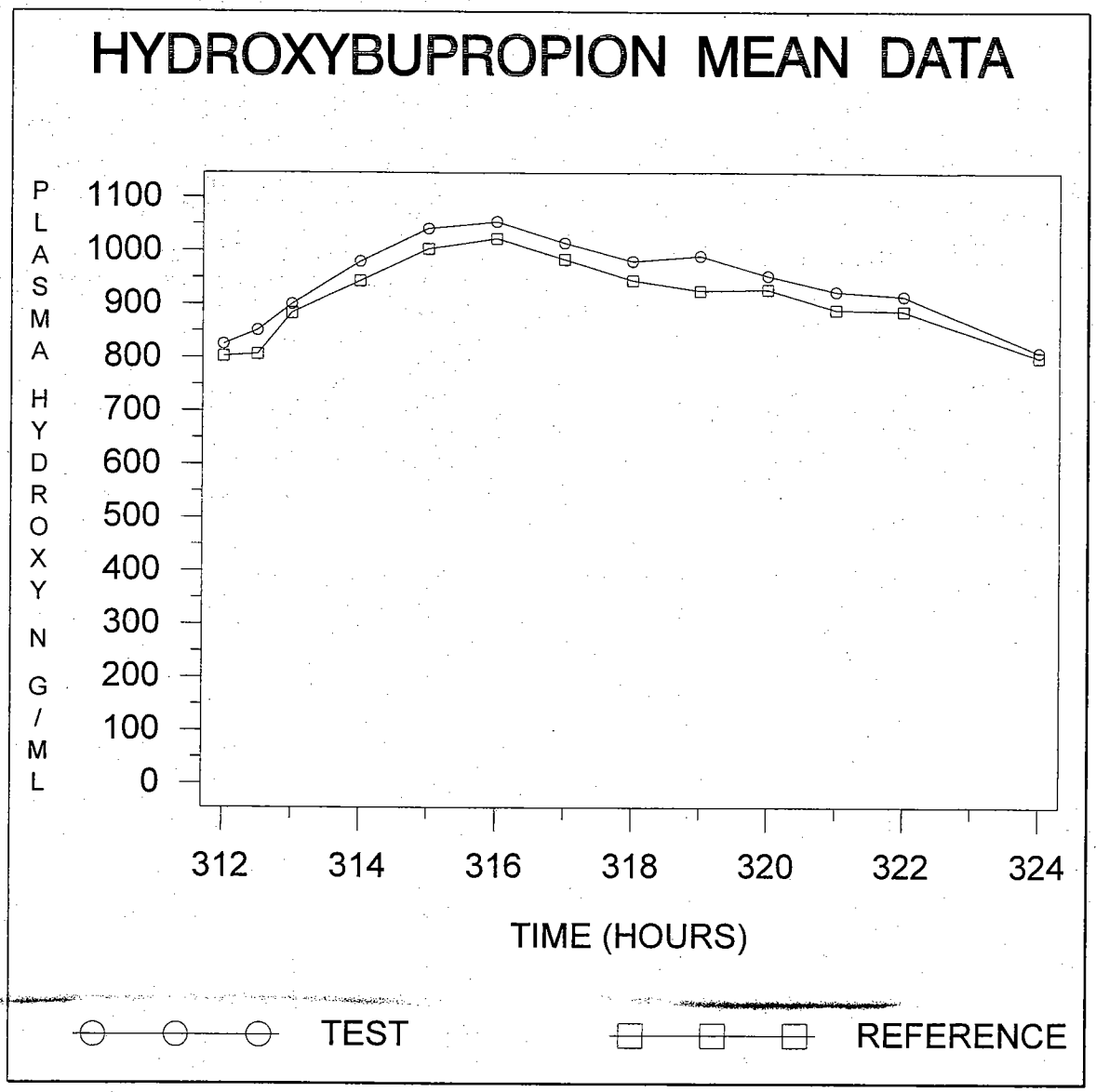


Figure 6 - B-04209 Plasma Concentrations (ng/mL) vs. Time: Erythroamino-Alcohol Bupropion

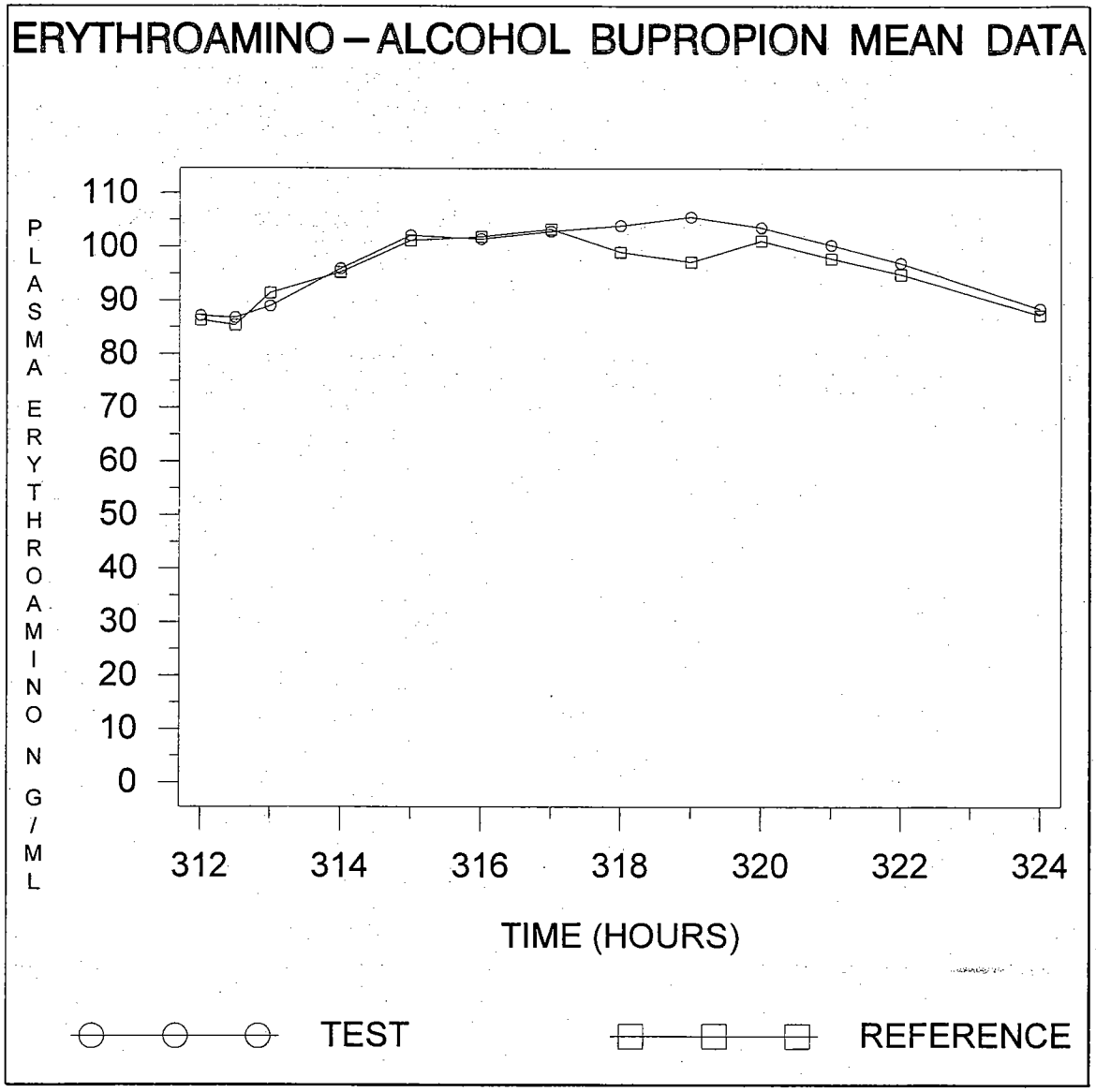
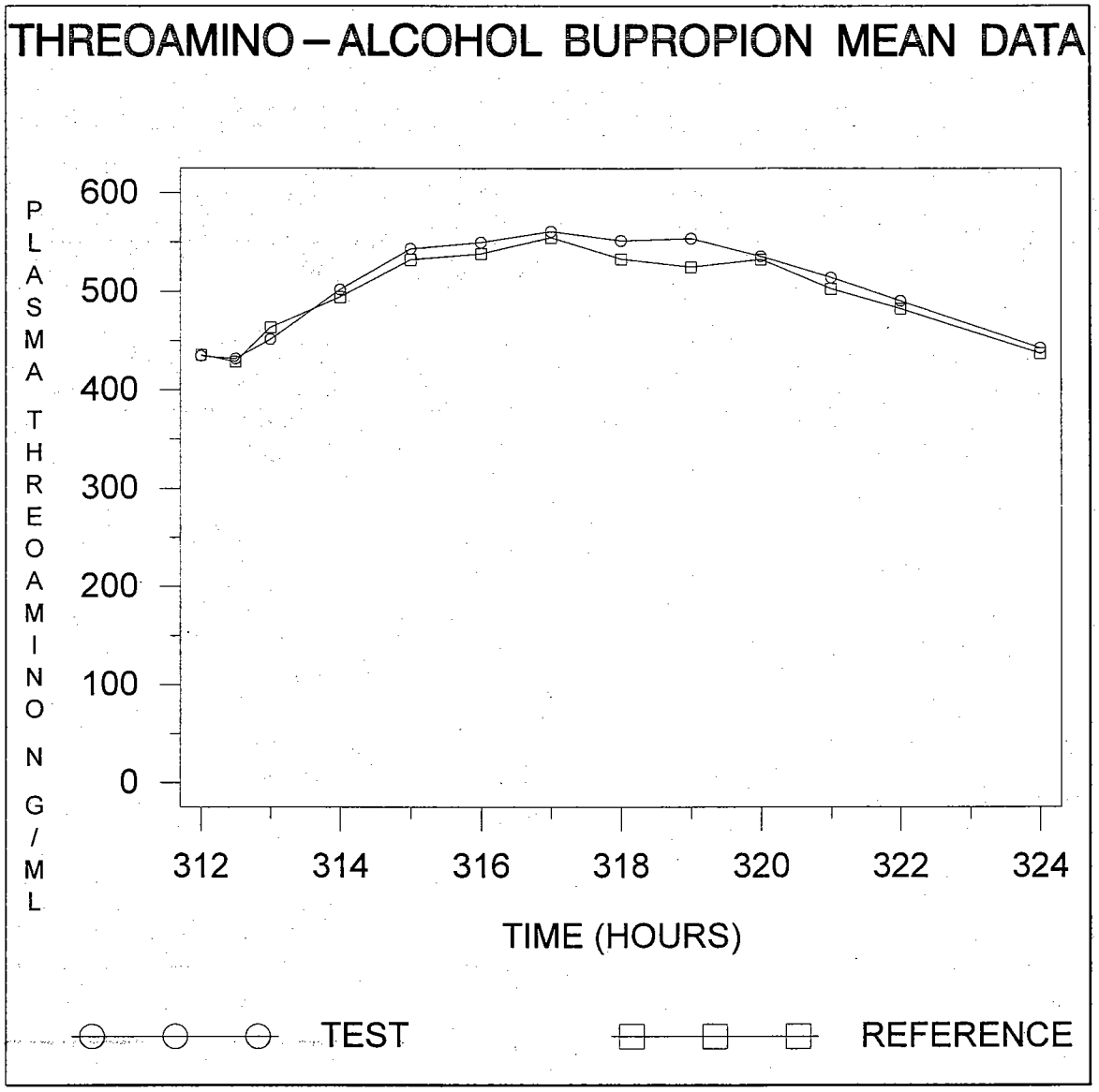


Figure 7 - B-04209 Plasma Concentrations (ng/mL) vs. Time: Threoamino-Alcohol Bupropion



4) Statistical Analysis: Twenty-five of 30 enrolled subjects completed the clinical portion of the study (See Clinical section above for dropouts). Per protocol, the plasma samples from the first 24 completing subjects were assayed by the analytical laboratory and a total of 24 sets of data was used in the statistical analysis for this study.

Individual subject CMIN plasma concentration-time curves from time 0 to 312 hours show that for most cases, the subjects were at steady-state by the 312 hour dose.

There was no statistically significant difference (alpha=0.05) between treatment for %FLUCTUATION, LAUC, LCMAX or LCAV of any analyte except for %FLUCTUATION of bupropion (p=0.0281).

5) **Conclusion:** The study is acceptable.

Protocol No.: B-04219, A RELATIVE BIOAVAILABILITY FOOD CHALLENGE STUDY OF BUPROPION HCl 150 MG SUSTAINED-RELEASE TABLETS

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Medical Director:	[redacted], M.D.
Scientific Director:	[redacted] PH.D.
Clinical Study Dates:	01/05/00 to 02/24/00
Analytical Facility	[redacted]
Principal Investigator:	[redacted] M.S.
Analytical Study Dates:	03/03/00 to 03/27/00
Storage Period:	82 days

TREATMENT INFORMATION Same as the single-dose, fasting study above except :

	1	2	3
Treatment ID:			
Test or Reference:	T	T	R
Study Condition:	fasting	fed	fed
Length of Fasting:	14 HOURS	N/A	N/A
Breakfast:	N	Y	Y
Breakfast Specifics:	N/A	ONE BUTTERED ENGLISH MUFFIN, ONE FRIED EGG, ONE SLICE AMERICAN CHEESE, ONE SLICE CANADIAN BACON, ONE SERVING HASH BROWN POTATOES, SIX FLUID OUNCES OF ORANGE JUICE, EIGHT FLUID OUNCES OF WHOLE MILK	ONE BUTTERED ENGLISH MUFFIN, ONE FRIED EGG, ONE SLICE AMERICAN CHEESE, ONE SLICE CANADIAN BACON, ONE SERVING HASH BROWN POTATOES, SIX FLUID OUNCES OF ORANGE JUICE, EIGHT FLUID OUNCES OF WHOLE MILK

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	6	**Replicated Treatment :**	N
No. of Periods:	3	**Balanced:**	Y
No. of Treatments:	3	**Washout Period:**	21 DAYS
DOSING		**SUBJECTS**	
Single or Multiple Dose:	Single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent :**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	22
Route of Administration:	ORAL	**No. of Subjects Completing:**	20
Dosing Interval:	N/A	**No. of Subjects Analyzed:**	18
Number of Doses:	N/A	**No. of Dropouts:**	2
Loading Dose:	N/A	**Sex(es) Included:**	male
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y

DOSING(Cont'd)		SUBJECTS(Cont'd)
Length of Infusion:	N/A	**Mean age:** 29 yrs (19-43) **Mean height:** 71 in. **Mean weight:** 167 lbs.

Dietary/Activity/Drug Restrictions: Same as in the B-01059 Study above.
Confinement: At least 10.5 hours pre-dose until 24 hours post-dose
Blood sampling: Same as in the B-01059 Study above.

Study Results

1) Clinical
Adverse Events: None serious event was reported. Two, eleven and four mild to moderate drug-related adverse events were reported during the test(fasted), test(fed) and reference(fed) treatments, respectively. They were drowsiness, sore throat, elevated AST, cough, elevated blood pressure, runny nose, watering eyes, headache and decreased blood pressure.

Protocol Deviations: None is significant.

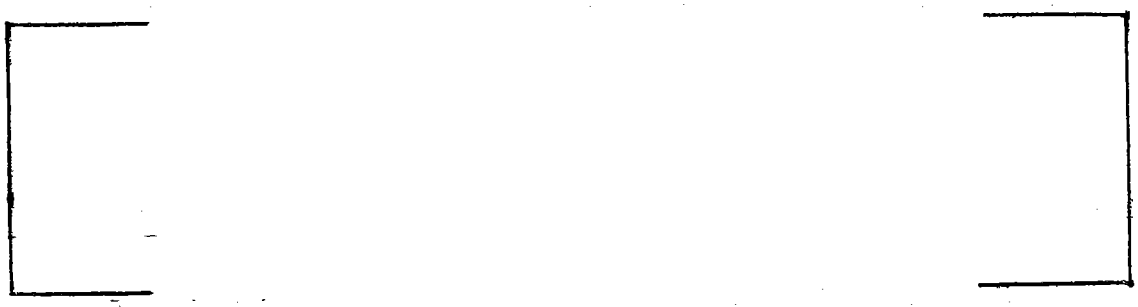
Dropouts:

SUBJECT NO.:	15	2
REASON:	REPEATED MISSED BLOOD SAMPLES	REPEATED MISSED BLOOD SAMPLES
PERIOD:	3	3
REPLACEMENT:	Y	Y

Comments:

2) Analytical (Not to be Released Under FOI) Same as in the B-01059 Study above except:

Bupropion:



Hydroxybupropion:

Threo/Erythroamino-Alcohol Bupropion:

APPEARS THIS WAY
ON ORIGINAL

3) Pharmacokinetic: Parameters, programs used and calculation methods were the same as in the B-01059 Study above.

Table 15 - B-04219 Arithmetic Means, LSMeans & 90% CI of PK Parameters: Bupropion

BUPROPION HCl 150 MG SR TABLET FOOD STUDY
EON B-04219
BUPROPION DATA
TEST FED VS REFERENCE FED
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTLQC	927.2969	913.4248	102
AUCINF	959.9253	946.2102	101
CMAX	149.5931	134.7536	111
TMAX	3.523148	3.805199	92.6
KELM	0.055785	0.050735	110
THALF	14.8835	15.80739	94.2

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTLQC	(92.0; 111)	0.93026	0.7891
AUCINF	(92.5; 110)	0.95605	0.7849
CMAX	(94.2; 128)	0.48921	0.2767
TMAX	(76.5; 109)	0.52535	0.4419
KELM	(98.4; 121)	0.81207	0.1538
THALF	(83.0; 105)	0.83844	0.3809

SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTLQC	6.790571	6.793814	889.421	892.310
AUCINF	6.824528	6.83001	920.142	925.200
CMAX	4.942704	4.855224	140.149	128.409

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTLQC	99.7	(91.0; 109)	0.94683	0.9525
AUCINF	99.5	(91.1; 109)	0.96264	0.9160
CMAX	109	(93.1; 128)	0.53888	0.3573

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

Table 16 - B-04219 Arithmetic Means, LSMeans & 90% CI of PK Parameters:

Hydroxybupropion

BUPROPION HCl 150 MG SR TABLET FOOD STUDY
EON B-04219
HYDROXYBUPROPION DATA
TEST FED VS REFERENCE FED
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTLQC	9218.846	9564.974	96.4
AUCINF	9379	9663.947	97.1
CMAX	259.975	271.4397	95.8
TMAX	5.99537	6.492165	92.3
KELM	0.032272	0.035828	90.1
THALF	22.88419	20.1628	113

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTLQC	(83.8; 109)	0.73920	0.6304
AUCINF	(84.4; 110)	0.73473	0.6964
CMAX	(87.4; 104)	0.97307	0.4001
TMAX	(73.0; 112)	0.38905	0.5073
KELM	(80.0; 100)	0.90016	0.1065
THALF	(101; 126)	0.72893	0.0828

SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTLQC	9.008106	9.073956	8169.04	8725.07
AUCINF	9.029587	9.086436	8346.41	8834.64
CMAX	5.464529	5.526544	236.16	251.27

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTLQC	93.6	(83.2; 105)	0.79580	0.3510
AUCINF	94.5	(84.1; 106)	0.80221	0.4162
CMAX	94.0	(86.5; 102)	0.97457	0.2165

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

Table 17 - B-04219 Arithmetic Means, LSMeans & 90% CI of PK Parameters:

Threo/Erythroamino-Alcohol Bupropion

BUPROPION HCl 150 MG SR TABLET FOOD STUDY
EON B-04219
THREO/ERYTHROAMINO-ALCOHOL BUPROPION DATA
TEST FED VS REFERENCE FED
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTLQC	6456.907	6145.487	105
AUCINF	7008.148	6647.314	105
CMAX	163.5005	155.3097	105
TMAX	4.606481	4.852208	94.9
KELM	0.016503	0.016701	98.8
THALF	51.58399	47.43262	109

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTLQC	(93.2; 117)	0.79091	0.4744
AUCINF	(92.9; 118)	0.74605	0.4679
CMAX	(93.0; 118)	0.76581	0.4703
TMAX	(79.8; 110)	0.57788	0.5754
KELM	(86.5; 111)	0.76263	0.8712
THALF	(93.6; 124)	0.57665	0.3361

SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTLQC	8.715498	8.672648	6096.67	5840.95
AUCINF	8.787098	8.741339	6549.20	6256.26
CMAX	5.055129	4.999669	156.82	148.36

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTLQC	104	(94.5; 115)	0.91213	0.4689
AUCINF	105	(94.3; 116)	0.87999	0.4647
CMAX	106	(94.9; 118)	0.86234	0.3894

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

Table 18 - B-04219 Arithmetic Mean Plasma Concentrations (ng/mL): Bupropion

Time	Fasting Test Treatment A	(CV%)	Non-Fasting Test Treatment B	(CV%)	Non-Fasting Reference Treatment C	(CV%)	Ratio (A/B)	Ratio (B/C)
0.00 HR	0.000	.	0.000	.	0.000	.	0.000	0.000
0.50 HR	8.377	72.399	4.906	100.485	5.199	120.530	1.708	0.944
1.00 HR	57.800	64.159	45.028	67.943	39.638	70.327	1.284	1.136
2.00 HR	98.228	31.295	99.900	73.027	81.109	61.330	0.983	1.232
3.00 HR	91.811	32.334	114.817	44.441	111.633	50.497	0.800	1.029
4.00 HR	76.172	31.774	98.656	20.592	105.872	27.085	0.772	0.932
5.00 HR	69.589	24.747	88.833	39.786	95.072	24.320	0.783	0.934
6.00 HR	55.344	25.979	67.794	82.527	62.628	26.072	0.816	1.082
7.00 HR	42.122	26.475	48.572	72.594	47.294	27.073	0.867	1.027
8.00 HR	34.328	28.278	38.689	61.933	38.306	29.466	0.887	1.010
10.0 HR	23.244	28.269	27.533	58.358	26.450	32.145	0.844	1.041
12.0 HR	15.353	30.709	18.008	53.562	17.696	30.160	0.853	1.018
14.0 HR	12.351	34.819	13.805	44.379	13.638	29.610	0.895	1.012
24.0 HR	5.132	32.315	5.814	40.974	5.700	35.430	0.883	1.020
36.0 HR	2.580	43.835	3.116	60.161	3.157	39.956	0.828	0.987
48.0 HR	1.509	81.320	1.794	65.139	2.086	55.440	0.841	0.860
60.0 HR	0.689	139.216	0.739	140.464	0.782	134.917	0.932	0.945
72.0 HR	0.535	199.517	0.438	164.755	0.452	173.569	1.221	0.969
96.0 HR	0.000	.	0.065	412.311	0.112	291.059	0.000	0.580
120 HR	0.000	.	0.000	.	0.000	.	.	.
144 HR	0.000	.	0.000	.	0.000	.	.	.
168 HR	0.000	.	0.000	.	0.000	.	.	.
192 HR	0.000	.	0.000	.	0.000	.	.	.

Table 19 - B-04219 Arithmetic Mean Plasma Concentrations (ng/mL):

Hydroxybupropion

Time	Fasting Test Treatment A	(CV%)	Non-Fasting Test Treatment B	(CV%)	Non-Fasting Reference Treatment C	(CV%)	Ratio (A/B)	Ratio (B/C)
0.00 HR	0.000	.	0.000	.	0.000	.	0.000	0.000
0.50 HR	14.448	61.964	3.868	90.806	4.101	120.565	3.735	0.943
1.00 HR	70.056	68.381	38.493	94.420	35.349	70.237	1.820	1.089
2.00 HR	157.489	63.235	126.211	88.298	108.216	77.828	1.248	1.166
3.00 HR	195.783	55.699	194.022	69.321	184.733	65.660	1.009	1.050
4.00 HR	219.806	57.350	221.383	57.585	232.522	56.206	0.993	0.952
5.00 HR	222.878	51.339	224.061	47.086	237.494	45.284	0.995	0.943
6.00 HR	225.556	51.478	227.278	43.534	232.956	45.181	0.992	0.976
7.00 HR	222.583	49.560	223.361	43.375	239.444	42.092	0.997	0.933
8.00 HR	230.722	48.653	229.206	42.247	245.722	43.243	1.007	0.933
10.0 HR	223.311	47.494	230.433	42.584	238.500	38.609	0.969	0.966
12.0 HR	189.256	45.870	195.600	40.841	208.167	39.815	0.968	0.940
14.0 HR	184.517	48.004	185.989	42.737	195.978	43.472	0.992	0.949
24.0 HR	152.261	50.285	151.028	44.587	158.406	44.863	1.008	0.953
36.0 HR	101.111	69.915	102.178	57.005	105.961	48.574	0.990	0.964
48.0 HR	72.944	71.455	70.400	57.472	73.094	49.255	1.036	0.963
60.0 HR	50.311	78.143	43.761	67.162	49.661	72.908	1.150	0.881
72.0 HR	38.998	98.166	30.131	81.903	31.606	60.659	1.294	0.953
96.0 HR	16.177	105.058	13.696	91.961	13.489	72.460	1.181	1.015
120 HR	7.502	120.297	7.982	98.410	5.396	101.603	0.940	1.479
144 HR	3.152	179.609	3.049	162.679	2.091	133.478	1.034	1.458
168 HR	1.092	277.110	1.294	276.049	0.489	315.880	0.844	2.646
192 HR	0.378	424.264	0.448	424.264	0.267	291.769	0.844	1.678

Table 20 - B-04219 Arithmetic Mean Plasma Concentrations (ng/mL):

Threo/Erythroamino-Alcohol Bupropion

Time	Fasting Test Treatment A	(CV%)	Non-Fasting Test Treatment B	(CV%)	Non-Fasting Reference Treatment C	(CV%)	Ratio (A/B)	Ratio (B/C)
0.00 HR	0.000	.	0.091	424.264	0.120	424.264	0.000	0.758
0.50 HR	0.853	126.725	0.677	185.345	0.903	186.126	1.260	0.750
1.00 HR	23.330	66.472	16.112	59.468	16.490	93.353	1.448	0.977
2.00 HR	79.572	41.826	71.598	69.231	53.562	60.589	1.111	1.337
3.00 HR	106.244	38.232	113.183	52.489	99.861	52.648	0.939	1.133
4.00 HR	115.856	36.893	126.306	37.379	121.283	36.501	0.917	1.041
5.00 HR	128.061	31.799	140.572	25.060	144.600	35.269	0.911	0.972
6.00 HR	126.039	33.757	139.589	37.248	130.017	31.911	0.903	1.074
7.00 HR	124.078	38.567	130.511	34.245	127.606	32.980	0.951	1.023
8.00 HR	124.139	38.390	127.372	34.544	126.511	34.993	0.975	1.007
10.0 HR	111.072	34.617	116.883	34.690	112.094	36.304	0.950	1.043
12.0 HR	92.467	35.306	97.872	39.377	95.844	37.952	0.945	1.021
14.0 HR	91.811	38.487	92.989	35.134	90.128	37.483	0.987	1.032
24.0 HR	74.122	47.850	73.550	38.723	71.528	48.158	1.008	1.028
36.0 HR	58.833	48.220	56.317	38.758	54.950	41.324	1.045	1.025
48.0 HR	48.989	49.433	47.689	39.271	46.718	42.918	1.027	1.021
60.0 HR	40.911	47.226	36.872	39.354	38.294	38.615	1.110	0.963
72.0 HR	35.056	48.726	33.406	49.391	31.883	52.347	1.049	1.048
96.0 HR	23.321	57.708	21.659	61.989	21.349	55.044	1.077	1.015
120 HR	16.839	71.144	18.756	61.475	13.442	55.026	0.898	1.395
144 HR	11.701	76.284	12.671	74.552	11.326	71.069	0.923	1.119
168 HR	9.154	83.141	8.944	81.400	7.644	70.817	1.023	1.170
192 HR	6.299	79.295	6.658	85.891	5.940	85.458	0.946	1.121

Figure 8 - B-04219 Plasma Concentrations (ng/mL) vs. Time: Bupropion

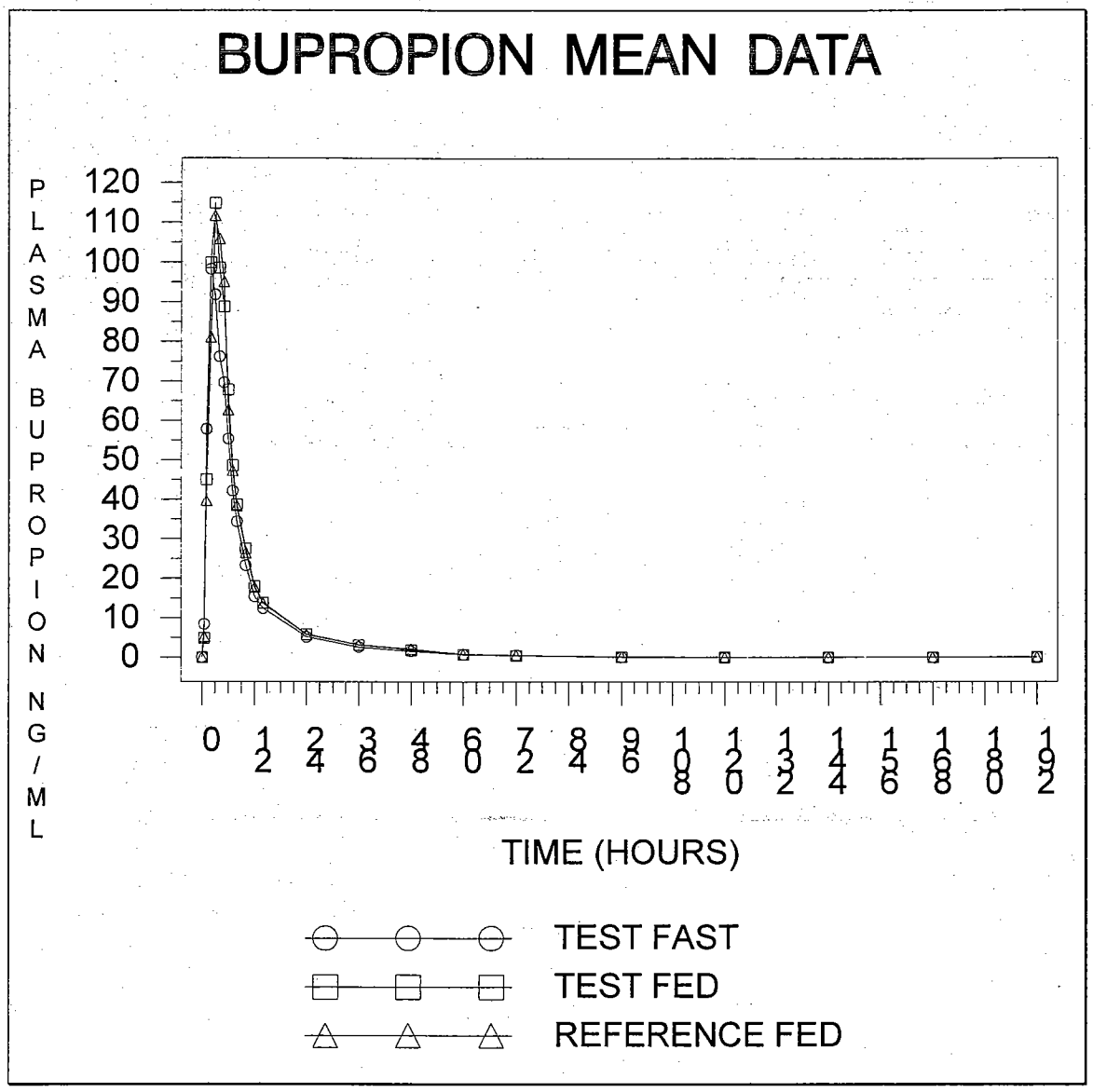


Figure 9 - B-04219 Plasma Concentrations (ng/mL) vs. Time: Hydroxybupropion

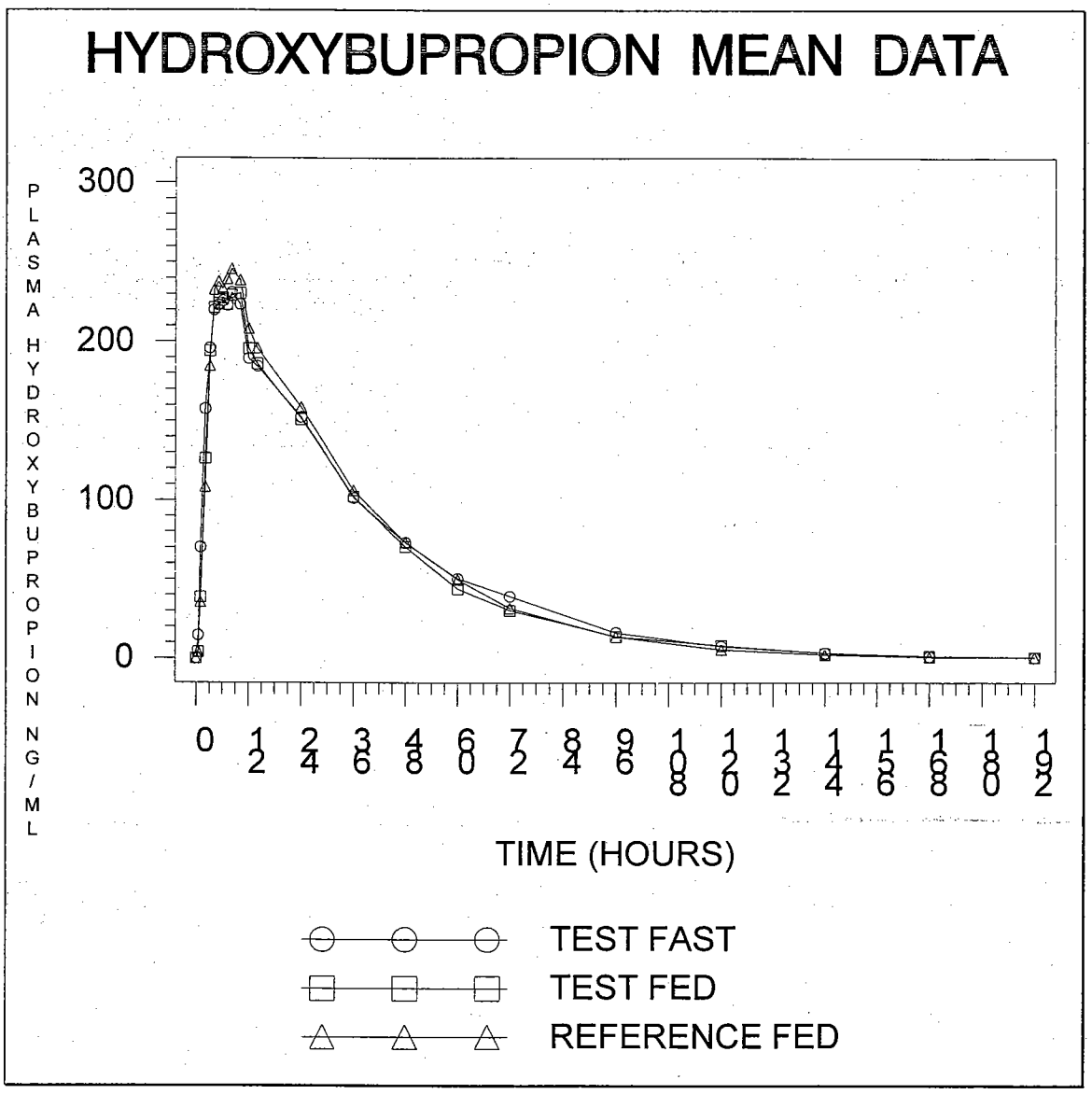
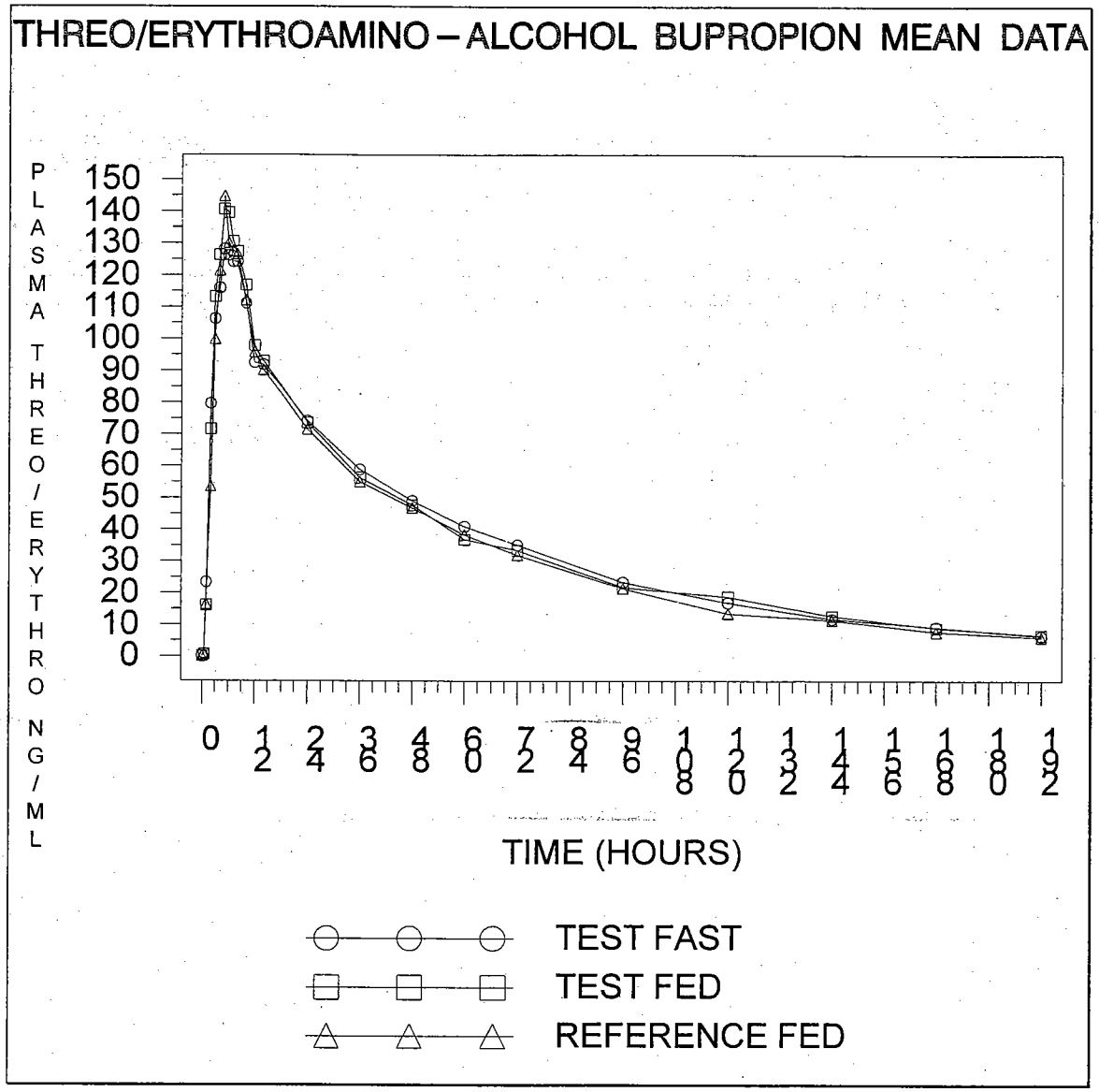


Figure 10 - B-04219 Plasma Concentrations (ng/mL) vs. Time: Threo/Erythroamino-Alcohol Bupropion



4) Statistical Analysis: Twenty of 22 enrolled subjects completed the clinical portion of the study (See Clinical section above for dropouts). Per protocol, the plasma samples from the first 18 completing subjects were assayed by the analytical laboratory and a total of 18 sets of data was used in the statistical analysis for this study.

There were statistically significant difference (alpha=0.05) between treatment for LAUC(0-T) (p=0.0228), LAUC(0-Inf) (p=0.0197) and LCMAX (p=0.0042) of bupropion, and LCMAX (p=0.0478) of threo-erythreoamino-alcohol bupropion.

5) Conclusion: The study is acceptable.

Protocol No.: B-06269, A SINGLE-DOSE, RELATIVE BIOAVAILABILITY STUDY OF BUPROPION HCl 100 MG SUSTAINED-RELEASE TABLETS UNDER FASTING CONDITIONS

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Medical Director:	[redacted] M.D.
Scientific Director:	[redacted] PH.D.
Clinical Study Dates:	01/22/00 to 02/20/00
Analytical Facility	[redacted]
Principal Investigator:	[redacted], M.S.
Analytical Study Dates:	02/24/00 to 03/16/00
Storage Period:	54 days

TREATMENT INFORMATION

Treatment ID:	1	2
Test or Reference:	T	R
Product Name:	Bupropion Hydrochloride ER Tablets, 100 mg	WELLBUTRIN SR Tablets, 100 mg
Manufacturer:	EON LABS MANUFACTURING, INC.	CATALYTICA PHARMACEUTICALS, INC. FOR GLAXO WELLCOME INC.
Manufacture Date:	8/6/99	N/A
Expiration Date:	N/A	2/2000
ANDA Batch Size:	[redacted]	
Full Batch Size:	[redacted]	
Batch/Lot Number:	990706	9D2093
Potency:	100.1%	100.8%
Strength:	100 mg	100 mg
Dosage Form:	TABLET	TABLET
Dose Administered:	100 mg	100 mg
Study Condition:	fasting	fasting
Length of Fasting:	14 HOURS	14 HOURS

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	21 DAYS

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 ML	**No. of Subjects Enrolled:**	28
Route of Administration:	ORAL	**No. of Subjects Completing:**	25
Dosing Interval:	N/A	**No. of Subjects Plasma Analyzed:**	24
Number of Doses:	N/A	**No. of Dropouts:**	3
Loading Dose:	N/A	**Sex(es) Included:**	male
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**Mean age:** 26 yrs (19-38)	
		Mean height: 70 in.	
		Mean weight: 167 lbs.	

Dietary/Activity/Drug Restrictions/Confinement: Same as in the B-01059 Study above.
Blood sampling: Same as in the B-01059 Study above.

Study Results

1) Clinical
Adverse Events: None serious event was reported. Nine and seven mild to moderate drug-related adverse events were reported during the test and reference treatments, respectively. They were headache, nausea, epigastric pain, elevated blood pressure, WBC's in urine, stomachache, lightheadedness and elevated glucose.

Protocol Deviations: None is significant.
Dropouts:

SUBJECT NO.:	10	17	5
REASON:	ELEVATED BLOOD PRESSURE AT PRE-DOSE PERIOD II	REPEATED MISSED BLOOD SAMPLES	VOLUNTARILY DROPPED AS HE DID NOT REPORT FOR PERIOD II CHECK-IN
PERIOD:	I	2	1
REPLACEMENT:	Y	Y	Y

2) Analytical (Not to be Released Under FOI) Same as in the B-01059 Study except:

Bupropion:

[redacted]

Hydroxybupropion:

Threo/Erythroamino-Alcohol Bupropion:

3) Pharmacokinetic: Parameters, programs used and calculation methods were same as in the B-01059 Study above.

APPEARS THIS WAY
ON ORIGINAL

Table 21 - B-06269 Arithmetic Means, LSMeans & 90% CI of PK Parameters:

Bupropion

BUPROPION HCl 100 MG SR TABLET FASTING STUDY
EON B-06269
BUPROPION DATA
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTLQC	410.2401	430.4717	95.3
AUCINF	435.1449	452.3517	96.2
CMAX	58.46667	54.45417	107
TMAX	3.041667	3.333333	91.3
KELM	0.069457	0.067696	103
THALF	12.15536	11.3074	107

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTLQC	(90.7;99.9)	0.99999	0.0965
AUCINF	(91.9; 100)	1.00000	0.1398
CMAX	(101; 114)	0.99651	0.0763
TMAX	(81.1; 101)	0.89691	0.1538
KELM	(91.4; 114)	0.83235	0.6946
THALF	(93.4; 122)	0.64243	0.3695

SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTLQC	5.996833	6.040901	402.153	420.271
AUCINF	6.058219	6.091782	427.613	442.209
CMAX	4.045435	3.969918	57.136	52.980

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTLQC	95.7	(90.9; 101)	0.99993	0.1540
AUCINF	96.7	(92.3; 101)	0.99999	0.2312
CMAX	108	(102; 115)	0.99923	0.0431

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

Table 22 - B-06269 Arithmetic Means, LSMeans & 90% CI of PK Parameters:

Hydroxybupropion

BUPROPION HCl 100 MG SR TABLET FASTING STUDY
EON B-06269
HYDROXYBUPROPION DATA
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTLQC	5488.071	5784.421	94.9
AUCINF	5577.548	5899.89	94.5
CMAX	186.0742	176.3761	105
TMAX	8.287879	6.534091	127
KELM	0.03522	0.036108	97.5
THALF	20.60385	20.89223	98.6

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTLQC	(86.0; 104)	0.95615	0.3327
AUCINF	(85.9; 103)	0.96536	0.2876
CMAX	(97.6; 113)	0.98257	0.2466
TMAX	(51.2; 203)	0.05955	0.5483
KELM	(88.3; 107)	0.94137	0.6529
THALF	(89.1; 108)	0.93157	0.8048

SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTLQC	8.456351	8.486884	4704.86	4850.73
AUCINF	8.481318	8.52156	4823.81	5021.88
CMAX	5.079227	5.016344	160.65	150.86

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTLQC	97.0	(90.8; 104)	0.99728	0.4381
AUCINF	96.1	(90.1; 102)	0.99820	0.2935
CMAX	106	(99.2; 114)	0.99415	0.1429

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

Table 23 - B-06269 Arithmetic Means, LSMeans & 90% CI of PK Parameters:

Threo/Erythroamino-Alcohol Bupropion

BUPROPION HCl 100 MG SR TABLET FASTING STUDY
EON B-06269
THREO/ERYTHROAMINO-ALCOHOL BUPROPION DATA
SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN	REFERENCE LEAST SQUARES MEAN	100* TEST/REFERENCE RATIO
AUCTLQC	3616.127	3749.45	96.4
AUCINF	3864.106	3973.513	97.2
CMAX	86.1	84.17083	102
TMAX	5.000000	5.791667	86.3
KELM	0.017845	0.017338	103
THALF	45.17864	44.46728	102

TITLE	90% CI	POWER OF ANOVA	P VALUE
AUCTLQC	(89.3; 104)	0.99372	0.4034
AUCINF	(89.3; 105)	0.98317	0.5563
CMAX	(96.4; 108)	0.99942	0.5126
TMAX	(77.1;95.5)	0.94406	0.0183
KELM	(92.8; 113)	0.89677	0.6264
THALF	(90.2; 113)	0.82031	0.8120

SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

TITLE	TEST LEAST SQUARES MEAN LOG DATA	REFERENCE LEAST SQUARES MEAN LOG DATA	TEST GEOMETRIC MEAN	REFERENCE GEOMETRIC MEAN
AUCTLQC	8.113086	8.166417	3337.86	3520.71
AUCINF	8.178165	8.225205	3562.31	3733.89
CMAX	4.370119	4.352369	79.05	77.66

TITLE	100* RATIO OF GEOMETRIC MEANS	90% CI ON LOG TRANSFORMED DATA	POWER OF ANOVA FOR LOG TRANSFORMED DATA	P VALUE
AUCTLQC	94.8	(89.2; 101)	0.99922	0.1440
AUCINF	95.4	(89.2; 102)	0.99683	0.2439
CMAX	102	(96.7; 107)	0.99994	0.5563

GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS
OF LOG TRANSFORMED VALUES.

Table 24 - B-06269 Arithmetic Mean Plasma Concentrations (ng/mL): Bupropion

Time	Test Treatment A	(CV%)	Reference Treatment B	(CV%)	Ratio (A/B)
0.00 HR	0.000	.	0.000	.	0.000
0.50 HR	2.760	123.538	3.709	176.038	0.744
1.00 HR	25.695	46.792	22.868	58.330	1.124
2.00 HR	49.554	31.916	43.850	27.509	1.130
3.00 HR	56.133	23.859	50.737	23.851	1.106
4.00 HR	49.142	21.572	49.058	23.124	1.002
5.00 HR	39.904	23.866	43.904	23.253	0.909
6.00 HR	29.483	27.818	31.692	23.343	0.930
7.00 HR	22.292	28.974	24.563	25.902	0.908
8.00 HR	17.597	29.865	19.683	24.218	0.894
10.0 HR	11.644	28.012	13.404	26.848	0.869
12.0 HR	8.138	26.994	9.307	24.991	0.874
14.0 HR	6.283	23.510	7.123	25.178	0.882
24.0 HR	2.646	26.288	2.983	27.077	0.887
36.0 HR	1.347	46.342	1.641	28.409	0.821
48.0 HR	0.309	178.513	0.372	163.204	0.831
60.0 HR	0.000	.	0.086	338.835	0.000
72.0 HR	0.000	.	0.000	.	.
96.0 HR	0.000	.	0.000	.	.
120 HR	0.000	.	0.000	.	.
144 HR	0.000	.	0.000	.	.
168 HR	0.000	.	0.000	.	.
192 HR	0.000	.	0.000	.	.

Table 25 - B-06269 Arithmetic Mean Plasma Concentrations (ng/mL):

Hydroxybupropion

Time	Test Treatment A	(CV%)	Reference Treatment B	(CV%)	Ratio (A/B)
0.00 HR	0.350	479.583	0.000	.	.
0.50 HR	6.983	103.317	6.060	72.221	1.152
1.00 HR	41.436	57.893	34.531	55.852	1.200
2.00 HR	101.103	51.130	88.000	51.403	1.149
3.00 HR	150.752	58.040	126.801	45.672	1.189
4.00 HR	175.513	58.665	153.291	45.819	1.145
5.00 HR	175.722	56.153	161.704	47.255	1.087
6.00 HR	171.189	52.696	161.352	52.804	1.061
7.00 HR	168.065	50.193	163.352	54.830	1.029
8.00 HR	165.378	47.293	161.787	50.528	1.022
10.0 HR	156.591	56.286	159.504	55.335	0.982
12.0 HR	135.311	55.746	136.320	53.406	0.993
14.0 HR	118.469	54.864	121.256	55.665	0.977
24.0 HR	95.605	50.385	101.897	56.148	0.938
36.0 HR	57.245	51.692	66.413	67.799	0.862
48.0 HR	37.300	54.927	42.595	71.901	0.876
60.0 HR	22.172	61.552	27.990	92.804	0.792
72.0 HR	15.802	71.171	17.176	86.829	0.920
96.0 HR	6.370	101.605	7.639	85.355	0.834
120 HR	2.565	155.203	2.852	110.441	0.899
144 HR	0.767	282.116	0.707	251.908	1.085
168 HR	0.442	326.810	0.272	344.634	1.625
192 HR	0.131	479.583	0.115	479.583	1.139

Table 26 - B-06269 Arithmetic Mean Plasma Concentrations (ng/mL):

Threo/Erythroamino-Alcohol Bupropion

Time	Test Treatment A	(CV%)	Reference Treatment B	(CV%)	Ratio (A/B)
0.00 HR	2.033	489.898	0.000	.	.
0.50 HR	2.403	450.342	0.482	319.309	4.985
1.00 HR	12.112	117.149	9.347	90.353	1.296
2.00 HR	42.083	51.243	33.979	40.902	1.239
3.00 HR	65.979	45.869	56.621	42.977	1.165
4.00 HR	77.392	46.216	71.942	44.775	1.076
5.00 HR	82.908	49.124	81.425	43.284	1.018
6.00 HR	80.217	47.734	80.217	46.235	1.000
7.00 HR	79.071	52.630	78.021	48.266	1.013
8.00 HR	75.787	54.883	75.704	49.603	1.001
10.0 HR	68.325	57.345	69.796	53.826	0.979
12.0 HR	59.642	55.549	61.679	51.524	0.967
14.0 HR	54.850	54.053	57.475	50.774	0.954
24.0 HR	42.658	55.844	44.388	46.564	0.961
36.0 HR	33.148	56.884	34.529	48.499	0.960
48.0 HR	25.604	48.127	26.413	46.018	0.969
60.0 HR	21.390	51.399	22.913	52.343	0.934
72.0 HR	17.525	47.900	18.615	48.928	0.941
96.0 HR	12.236	45.284	12.707	45.656	0.963
120 HR	8.416	56.257	8.863	44.283	0.950
144 HR	5.383	58.852	6.085	54.030	0.885
168 HR	4.226	66.747	3.941	61.268	1.072
192 HR	2.601	95.450	2.643	78.842	0.984

Figure 11 - B-06269 Plasma Concentrations (ng/mL) vs. Time: Bupropion

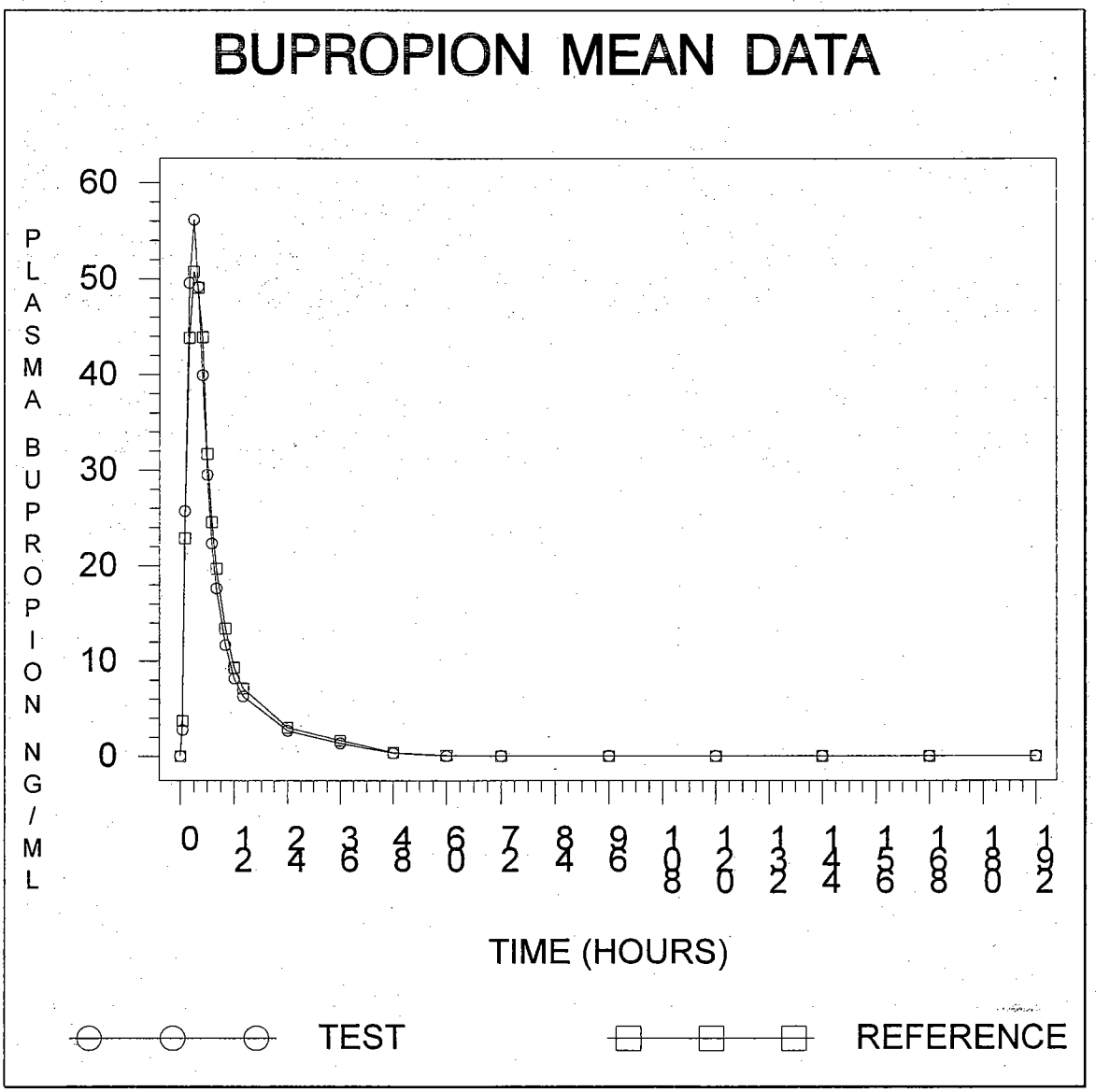


Figure 12 - B-06269 Plasma Concentrations (ng/mL) vs. Time: Hydroxybupropion

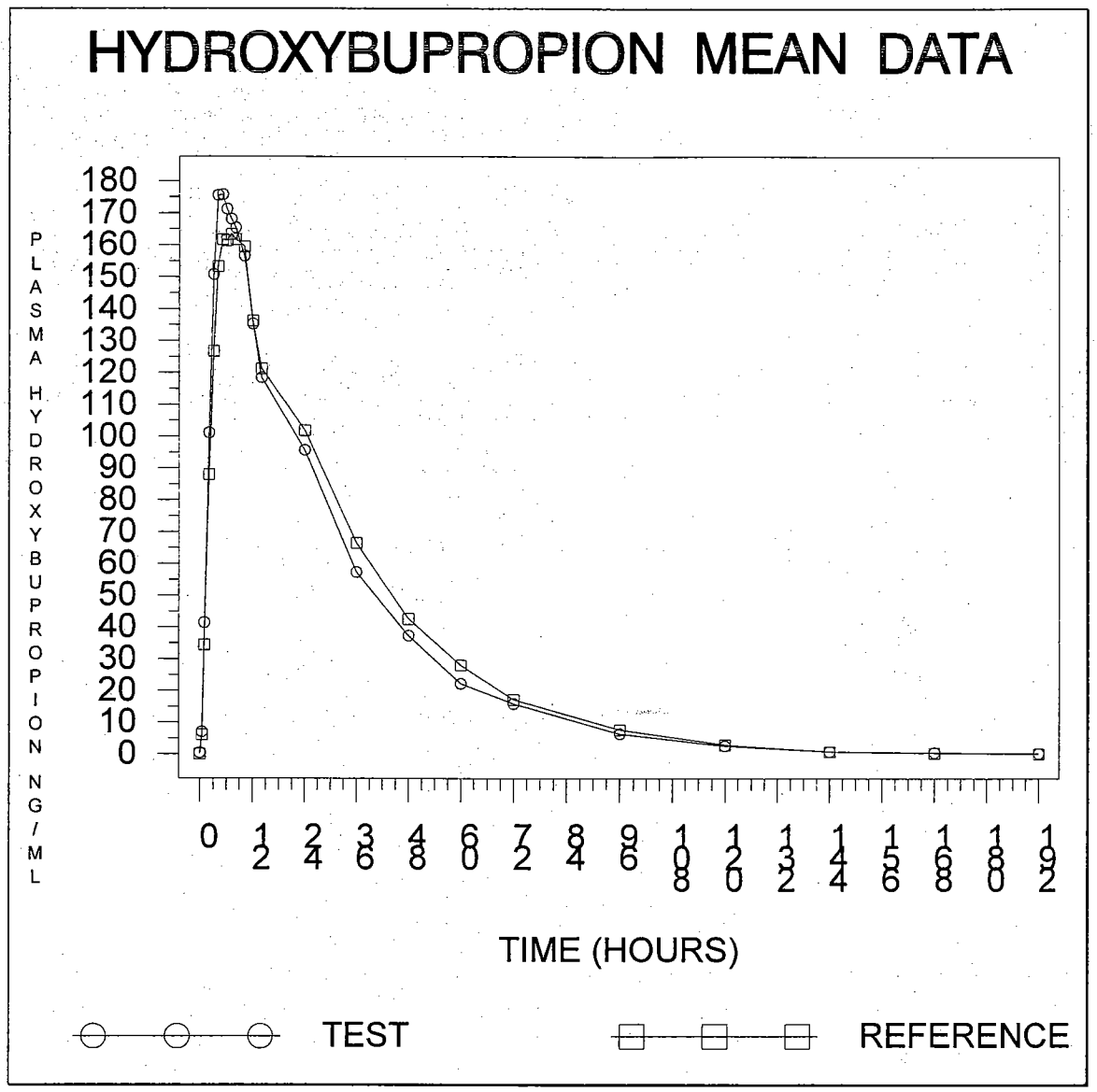
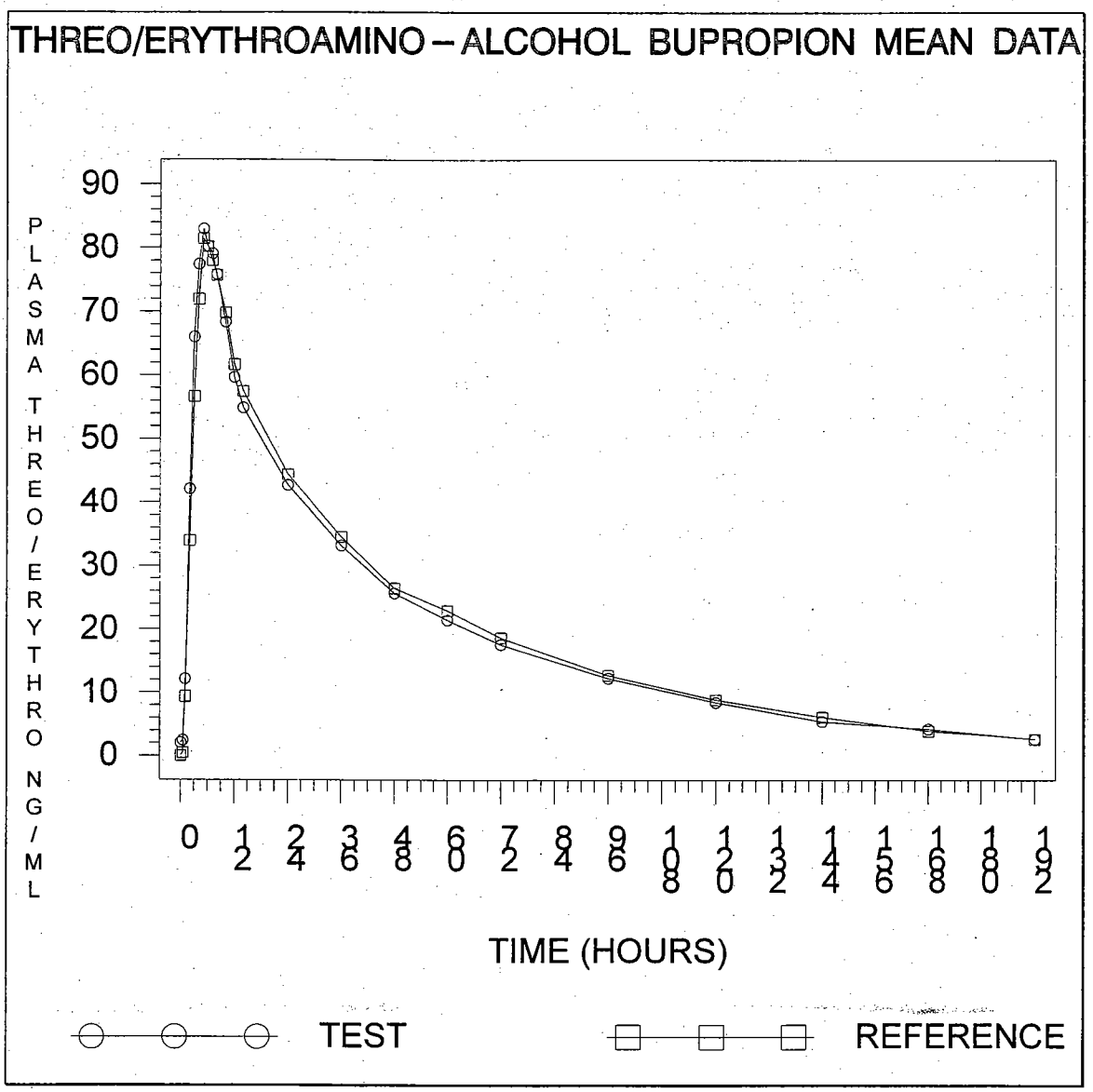


Figure 13 - B-06269 Plasma Concentrations (ng/mL) vs. Time:
Threo/Erythroamino-Alcohol Bupropion



4) Statistical Analysis: Twenty-five of 28 enrolled subjects completed the clinical portion of the study (See Clinical section above for dropouts). Per protocol, the plasma samples from the first 24 completing subjects were assayed by the analytical laboratory and a total of 24 sets of data was used in the statistical analysis for this study.

There was statistically significant difference (alpha=0.05) between treatment for LCMAX of bupropion (p=0.0431) only.

5) Conclusion: The study is acceptable.

Waiver Request: Waiver request for the 100 mg is granted based on the acceptable single-dose, fasting study, proportional formulation (see below) and acceptable dissolution data (see below).

Formulation(Not to be released under FOI)

Ingredient	%w/w	Strength 150 mg	Strength 100 mg
BUPROPION HYDROCHLORIDE		150	100
CARNAUBA WAX, NF			
[redacted]			
HYDROXYPROPYL CELLULOSE, NF,			
HYDROXYPROPYL CELLULOSE, NF,			
MAGNESIUM STEARATE, NF			
MICROCRYSTALLINE CELLULOSE, NF			
[redacted]			
OPADRY BLUE			

Formulation Comments: Formulations of the 100 mg and 150 mg strengths of the test product are proportionally similar.

Dissolution(Not to be released under FOI)

The firm has conducted dissolution testing on the 150 mg strength of the test and reference products at pH 1.5, 4.5, 6.8 and 7.5(water), changing the dissolution apparatus and speed. The results of the experimental dissolution testing are given in the pages 123-134, Vol. 1.1.

Based on the experimental testing results, the firm has proposed the following dissolution testing procedure for the test product. The dissolution profiles for all strengths of the test and reference products are summarized below.

Dissolution Methods / Results

Dissolution Medium: 0.1 N Hydrochloric Acid, pH 1.5
Volume: 900 ml
Dissolution Apparatus: USP Apparatus 1, baskets
Speed: 50 RPM

Mean Dissolution Data

Test				REFERENCE		
Lot No.: 990707				Lot No.: 8I1890		
Strength: 150 mg				Strength: 150 mg		
No. of Units: 12				No. of Units: 12		
Time(hours)	Mean	Range	%CV	Mean	Range	%CV
1	33.8		3.12	37.5		4.73
2	50.0		2.09	58.1		2.51
4	72.2		1.6	85.2		1.6
6	87.1		1.55	99.7		1.33
8	97.1		1.16	102.9		1.55

Mean Dissolution Data

Test				REFERENCE		
Lot No.: 990706				Lot No.: 9D2093		
Strength: 100 mg				Strength: 100 mg		
No. of Units: 12				No. of Units: 12		
Time(hours)	Mean	Range	%CV	Mean	Range	%CV
1	40.8		1.65	36.7		6.72
2	59.6		1.48	56.6		3.12
4	84.8		1.89	82.9		1.47
6	99.6		1.82	96.6		1.64
8	102.3		1.26	101.8		1.46

Dissolution Comments: The dissolution testing method and data are acceptable. Based on the submitted data, the following interim specifications are recommended:

1st hour: —— %
2nd hour: —— %
4th hour: —— %
6th hour: NLT —%

Recommendations:

1. The single-dose, fasting bioequivalence study, the single-dose post-prandial bioequivalence study and the multiple-dose, fasting bioequivalence study conducted by Eon Labs on the test product, Bupropion HCl ER Tablets, 150 mg, lot # 990707, comparing it with the reference product, Glaxo's Wellbutrin SR 150 mg bupropion HCl tablets, lot # 8I1890, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that the test product, Eon's Bupropion HCl ER Tablets, 150 mg, is bioequivalent to the reference product, Glaxo's Wellbutrin SR 150 mg bupropion HCl tablets, under fasting, non-fasting and steady-state conditions.

2. The single-dose, fasting bioequivalence study conducted by Eon Labs on the test product, Bupropion HCl ER 100 mg Tablets, lot # 990706, comparing it with the reference product, Glaxo's Wellbutrin SR 100 mg bupropion HCl tablets, lot # 9D2093 has been found acceptable by the Division of Bioequivalence. The studies demonstrate that the test product, Eon's

Bupropion HCl ER Tablets, 100 mg, is bioequivalent to the reference product, Glaxo's Wellbutrin SR 100 mg bupropion HCl tablets, under fasting conditions.

3. The in-vitro dissolution testing conducted by Eon Labs on its Bupropion HCl ER Tablets, 150 mg and 100 mg, has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1 N HCl , pH 1.5, at 37° C using USP XXIV apparatus I(basket) at 50 rpm. The test product should meet the following interim specifications:

1st hour: ——%
2nd hour: ——%
4th hour: ——%
6th hour: NLT —%

4. The firm has demonstrated that the formulation of its Bupropion HCl ER Tablets, 100 mg, is proportionally similar to that of the 150 mg strength that underwent complete, acceptable *in vivo* bioequivalence testing. The waiver of further *in vivo* bioequivalence study requirements for the 100 mg tablets is granted. The firm's Bupropion HCl ER Tablets, 100 mg, is therefore deemed bioequivalent to Glaxo's Wellbutrin SR 100 mg bupropion HCl tablets

Hoaihon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 9/21/2000

Concur: Barbara M Davis Date: 10/18/00
for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
cc: ANDA # 75-932 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/09-18-00/W #75932sdw.700
Also as V:\firmsam\eon\ltrs&rev\75932sdw.700
Attachment: 0 page

BIOEQUIVALENCY COMMENTS

ANDA: 75-932 APPLICANT: Eon Labs

DRUG PRODUCT: Bupropion Hydrochloride ER Tablets, 150 mg & 100 mg

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

The Division of Bioequivalence acknowledges that the following dissolution testing is being incorporated into your stability and quality control programs:

> The dissolution testing is conducted in 900 mL of 0.1 N HCl, pH 1.5, at 37°C using USP24 Apparatus I(basket) at 50 rpm.

Based on the dissolution data submitted for the test product, the following **interim** specifications are recommended:

1st hour	——— %
2nd hour	——— %
4th hour	——— %
6th hour	NLT —— %

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 Barbara Myers Davit

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

CC:ANDA 75-932
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen HNV
HFD-652/ YHuang YH 9/21/2000
HFD-617/ K. Scardina (B) 10/16/00
HFD-650/ D. Conner DW 10/18/00

V:\FIRMSAM\eon\ltrs&rev\75932SDW.700
Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE Submission date: 07-26-00

1. FASTING STUDY (STF) o/c
   Clinical: ———
   Analytical. ———
   Strength: 150 MG
   Outcome: AC

2. NON-FASTING STUDY (STP) o/c
   Clinical: ———
   Analytical. ———
   Strength: 150 MG
   Outcome: AC

3. FASTING, MULTIPLE-DOSE STUDY (STM) o/c
   Clinical: ———
   Analytical. ———
   Strength: 150 MG
   Outcome: AC

4. FASTING STUDY (STF) o/c
   Clinical: ———
   Analytical. ———
   Strength: 100 MG
   Outcome: AC

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

WINBIO COMMENTS:

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-932 SPONSOR : Eon Labs
DRUG AND DOSAGE FORM : Bupropion HCl ER Tablets
STRENGTH(S) : 150 mg & 100 mg
TYPES OF STUDIES : Fasting Study (150 mg & 100 mg), Non-Fasting Study (150 mg only) and Multiple-Dose Study (150 mg only)
CINICAL STUDY SITE(S) : ———
ANALYTICAL SITE(S) : ———

STUDY SUMMARY : Acceptable
DISSOLUTION : Acceptable

DSI INSPECTION STATUS

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

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : HN DATE : 9-21-00

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : YCH DATE : 9/21/2000

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
INITIAL : Barbara M Davit DATE : 10/18/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-932

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

The firm requested a telecon to discuss items in the deficiency letter of August 31, 2001. Sadie Ciganek submitted a fax dated 9/10/01 listing the points for discussion.
Our deficiency letter stated:
2. Your responses regarding comments 1 & 2 in the July 17, 2001 submission are not satisfactory. Please submit the necessary data and/or literature that supports your argument that

[redacted]

the product.
The firm agreed to submit this information and revise the Components/Composition section of the ANDA. The firm also stated they had measured the [redacted] content in the finished product. They will submit the data.

DATE September 20, 2001

APPLICATION NUMBER
75-932

TELECON

INITIATED BY APPLICANT/ FDA
Eon

PRODUCT NAME
Bupropion ER Tablets, 100 and 150 mg

FIRM NAME
Eon Labs manufacturing, Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Sadie Ciganek, V.P., Regulatory Affairs and Dr. Siya Moghaddam, Dir. Analytical Research and Development

TELEPHONE NUMBER
718-276-8607 X330

SIGNATURE U.V. Venkataram
U. Venkataram
L. Tang 9/21/01
B. McNeal B. McNeal 9/21/01

CC: ANDA 75-932
Division File

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

9/20/2001 RECORD OF TCON

OGD APPROVAL ROUTING SUMMARY

ANDA # 75932 Applicant Eon

Drug Bupropion Hydrochloride Extended-Release Tablets Strength 100 mg and 150 mg

[AP]PROVAL ☐ TENTATIVE APPROVAL ☒ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:

		DRAFT RECEIPT	FINAL ACTION
1.	Project Manager Stanley Shepperson Review Support Br	Date 12/5/01 Initials [illegible]	Date 12/27/01 Initials [illegible]

Application Summary:

Original Rec'd date 7/26/00

Date Acceptable for Filing 7/27/00

Patent Certification (type) Para IV

Date Patent/Exclus.expires 8/12/13

Citizens Petition/Legal Case Yes ☐ No ☒

(If YES, attach email from PM to CP coord)

First Generic Yes ☒ No

(If YES, check PETS)

Pediatric Exclusivity Tracking System(PETS)

Date checked 12/27/01 NDA#

Nothing Submitted ☒

Written request issued ☐

Study Submitted ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐

Date of EER Status 12/10/01

Date of Office Bio Review 10/18/00

Date of Labeling Approv. Sum 8/1/01

Date of Sterility Assur. App. N/A

Methods Val. Samples Pending Yes ☐ No ☒

30 Day Clock Start ______ End ______

Commitment Rcd. from Firm Yes ☐ No

Modified-release dosage form: Yes ☒ No ☐

Previously reviewed and tentatively approved ☐ Date ______

Previously reviewed and CGMP def./N/A Minor issued ☐ Date ______

Comments:

2.	Div. Dir./Deputy Dir. Chemistry Div. I or II Comments:	Date 12/27/01 Initials [illegible]	Date 12/31/01 Initials [illegible]

CMC satisfactory.

3.	Frank Holcombe Assoc. Dir. For Chemistry Comments: (First generic drug review)	Date ______ Initials ______	Date 1/2/02 Initials [illegible]

Acceptable with 1/2/02 [illegible] satisfactory [illegible] pending withdrawal of [illegible] letter. [illegible] 1/17/02 [illegible] will [illegible] with the [illegible]

4.	Pat Beers Block Supv. Review Support Branch	Date Rec'd. 1/17/02 Initials PMB	Date 1/18/02 Initials PMB

EER Status: Acceptable for all facilities as of 12/10/01 (see [illegible])

Bioequivalence sites:

Clinical site: ______

Inspection needed: ☐ yes ☒ no

Status: ☒acceptable ☐unacceptable ☐ pending

Date of status:

Reason: Based on DSI inspection history

Analytical site: ______

Inspection needed: ☐ yes ☒ no

Status: ☒acceptable ☐unacceptable ☐pending

Date of status:

Reason: Based on DSI inspection history

Bioequivalence office level sign off: Fasting, fed (150 mg) and multiple-dose studies (150 mg) were found acceptable by DBE on 10/18/00.

Labeling Status: Acceptable for Tentative approval as of 8/1/01.

NOTE - I asked labeling group to address the "M-10"

Microbiology status: N/A

Patent Certification: Para IV (and [illegible]). Exclusivity (M+10) granted to RLD

Controlled Correspondence/Cit.Pet:

Comments: RLD = 20-358

M.V. sample analyses acceptable 2/21/01

[illegible] exclusivity. Adolph Vezza noted in his review that the issue of extended use will be referred to ORM review Division for comment [illegible]

REVIEWER: DRAFT RECEIPT FINAL ACTION

5. ~~Nasser Mahmud~~ Gregg Davis
Supv. Reg. Support Branch

Date 22-JAN-2002 Initials [initials] — Date 22-JAN-2002 Initials [initials]

Contains GDEA certification: Yes ☑ No ☐
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☑ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐
Has case been settled: Yes ☐ No ☒
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒

Determ. of Involvement? Yes ☐ No ☑
Pediatric Exclusivity System
Date Checked 22-JAN-2002
Nothing Submitted ☐
Written request issued ☒ 21-JUL-2000
Study Submitted ☐
RLD = Wellbutrin SR Tablets 100mg 150mg
Glaxo Wellcome INC.
NDA 20-358

Comments: Basis is Wellbutrin SR 20-358, pIV to '970, '798, 000, '493, '994, no exclusiv. issues, ack. 7/27/00 w/ piv Glaxo 10/18/00, sued 11/29/00 CA 00-9089 w/in 45 days - litigation still pending - 30 mos exp. 4/18/2003
M-10 exclusiv. may preclude full approval until 6/11/04 - OK for TA

6. Peter Rickman
Acting Director, DLPS

Date 1/24/02 Initials [initials] — Date 1/24/02 Initials [initials] West for

Comments: Acceptable EES dated 12/10/01 (verified 1/17/02). No OAI alerts noted. Bioequivalence studies (fasting + fed on 150mg strength, fasting on 100mg strength) found acceptable 9/21/00. Waiver granted to 100mg strength. Dissolution data acceptable. DSI inspectional history of test and analytical facilities is acceptable. Office-level bio endorsed 10/18/00. Labeling satisfactory for TA 8/1/01. - Need to address the M-10 labeling statement and associated exclusivity. CMC acceptable 12/18/01. Methods validation completed and acceptable. First generic CMC audit completed.

7. Robert L. West
Acting Deputy Director, OGD

Date 1/24/02 Initials [initials] — Date 1/24/2002 Initials Robert L West

Para.IV Patent Cert: Yes ☒ No ☐; Pending Legal Action: Yes ☒ No ☐; Petition: Yes ☐ No ☒
Comments: Eon has been sued by Glaxo Wellcome Inc. over several of the listed patents. The 30-month period expires on 4/18/03. The M-10 labeling exclusivity will also need to be addressed prior to final approval.
This application is recommended for tentative approval.

8. Gary Buehler
Acting Director, OGD
Comments:

Date 1/24/02 Initials GB — Date 1/24/02 Initials GB

First Generic ~~Approval~~ Tentative Approval ☒ for Extended-release Tablets PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

9. Project Manager
Review Support Branch Stan Shepperson

Date ______ Initials ______ — Date 1/25/02 Initials [initials]

N/A Date PETS checked for first generic drug (just prior to notification to firm)
Note: Written request issued to Glaxo Wellcome on 7/21/00. No response has been received
Applicant notification:
4:05 AM Time notified of approval by phone 4:10 AM Time approval letter faxed

FDA Notification:
1/25/02 Date e-mail message sent to "OGD approvals" account
1/25/02 Date Approval letter copied to "//cder/drugapp" directory

reports\approval\approvrou

RECORD OF TELEPHONE CONVERSATION

I called firm with U.Venkataram to request that the firm obtain USP reference standards for their bupropion products. Firms states standards are unavailable from vendor and USP. Agency requests firm to attempt again with Drug substance supplier or USP as the firm will need to run the USP tests. Sadie Ciganek and Enna Krivitsky attended the telecon. Sadie will contact the Agency regarding the outcome of their attempts. Tel amendment received 9-8-03 stating that the firm is unable to obtain USP standards. APPEARS THIS WAY ON ORIGINAL	03-SEP-03 **ANDA NUMBER** 75-932 **TELECON INITIATED BY AGENCY** **PRODUCT NAME:** Bupropion HCl ER 100 mg and 150 mg **FIRM NAME:** Eon **FIRM REPRESENTATIVES:** Sadie Ciganek Enna Krivitsky **TELEPHONE NUMBER:** **FDA REPRESENTATIVES** U.Venkataram, Ph.D. S.Shepperson, Project Manager **SIGNATURES:** S. Shepperson

Orig: ANDA 75-932
Cc: Division File
Chem. II Telecon Binder
V:\firmsam\eon\telecons\75932~~Jul~~Sep08

MEMORANDUM

Subject: Teleconference with Eon Labs
ANDA: 75932
Drug Product: Bupropion HCl EXT
Reference: Eon's minor amendment and telephone amendment dated 9/8/03

Date: 9/26/03

FDA Participants: Dr. V. Sayeed and Dr. Ubrani V. Venkataram U.V. Venkataram

Eon Representatives: E. Krivitsky, S. Siganek, P. Bhattacharyya, M. Siya 9/26/03

The firm was called by us to resolve the issue of non-availability of USP reference standards for this product and to discuss alternate pathways.

Dr. Sayeed clarified to the firm issues surrounding the non-availability of USP reference standards. The firm acknowledged that the monograph becomes official the day USP releases the standard and they will have to meet the compendial standards. However, they asked for alternatives to move the approval process forward.

One of the identified impurity occurs at a RRT of 1.7 and the firm has proposed a limit of ———. The firm said that the same impurity is observed in RLD at ——— concentrations. They argued that the sameness in RRT between generic and RLD peaks was sufficient identification for the peak. The Agency representatives did not agree to this. Many alternatives were discussed. The firm agreed:

1. to submit data to demonstrate that the peak @ RRT 1.7 in Eon's product is the same as that in RLD
2. to provide a commitment to submit data to the Agency to demonstrate that their product meets USP specifications when the reference standards become available
3. to revise the stability report to include limits for ——— (same as at release

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-932 Applicant Ean Labs
Bupropion HCl Ext. release tablets Strength 100 mg + 150 mg

APPROVAL ☒ TENTATIVE APPROVAL ☒ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐
split

REVIEWER:	DRAFT Package	FINAL Package
1. Project Manager, Stan Shepperson Review Support Br Team 8	Date 11-14-03 Initials SMS	Date Initials

Application Summary:

Original Rec'd date
Date Acceptable for Filing
Patent Certification (type) Para 4
Date Patent/Exclus.expires 8-12-2013
Citizens' Petition/Legal Case Yes ☐ No ☑
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☑
(If YES, Pediatric Exclusivity Tracking System (PETS)
RLD = Wellbutrin SR
Date checked 11-7-03 NDA# 20-358
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☐ OAI ☐
Date of EER Status
Date of Office Bio Review
Date of Labeling Approv. Sum 11-25-03
Date of Sterility Assur. App.
Methods Val. Samples Pending Yes ☐ No ☒
Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and tentatively approved ☒ Date 1-24-02
Previously reviewed and CGMP def./N/A Minor issued ☐ Date
Comments:

2. Martin Shimer Chief, Regulatory Support	**PPIII and IV ANDAs Only** Date 11/17/2003 Initials MMS	Date 11/17/2003 Initials MMS

Contains GDEA certification: Yes ☑ No ☐
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☑ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☑ No ☐
Was applicant sued w/in 45 days: Yes ☑ No ☐
Has case been settled: Yes ☐ No ☑
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☑

Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
Date Checked
Nothing Submitted ☑
Written request issued ☐
Study Submitted ☐

Comments: 30 month stay for the '798 patent exp 11/18/2003. firm was also sued on the '994 patent. However the '994 patent was subsequently delisted from the O.B.
(ANDA) was the first applicant to file PIV for all patents on the 100 mg strength. this is first to file PIV to all patents for the 150 mg strength... is entitled to 180 day for 150 mg NDA
Full approval for 150 mg 2nd TA for 150 mg

3. Div. Dir./Deputy Dir. Chemistry Div. II	Date 11/25/03 Initials	Date 11/25/03 Initials

Comments:

CMC OK

REVIEWER:	DRAFT Package	FINAL Package

4. Frank Holcombe
Assoc. Dir. For Chemistry
Comments: (First generic drug review)

Date_____ Initials_____ Date_____ Initials_____

5. Peter Rickman
Director, DLPS

Date_____ Initials_____ Date 11/24/2003 Initials [signature]

Para.IV Patent Cert: Yes☑ No☐; Pending Legal Action: Yes☐ No☐; Petition:Yes☐ No☐
Comments:

Patents '970, '798, '000, '493 = applicant made PIV - Glaxo Wellcome sued on '798 and 1994 patents. = 30 month stay expired 4/18/2003 (See Moxay's note on patent issues)
M-10 exclusivity expires 6/11/2004 - Called applicant changed exclusivity statement, will not seek pediatrics during - Submitted revised labeling with pediatric areas carved out.
OK to full approve 100 mg strength - TA for 150 mg strength
Office Level Bio acceptable 10/18/2001 (Fasting 150 mg & 100 mg non-fasting 150 mg and multidose - 150 mg)
OR Labeling acceptable 11/21/03 OK to approve 100 mg only
DER acceptable 10/12/2001 TA 150 mg

5. Robert L. West
Deputy Director, OGD

Date_____ Initials_____ Date_____ Initials_____

Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition:Yes☐ No☐
Comments:

6. Gary Buehler
Director, OGD
Comments:

Date 11/25/03 Initials GB Date 11/25/03 Initials GB

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

7. Project Manager, Stan Shepperson
Review Support Br Team 8

Date 11/25/03 Initials SMS Date_____ Initials_____

11/25/03 Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
3:45p Time notified of approval by phone 3:30p Time approval letter faxed

FDA Notification:
11/25/03 Date e-mail message sent to "CDER-OGDAPPROVALS☐ distribution list.
11/25/03 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-932

CORRESPONDENCE

Eon Labs

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

labeling review drafted 10/18/00 A. Vega

July 26, 2000

Gary J. Buehler
Acting 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

PAPER AND ELECTRONIC SUBMISSION

RE: Original ANDA
Bupropion Hydrochloride Tablets, Extended Release, 100 mg and 150 mg

Dear Mr. Buehler:

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, Extended Release, 100 mg and150 mg. In addition to submitting a hard copy of this ANDA, the application will be submitted electronically within 30 days. This application consists of the following volumes:

Volume 1	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, samples, debarment, and environmental impact statement.
Volume 4	through 16 Biostudy summary and test results including diskettes, which contain the raw data in electronic format.

A full table of content precedes each appropriately paginated volume.

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

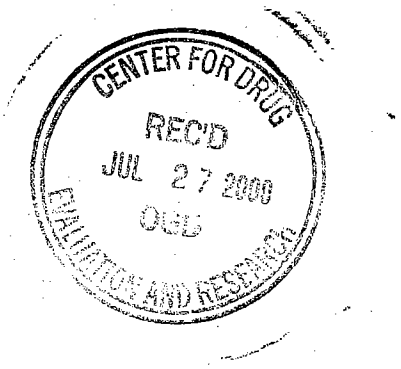
In addition to the archival and review copies, we are submitting a certified true copy of the
chemistry, manufacturing and controls data to the District Field Office, Brooklyn, New York. Subsequent amendments or supplements containing chemistry, manufacturing and controls data will also be submitted to the District Field Office.

If there are any comments or questions about this application, please contact me at (718) 276-8607, extension 330.

Sincerely,
Eon Labs Manufacturing, Inc.

Sadie M. Ciganek

Sadie M. Ciganek
Vice President Regulatory Affairs



Eon Labs

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

August 21, 2000

Gary J. Buehler
Acting Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP

NC
75-932

RE: Original ANDA – PAPER AND ELECTRONIC (BOTH CMC AND BA/BE)
Bupropion Hydrochloride Extended Release Tablets, 100 mg and 150 mg

Dear Mr. Buehler:

Enclosed are three diskettes, each submitted in duplicate, for the electronic portion of the original Abbreviated New Drug Application for Bupropion Hydrochloride Extended Release Tablets, 100 mg and 150 mg. The hard copy was submitted on July 26, 2000, and we are now submitting the electronic portion within 30 days. Included on the three diskettes are the following files:

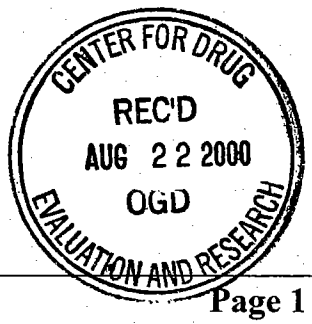
CMC Diskette:

EON0002.003 (ESD file exported from EVA)
EON 0002.004 (Companion document)
EON 0002.rtc (User verification report)
EON 0002.lgc (Log file)

Two BA/BE Diskettes (Bioassay Laboratory, Inc. bioequivalence studies, project numbers B-01059, B-04209, B-04219, and B-06269):

BA/BE Diskette # 1 (WinZipped):

EON0002.002 (Companion document)



BA/BE Diskette # 2:

EON0002.001 (main ESD file)
EON0002.lgb (Log file)
EON0002.rtb (Review file)

Also included are *in-vitro* dissolution files, clinical, analytical and pharmacokinetic files.

Please note:

1) The main BA/BE ESD file EON0002.001 shows the number of files 93, which is not correct. There are additional 12 files for the pre-study validation for the multiple dose study (the only analyte in the EVA is the threoamino-alcohol bupropion. The other three analytes and their four pre-study validation files each are not listed because of the restrictions of the program).

2) There are also the 4 adverse event files.

3) The KELM files for the multiple dose study EON0002.naj, EON0002.nak, EON0002.nal, and EON0002.nam are intentionally left empty, since there is no KELM for the study.

Please, note that the BA/BE diskette # 1 has been WinZipped and needs to be unzipped in order to open files.

Also included are declaration letters from Eon Labs Manufacturing, Inc. and ——— ——————, (the CRO for bioequivalence studies).

If there are any questions, please do not hesitate to call me at (718) 276-8607, extension 235 or email at ra@eonlabs.com. Our fax number is (718) 276-8635.

Sincerely,
Eon Labs Manufacturing, Inc.

Enna Krivitsky

Enna Krivitsky
Sr. Regulatory Affairs Associate

ANDA 75-932

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

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 the telephone conversation dated August 24, 2000 and your correspondence dated August 25, 2000.

NAME OF DRUG: Buproprion Hydrochloride Extended-release Tablets, 100 mg and 150 mg

DATE OF APPLICATION: July 26, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 27, 2000

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Nasser Mahmud, Chief, Regulatory Support Branch, at (301)827-5862.

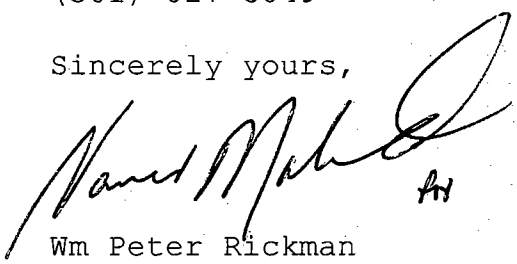
We will correspond with you further after we have had the opportunity to review the application.

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,



Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-932
DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement:
HFD-615/NMahmud, Chief, RSB _____ date 9/12/00
HFD-615/MShimer, CSO _____ date 9/12/00
Word File V:\Firmsam\Eon\Ltrs&rev\75932.PIV
FT/mjl/9/5/00
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

Eon Labs

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

12/22/00
"NAS"

NEW CORRESP
NC

December 11, 2000

Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room E150
Rockville, MD 20855-2773

- PATENT AMENDMENT -

RE: Bupropion Hydrochloride Tablets, Extended-Release, 100 mg and 150 mg
ANDA 75-932

Dear Mr. Rickman:

Reference is made to our original Abbreviated New Drug Application for Bupropion Hydrochloride Tablets, Extended-Release, 100 mg and 150 mg, ANDA 75-932. In accordance with 21 CFR 314.95(b), we certify that we have provided a Patent Certification Notice to the patent holder who is the approved NDA holder for the reference listed drug Wellbutrin SR® as defined in 21 CFR 314.95(a) and that the notice has met the content requirement under 21 CFR 314.95(c). The notice was sent to:

President
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

In accordance with 21 CFR 314.95(e), submitted herein is a copy of the return receipt from the address for which the notice was served.

If you have any further comments or questions, please contact me at (718) 276-8607, extension 404.

Sincerely,
Eon Labs Manufacturing, Inc.

Blessy Johns
Regulatory Affairs Associate

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
DEC 12 2000
OGD

MAJOR AMENDMENT

ANDA 75-932

JAN 2001

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Eon Labs Manufacturing, Inc. TEL: 718-276-8600

ATTN: Sadie M. Ciganek FAX: 718-276-8635

FROM: Bonnie McNeal PROJECT MANAGER: 301-827-5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 26, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (9 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance

SPECIAL INSTRUCTIONS:

Enclosed are CMC and labeling deficiencies and bioequivalence comments.

B. Mc
1/2/00

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

1/2/2001 FDA FAX

5. Please submit USP <671> data for the proposed container closure systems to support the labeling requirement of "store in tight containers".

6. Regarding stability:

   a. The stability protocol should specify that the smallest and largest packaging sizes are placed on stability studies.

   b. Please submit the revised stability protocol and stability data based on the above comments and comments 4.a., 4.b., 4.d. & 4.e.

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

1. Please indicate excipient functionality in the composition statement.

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

3. A satisfactory compliance evaluation for the firms referenced in the ANDA is required for approval.

Sincerely yours,

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

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

ANDA Number: **75-932** Date of Submission: **July 26, 2000**

Applicant's Name: **Eon Labs Manufacturing, Inc.**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg**

Labeling Deficiencies:

1. GENERAL COMMENTS:

   a. Please revise your storage temperature recommendations throughout your labels and labeling as follows:

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

   b. "Zyban®" and "ZYBAN®" rather than "Zyban", "ZYBAN", "Zyban™", and "ZYBAN™"

2. CONTAINER 60s, 100s, and 500s

   See GENERAL COMMENTS above.

3. PHYSICIAN INSERT

   a. GENERAL COMMENTS

      i. "in vitro" and "in vivo" (italics) throughout the insert labeling

      ii. Delete the hyphen between the number and the units when expressing a dose (e.g., "150 mg" rather than "150-mg").

      iii. Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert

      iv. Replace "Bupropion ER" with "bupropion hydrochloride extended-release tablets" throughout the insert labeling.

   b. CLINICAL PHARMACOLOGY

      i. Pharmacokinetics, seventh paragraph, last sentence

         A). "coadministered" (delete hyphen)

         B). "(see PRECAUTIONS: Drug Interactions)" (plural)

      ii. Population Subgroups

         A). The title is plural.

B). Age, last sentence - "... 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).

C). Gender - "pharmacokinetic" (singular)

c. CLINICAL TRIALS

i. The title is plural.

ii. First paragraph, third sentence - "... Clinical ..."

d. INDICATIONS AND USAGE

The title is plural.

e. WARNINGS

i. The title is plural.

ii. Paragraph beginning "Data for ...", last sentence - "conditions" (plural)

f. PRECAUTIONS

i. General

A). Allergic Reactions, add the following text as the last paragraph:

... 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.

B). Replace the ~~subsection~~ with the following sub-subsections:

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 extended-release formulation of bupropion (Zyban™ Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of extended-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 extended-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of extended-release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with extended-release bupropion, NTS, and placebo, respectively. The majority of these patients had evidence of preexisting hypertension. Three patients (1.2%) treated with the combination of Zyban and NTS and one patient (0.4%) treated with NTS had study

medication discontinued due to hypertension compared to none of the patients treated with Zyban or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

There is no clinical experience establishing the safety of bupropion hydrochloride extended-release in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Bupropion was well tolerated in depressed patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine blood pressure in the study of patients with 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 a greater extent than usual. The patient should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.

ii. Information for Patients, fourth paragraph - "seizures" (plural)

iii. Drug Interactions

A). The title is plural.

B). Second paragraph, sixth sentence - "tablets" rather than "Ttablets"

C). Drugs Metabolized By Cytochrome P450IID6 ..., second paragraph, first sentence - "coadministration" (delete hyphen)

D). Nicotine Transdermal System - Delete the text of this sub-subsection and replace with "(see PRECAUTIONS: Cardiovascular Effects)."

iv. Geriatric Use

A). Second paragraph - "... 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 PRECAUTIONS: Geriatric Use)."

B). Last sentence - Delete ": [redacted]"

g. ADVERSE REACTIONS

i. First sentence - "ADVERSE REACTIONS" (plural)

ii. Incidence in Controlled Trials With Bupropion Hydrochloride Extended-release, Adverse Events Occurring at an Incidence of 1% or More ...

A). First paragraph, last sentence - "COSTART" (spelling)

B). Second paragraph, second sentence - "judgments" (plural)

iii. Other Events Observed During the Clinical Development ...

A). Second paragraph, third sentence - "Tables" (plural)

B). Third paragraph, first sentence - "1/100" rather than "1/1000"

C). Body (General) - Add the following as the last two sentences:

... malaise. Also observed were arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness (see PRECAUTIONS).

D). Cardiovascular - ... hypotension, hypertension (in some cases severe, see PRECAUTIONS), myocardial ...

h. DRUG ABUSE AND DEPENDENCE

i. Humans

A). First paragraph - "subjects" (plural)

B). Third paragraph, first sentence - "findings" (plural)

ii. Animals, last sentence - "amphetamine-like and cocaine-like" (add hyphens)

i. OVERDOSAGE

Replace the "Management of Overdose" subsection with the following text:

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 hydrochloride extended-release, 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).

j. HOW SUPPLIED

i. See GENERAL COMMENTS (1)(a).

ii. "Dispense contents with a child-resistant closure ..." ("with" rather than "in" to be in accord with your container labels)

4. PATIENT PACKAGE INSERT

a. GENERAL COMMENTS

i. Please submit the patient package insert as a separate labeling piece as well as it currently appears in conjunction with your physician insert.

ii. How and how many PPI's will be provided with each container size?

iii. See GENERAL COMMENTS (1)(b).

iv. See comments (3)(a)(iii) and (3)(a)(iv).

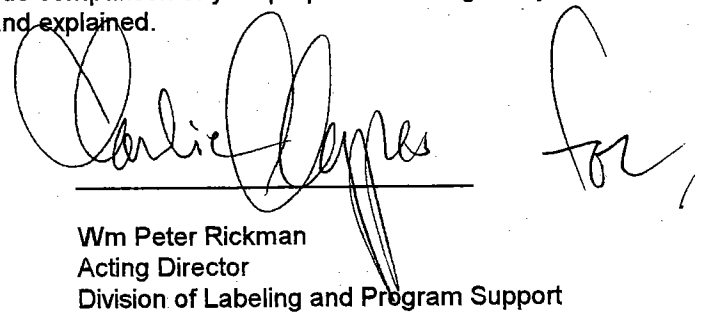
b. Item 7, penultimate paragraph - "... taking 400 mg/day gained more than 5 lbs., and 4 out of 100 people taking placebo (a sugar pill) lost more than 5 lbs."

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.



Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS

ANDA: 75-932 APPLICANT: Eon Labs

DRUG PRODUCT: Bupropion Hydrochloride ER Tablets, 150 mg & 100 mg

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

The Division of Bioequivalence acknowledges that the following dissolution testing is being incorporated into your stability and quality control programs:

> The dissolution testing is conducted in 900 mL of 0.1 N HCl, pH 1.5, at 37°C using USP24 Apparatus I(basket) at 50 rpm.

Based on the dissolution data submitted for the test product, the following **interim** specifications are recommended:

1st hour	——— %
2nd hour	——— %
4th hour	——— %
6th hour	NLT —— %

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,

Barbara Myers Saint

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

Eon Labs

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

labeling review drafted 2/5/01 9 Uzzo

January 31, 2001

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
7500 Standish Place
Metro Park North II
Rockville, MD 20857

ORIG AMENDMENT
N/AC

- MAJOR AMENDMENT -

Re: Bupropion Hydrochloride
Extended-Release Tablets, 100 mg and 150 mg
ANDA 75-932

Dear Ms. Fang:

Reference is made to your January 02, 2001 correspondence regarding our Abbreviated New Drug Application for Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg, ANDA 75-932. Enclosed herein are the responses to the deficiencies noted in your letter.

1. Regarding the composition of the drug product:

COMMENT 1

a. _____
composition statement. Please justify.

Response:

[ ]

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information from

1/31/2001 EON LETTER

Response:

We acknowledge that the firms referenced in our ANDA application must be satisfactorily in compliance at the time of approval.

Labeling Deficiencies

CONTAINER 60's, 100's, & 500's

The container labels have been revised according to your comments and we are submitting four (4) draft copies of the labels, **ATTACHMENT 9.**

PHYSICIAN PACKAGE INSERT

We have made all necessary corrections according to your comments and we are submitting four (4) draft copies of the insert, **ATTACHMENT 10.**

PATIENT PACKAGE INSERT

We have revised the Patient Package Insert (PPI) according to your comments and we are providing four (4) draft copies of the PPI, **ATTACHMENT 11.**

In regards to labeling comment 4(a)ii, we intend to distribute the PPI with the packaged product as pads of — sheets in each — of 60's and 100's, and as pads of —— sheets in each — of 500's. Each sheet will be torn off from the pad by the pharmacist and given to the patient upon dispensing.

To facilitate review of this submission, and in accordance with 21 CFR 314.94(a)(8)(iv), we are providing a side-by-side comparison of the previous submission and proposed submission with all differences highlighted and annotated, **ATTACHMENT 12.**

We hope our responses satisfactorily address the deficiencies noted in your letter. If you need further clarification or information, do not hesitate to call at (718) 276-8607, extension 404.

Sincerely,
Eon Labs Manufacturing, Inc.

Blessy Johns

Blessy Johns
Regulatory Affairs Associate

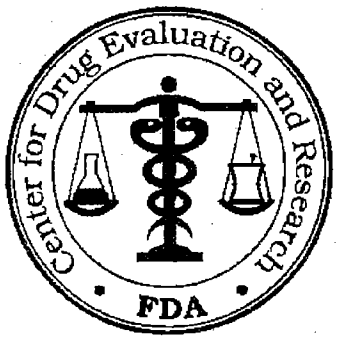
APPEARS THIS WAY
ON ORIGINAL

MINOR AMENDMENT

ANDA 75-932

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUN 28 2001



TO: APPLICANT: Eon labs Manufacturing, Inc. TEL: 718-276-8600

ATTN: Patricia A. Kaufold FAX: 718--276-8635

FROM: Bonnie McNeal PROJECT MANAGER: 301-827-5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 26, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg.

Reference is also made to your amendment dated: January 31, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (4 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Enclosed are CMC and labeling deficiencies.

6/28/01

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6/28/2001 FDA FAX

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

ANDA Number: **75-932** Date of Submission: **January 31, 2001**

Applicant's Name: **Eon Labs Manufacturing, Inc.**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg**

Labeling Deficiencies:

1. CONTAINER 100s (100 mg)

   Add "(see USP)" to the storage temperature recommendations.

2. PHYSICIAN INSERT

   a. PRECAUTIONS

      i. Cardiovascular Effects

         A). Second paragraph

            1). First sentence - "Zyban®" rather than "Zyban™"

            2). The sentence beginning "There is no ..." begins a new paragraph (the third).

         B). Third paragraph

            1). Third sentence - "... had previously developed orthostatic ..."

            2). Last sentence - "bupropion" rather than "bupropine"

      ii. Geriatric Use, last sentence - Add a period to the end of the sentence.

   b. ADVERSE REACTIONS

      Cardiovascular - "... see PRECAUTIONS), myocardial ..."

   c. DRUG ABUSE AND DEPENDENCE

      Animals, last sentence - "amphetamine-like" (add hyphen)

   d. OVERDOSAGE

      Overdosage Management

      i. Revise the subsection title as seen above.

      ii. Second sentence - "... vital signs. EEG monitoring ..."

3. PATIENT PACKAGE INSERT

Item 7

a. Paragraph beginning "For people who lost weight ..." - " ... and 6 out of 100 people taking placebo ..." rather than "- out of 100"

b. Paragraph beginning "For people who gained weight ..." - "... taking 400 mg/day gained more than 5 lbs., and 4 out of 100 people taking placebo (a sugar pill) lost more than 5 lbs."

Please revise your container labels and physician and patient package insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Eon Labs

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

July 17, 2001

labeling review drafted 7/31/01 A. Vezza

ORIG AMENDMENT
N/Am

Florence S. Fang
Director
Division of Chemistry II
Food and Drug Administration
Office of Generic Drugs, HFD-640
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

- MINOR AMENDMENT -

Re: Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg
ANDA 75-932

Dear Ms. Fang:

Reference is made to your letter dated June 28, 2001, commenting on our original Abbreviated New Drug Application for Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg, ANDA 75-932. Enclosed herein are the responses to the deficiencies noted in your letter.

CHEMISTRY DEFICIENCIES:

COMMENT 1

[redacted]

Response:

[redacted]

NDA 75-932

Redacted 4 page(s)

of trade secret and/or

confidential commercial

information from

7/17/2001 EON LETTER

COMMENT 2

PHYSICIAN INSERT

a. PRECAUTIONS

i. Cardiovascular Effects

A). Second Paragraph

1). First sentence - "Zyban®" rather than "Zyban™"

2). The sentence beginning "There is no..." begins a new paragraph (the third).

B). Third Paragraph

1). Third sentence - "... had previously developed orthostatic..."

2). Last sentence – "bupropion" rather than "bupropione"

ii. Generic Use, last sentence – Add a period to the end of the sentence.

b. ADVERSE REACTIONS

Cardiovascular – "... see PRECAUTIONS), myocardial..."

c. DRUG ABUSE AND DEPENDENCE

Animals, last sentence – "amphetamine-like" (add hyphen)

d. OVERDOSAGE

Overdosage Management

i. Revise the subsection title as seen above.

ii. Second sentence – "... vital signs, EEG monitoring..."

3. PATIENT PACKAGE INSERT

Item 7

a. **Paragraph beginning "For people who lost weight ..." – "... and 6 out of 100 people taking placebo ..." rather than '– out of 100"**

b. **Paragraph beginning "For people who gained weight ..." – "... taking 400 mg/day gained more than 5 lbs., and 4 out of 100 people taking placebo (a sugar pill) lost more than 5 lbs."**

Response:

The container and insert label changes have been revised according to your comments. Four copies of the draft labeling are provided, **ATTACHMENT 6**, along a side-by-side comparison with table of annotations, **ATTACHMENT 7**.

If there is any questions or if additional information or clarification is required, please contact me at (718) 276-8607, extension 235.

Sincerely,
Eon Labs Manufacturing, Inc.

Enna Krivitsky

Enna Krivitsky
Sr. Regulatory Affairs Associate

MINOR AMENDMENT

ANDA 75-932

AUG 31 2001

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Eon Labs Manufacturing, Inc. TEL: 718-276-8600

ATTN: Sadie M. Ciganek FAX: 718-276-~~8835~~ 8635

FROM: Bonnie McNeal PROJECT MANAGER: 301-827-5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 26, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg.

Reference is also made to your amendment dated: July 17, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Enclosed are CMC deficiencies only.

B. McNeal
8/31/01

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information from

8/31/2001 FDA FAX

5. Your response regarding the specification of any [redacted]. Please revise accordingly.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

Eon Labs

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

October 2, 2001

Florence S. Fang
Director
Division of Chemistry II
Food and Drug Administration
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

ORIG AMENDMENT
N/AM
- MINOR AMENDMENT -

Re: ANDA 75-932
Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg

Dear Ms. Fang,

Reference is made to your deficiency letter dated August 31, 2001, commenting on our original Abbreviated New Drug Application for Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg, ANDA 75-932. Enclosed herein are the responses to the deficiencies noted in your letter.

COMMENT 1

[redacted]

Response:

[redacted]

s is also provided for your review, **ATTACHMENT 1.**

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information from

10/2/2001 EON LETTER

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

November 13, 2001

Florence S. Fang
Director
Division of Chemistry II
Food and Drug Administration
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

ORIG AMENDMENT
N/AM

- TELEPHONE AMENDMENT -

Re: ANDA 75-932
Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg

Dear Ms. Fang,

Reference is made to the telephone call on November 13, 2001 from Mr. Stanley Shepardson of FDA to Ms. Sadie Ciganek of Eon commenting on our original Abbreviated New Drug Application for Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg, ANDA 75-932. Enclosed herein are the blank stability summary reports for Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg revised to include the updated specifications for ——————— **ATTACHMENT 1**.

If there are any questions or if additional information or clarification is required, please contact me at (718) 276-8607, extension 235.

Very truly yours,
Eon Labs Manufacturing, Inc.

Enna Krivitsky

Enna Krivitsky
Manager, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
NOV 14 2001
DDD

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

December 5, 2001

Stanley Sheperdson
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NC

NEW CORRESP

-General Correspondence-

Re: Bupropion Hydrochloride Tablets, Extended-Release, 100 mg and 150 mg
ANDA 75-932

Dear Mr. Sheperdson;

Reference is made to your telephone call of December 5th, 2001 requesting the current patent status for Bupropion Hydrochloride, Tablets, Extended-Release, 100 mg and 150 mg, ANDA 75-932.

Please be advised that legal action has been brought against our firm by Glaxo Wellcome Inc. for patent infringement after notification of a **PARAGRAPH IV** certification and that Eon Labs is currently in the process of defending the law suit. The suit was filed in the United States District Court - Southern District of New York, 00 Civ 9089.

If there are any further questions, do not hesitate to let me know.

Sincerely,
Eon Labs Manufacturing, inc.

Sadie M. Ciganek
Vice President Regulatory Affairs

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

January 2, 2002

Mr. Frank Holcombe
Associate Director for Chemistry
Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

- GENERAL CORRESPONDANCE-

Re: Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg
ANDA 75-932

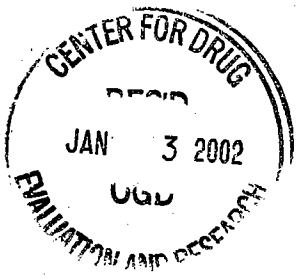
Dear Mr. Holcombe;

Reference is made to our Abbreviated New Drug Application for Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg, **ANDA 75-932.** Pursuant to our Minor Amendment dated October 2, 2001 which provided for an upgrade to the ——— system (———), we are withdrawing the new ——— information at this time and will maintain the ——— system filed in the original application until sufficient data is available for Eon Labs to make the change.

If further information is required to complete your review, do not hesitate to let me know.

Sincerely,
Eon Labs Manufacturing, Inc.

Sadie M. Ciganek
Vice President Regulatory Affairs



75932

Eon Labs

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

April 17, 2002

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NAI
PMP
4/29/02

GLOBAL SUPPLEMENT – CHANGES BEING EFFECTED (0 DAY)

RE: CORPORATE NAME CHANGE

Dear Mr. Buehler:

Submitted herein is a Global Supplement – Changes Being Effected (0 day) to change our corporate name from "EON LABS MANUFACTURING, INC" to "EON LABS, INC". This change has been filed and approved in Delaware, the state of incorporation. The relevant correspondence is included.

This supplemental application is to be considered a part of a global review affecting all our currently approved and pending applications. A list of these applications is provided in **ATTACHMENT 1.**

If you have any questions or need additional information, please do not hesitate to contact me at (718) 276-8607 ext. 370.

Sincerely,
Eon Labs, Inc.

Annie Lyubchenko
Regulatory Affairs Associate

RECEIVED
APR 19 2002
OGD / CDER

Eon Labs
The Pharmacy Drug Company

Eon Labs, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 276-1735

February 20, 2003

Mr. Gregory Davis
Branch Chief, HFD-615
Regulatory Support Branch
Office of Generic Drugs
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

NC
1 M.P 4/11/03
Patent Summary
+ Copy of Civil action.

- GENERAL CORRESPONDENCE -

RE: BUPROPION HYDROCHLORIDE TABLETS, EXTENDED-RELEASE, 100 MG AND 150 MG ANDA 75-932

Dear Mr. Davis:

Reference is made to your telephone conversation on February 14, 2003, with Ms. Sadie Ciganek, Vice President of Eon Labs, commenting on our original Abbreviated New Drug Application for Bupropion Hydrochloride Tablets, Extended-Release, 100 mg and 150 mg, ANDA 75-932.

Pursuant to your request, submitted herein is a copy of the complaint brought against Eon Labs, Inc. by Glaxo Wellcome, Inc. in the United States District Court - Southern District of New York, Case Number 00 CIV. 9089 for patent infringement of the following **US Patents:**

No. 5,427,798
No. 5,358,970
No. 5,763,493
No. 5,731,000
No. RE33994.

However, **US Patent No. RE33994** was recently deleted from the "Orange Book". Accordingly, Eon Labs submitted a Patent Amendment on February 19, 2003, withdrawing the patent certification for this patent.

If you require additional information regarding the on-going patent litigation, please contact me at (718) 276-8607 extension 235.

Sincerely,

Enna Krivitsky
Enna Krivitsky
Manager, Regulatory Affairs

Eon Labs
The Pharmacy Drug Company

Eon Labs, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 276-1735

NEW CORRESP

NC

4/4/03 pmt summary & civil action.

March 19, 2003

Mr. Gregory Davis
Branch Chief, HFD-615
Regulatory Support Branch
Office of Generic Drugs
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

- GENERAL CORRESPONDENCE -

RE: BUPROPION HYDROCHLORIDE TABLETS, EXTENDED-RELEASE, 100 MG AND 150 MG ANDA 75-932

Dear Mr. Davis:

Reference is made to our telephone conversation on March 17, 2003, commenting on our original Abbreviated New Drug Application for Bupropion Hydrochloride Tablets, Extended-Release, 100 mg and 150 mg, ANDA 75-932. Pursuant to your request, submitted herein is a brief summary as to the status of the bupropion hydrochloride ER patent litigation, Glaxo v. Eon, 00 CIV. 9089 (S.D.N.Y.).

Glaxo alleges Eon's filing of its ANDA for 100 and 150 mg generic bupropion hydrochloride ER tablets infringes U.S. Patent Nos. **5,427,798** (**"798 patent"**) and **RE 33,994** (**"994 patent"**). More specifically, concerning the **'994 patent**, the District Court granted Eon's motion for summary judgment and thereby rendered the **'994 patent** invalid. Glaxo appealed that decision, but later withdrew the appeal. Eon also alleged that the **'994 patent** is improperly listed. A recent check of the on-line Orange Book reveals that the **'994 patent** is no longer listed for the 100 mg, 150 mg, and 200 mg (recently introduced once daily) dosages. Accordingly, Eon Labs submitted a **Patent Amendment** on February 19, 2003, withdrawing the patent certification for this patent.

Concerning the **'798 patent**, Eon filed two summary judgment motions of invalidity and a summary judgment motion of non-infringement, all of which are fully briefed. The Court has not yet rendered any decisions on the summary judgment motions of invalidity. The Court denied Eon's summary judgment motion of non-infringement, finding that a question of fact existed that must be determined at trial.

Eon demanded attorneys' fees -- an issue that (by Court ordered Stipulation) will be addressed after the Court resolves all matters in this case or otherwise directs.

If you require additional information regarding the on-going patent litigation, please contact me at (718) 276-8607 extension 235.

Sincerely,

Enna Krivitsky

Enna Krivitsky
Manager, Regulatory Affairs

RECEIVED
MAR 2 0 2003
OGD / CDER

Eon Labs
The Pharmacy Drug Company

Eon Labs, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 276-1735

July 2, 2003

ORIG AMENDMENT
N/Am

Mr. Gary J. Buehler
Director, HFD-600
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT – FINAL APPROVAL REQUESTED

Re: Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg
ANDA # 75-932

Dear Mr. Buehler:

Reference is made to your letter dated January 24, 2002 granting **tentative approval** for Eon Labs' Abbreviated New Drug Application for Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg, **ANDA # 75-932**. Submitted herein is a **MINOR AMENDMENT – FINAL APPROVAL REQUESTED** providing updated chemistry and manufacturing control information in accordance with the provisions outlined in your letter.

The request for final approval is being made pursuant to the expiration of the 30 month stay (April 18th, 2003) that had been granted to the application under the requirements of section 505 (j) (5) (B) (iii) for an applicant that files a paragraph IV certification. A comprehensive summary relevant to the status of the on-going patent litigation between Eon Labs and the NDA holder, Glaxo-Wellcome, Inc., has been submitted to FDA in the **General Correspondence** dated March 19, 2003.

In support of our ANDA approval, we are providing updated chemistry and manufacturing control information for those records that have changed from the time the application was tentatively approved on January 24th, 2002.

CHEMISTRY AND MANUFACTURING CONTROL INFORMATION

1. The **Raw Material Specification and Analysis Report** forms for the following active and inactive ingredients have been updated to USP 26-NF 21, **ATTACHMENT 1:**

   - Bupropion Hydrochloride (Effective Date 04/01/03)
   - Microcrystalline Cellulose, NF (Effective Date 04/17/03)
   - Hydroxypropyl Cellulose (_____), NF (Effective Date 04/07/03)

RECEIVED
JUL 03 2003
OGD/CDER

NW 7-7-03

- Hydroxypropyl Cellulose (———), NF (Effective Date 04/07/03)
- ——————— (Effective Date 04/07/03)
- ——————— (Effective Date 01/01/03)
- Carnauba Wax, NF (Effective Date 01/02/03)
- Magnesium Stearate, NF (Effective Date 01/23/03)
- Opadry Blue (——— (Effective Date 01/01/03)
- ——————— (Effective Date 01/01/03)

2. Inadvertently the revised (Effective Date 08/31/01) analytical test method, **B-46, Testing of Bupropion Hydrochloride Raw Material** has not been submitted to FDA before tentative approval. The method has been revised to correct typographical errors and submitted for your review, **ATTACHMENT 2.**

3. [ ]

4. The master **Formulation Manufacturing Records** for Bupropion Hydrochloride ER Tablets, 100 mg and 150 mg have been updated with editorial changes, (Effective Date 01/03/03 and 02/13/03, respectively), **ATTACHMENT 4.**

USP 26 TEST METHODS AND SPECIFICATIONS

Eon Labs acknowledges the recently published monographs for bupropion hydrochloride, active pharmaceutical ingredient (API), and for Bupropion Hydrochloride Tablets, Extended-release in USP26/NF21. However, Eon Labs was not able to perform the compendial testing for related compounds, as described in the USP, due to the unavailability of reference standards. The USP was not able to provide any time frame as to when these standards would become available. Therefore, in accordance with current USP policies:

> *"The requirements for any new USP or NF standards, tests, or assays for which a new USP Reference Standard is specified are not in effect until the specified USP Reference Standard is available",*

Eon Labs will continue to apply its currently approved test method and specifications for Bupropion Hydrochloride Tablets, Extended-release at this time. We will commit, however, to performing a cross-over study between the official USP monograph and our in-house test method once reference standards for the impurities become available.

It should be noted that the API manufacturer, ——— independently contacted the USP regarding the same issue: availability of reference standards. The USP confirmed in a written communication to ———that not only were reference standards not available at

this time, but there were going to be further monograph changes which were expected to be published in the next PF - the extent of the changes were not disclosed. [redacted] concluded that because of the lack of reference standards and the uncertainty of the monograph changes for the API and finished product, the current USP methods and specifications for bupropion hydrochloride could not be applied at this time. A copy of the communications between [redacted] and the USP are provided, **ATTACHMENT 5.**

LABELING

Following tentative approval of the application on January 24th, 2002 Eon Labs has received multiple updates of Bupropion Hydrochloride ER Tablets, 100 mg and 150 mg labels and labeling dated October 8, 2002, October 9, 2002, and October 11, 2002. We have made all necessary revisions in accordance with the most recently approved labeling for the reference listed drug Wellbutrin SR®.

Submitted herein are twelve (12) copies each of final printed label text for the container label, package insert, and patient package information leaflet, **ATTACHMENT 6.** A side-by-side comparison of the final printed labeling versus the previously submitted version with a table of annotation is provided, **ATTACHMENT 7**. The 60 count of the 150 mg strength was used as the representative label for the side-by-side comparison.

All other chemistry, manufacturing and controls information remain the same as tentatively approved in the ANDA on January 24, 2002.

STABILITY

In addition to the changes submitted above, we are also submitting the most current thirty six (36) months CRT stability data for the finished product, **ATTACHMENT 8**.

With regards to the analytical methods validation studies performed by the FDA District Laboratory, Eon Labs commits to addressing any deficiencies found by the District Laboratory post approval.

We hope that the information provided is satisfactory to approve our Abbreviated New Drug Application for Bupropion Hydrochloride Tablets, 100 mg, and 150 mg. If you require further information or clarification, please feel free to contact me at (718) 276-8607, extension 235.

Sincerely,
Eon Labs, Inc.

Enna Krivitsky

Enna Krivitsky
Manager, Regulatory Affairs

Eon Labs
The Pharmacy Drug Company

Eon Labs, Inc.
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Telephone 718 276-8600
Fax 718 276-1735

September 8, 2003

ORIG AMENDMENT

N/Am

Stanley Shepperson, Pharm. D.
Project Manager
Division of Chemistry II, HFD-640
Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Document Control Room
7500 Standish Place, Room 150
Rockville, MD 20855-2773

-TELEPHONE AMENDMENT-

Re: Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg
ANDA # 75-932

Dear Dr. Shepperson:

Reference is made to our telephone conversation on September 3, 2003 regarding Eon Labs' Abbreviated New Drug Application for Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg, **ANDA # 75-932,** and to our **Minor Amendment – Final Approval Requested** dated July 2, 2003.

The agency has requested that Eon Labs perform testing of the bupropion hydrochloride, API and finished product according to the most current USP 26 monograph, specifically with regards to impurity testing.

At the time of filing our **Minor Amendment – Final Approval Requested** dated July 2, 2003, Eon Labs advised the agency that the USP impurity standards were not available. Eon Labs could not perform the compendial tests, which required the standards. In the USP 26, General Notices, USP Reference Standards section, page 5, the following requirement is clearly stated:

"*The requirements for any new USP or NF standards, tests, or assays for which a new USP Reference Standard is specified are not in effect until the specified USP Reference Standard is available".*

As a result, we requested final approval of our application based on the validated methods and specifications described in Eon's in-house Product Monograph filed in the original application.

In response to your query, Eon Labs has made another attempt to obtain the bupropion USP impurity standards. Dr. P. Bhattacharyya, Vice President Quality Management at Eon contacted Dr. V. Feyns, Director, Reference Standards Evaluation for the USP on September 4, 2003. Dr. Feyns confirmed that bupropion impurity standards were still not available at this time, nor was he aware as to when they might be supplied to the USP. As previously

stated, Eon Labs cannot test bupropion hydrochloride, API or the finished product according to the USP monographs without the required reference standards.

Eon Labs is requesting **FINAL APPROVAL** of its ANDA for Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg, **ANDA # 75-932,** based on the in-house methods and specifications filed in the original application. The FDA has always considered the USP to be the official standard for the pharmaceutical industry. Therefore, it stands to reason that the FDA must also accept USP's policy on this matter as outlined above in the quoted statement from the USP 26. To do otherwise would create conflicts within the industry that could potentially be used for the purpose of gaining unfair advantages.

Please review our **Telephone Amendment** at the earliest. If you have any questions, or require further information, do not hesitate to let me know. I can be reached at (718) 276-8607 x 235.

Sincerely
Eon Labs, Inc.

Enna Krivitsky

Enna Krivitsky
Manager, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Eon Labs
The Pharmacy Drug Company

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October 8, 2003

Stanley Shepperson, Pharm. D.
Project Manager
Division of Chemistry II, HFD-640
Office of Generic Drugs
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Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N|Am

- TELEPHONE AMENDMENT -

Re: Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg
ANDA # 75-932

Dear Dr. Shepperson:

Reference is made to the recent conference call on September 26th, 2003 between the FDA, Division of Chemistry II, and Eon Labs, Inc. regarding the Abbreviated New Drug Application for Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg, **ANDA # 75-932**.

Submitted herein is a **TELEPHONE AMENDMENT** addressing FDA's comments regarding implementation of the current USP monograph, availability of USP reference standards for the related compounds (RC), and identity of a related compound at relative retention time (RRT) of —

The following are our responses:

***1. Application of the USP Monograph and Availability of RC Reference Standards*:**

As stated in the two previous ANDA amendments dated September 8, 2003 and July 2, 2003, the USP reference standards for the related compound are still not available. Eon has attempted to obtain these standards on several occasions but without success. Furthermore, the USP has no knowledge as to when these standards may become available. Without the related compounds standards, it is not possible to apply the USP methods and specifications.

As agreed during the conference call, Eon Labs commits to adopting the USP method and specifications once the reference standards become available, or Eon Labs will perform a cross over study with our in-house method demonstrating that the two methods are equivalent and provide comparable results. Until that time, we are seeking final approval with the current method filed in the ANDA application.

2. Identity of the Related Compound:

Regarding the identity of the related compound at the RRT of —, Eon provided data in **MAJOR AMENDMENT** dated January 31, 2001, which showed that this related compound was present in both brand's and Eon's products at accelerated stability conditions. This data is provided again to facilitate your review, **ATTACHMENT 1**. It was demonstrated that the related compound at RRT of — was [redacted] in the brand product than in Eon's product.

Following the conference call on September 26th, 2003, Eon conducted additional laboratory studies, **ATTACHMENT 2**. From these studies the related compound at the RRT of — was shown to be Bupropion related compound F.

Hopefully this will resolve the issue regarding the identity of the related compound at the RRT of — Please review our request at the earliest and do not hesitate to call if you require additional information

Sincerely,

Enna Krivitsky

Enna Krivitsky
Manager, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

4-1

********** -COMM. JOURNAL- ********** DATE OCT-23-2003 ***** TIME 14:28 *********

MODE = MEMORY TRANSMISSION START=OCT-23 14:24 END=OCT-23 14:28

FILE NO.=559

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
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U.S. Department of Health and Human Services
Food and Drug Administration

{PRIVATE}

Fax Cover Sheet

Public Health Service
Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling & Program Support
Labeling Review Branch
Rockville, Maryland 20855

To: Enna Krivitsky **DATE:** **October 23, 2003**
Fax: **718-276-1735** **Phone:** 718-276-8600

SUBJECT: ANDA 75-932

From: Melaine Shin, R.Ph., Labeling Reviewer

Phone: (301) 594-1894 **Fax:** (301) 594-1174

Number of Pages:
(Including Cover Sheet)

Comments: Please send me a desk copy of your submission responding to this letter.

C,SS RS

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

ANDA Number: **75-932** Date of Submission: **July 2, 2003**

Applicant's Name: **Eon Labs Manufacturing, Inc.**

Established Name: **Bupropion Hydrochloride Extended-release Tablets, 100 mg and 150 mg**

Labeling Deficiencies:

- **GENERAL**

  a. You noted in your submission that all necessary revisions were made in accordance with the most recently approved labeling for the reference listed drug Wellbutrin SR, however, it appears that the most current labeling of Wellbutrin SR® approved October 22, 2002 was not used as a model. Please revise your labeling accordingly.

  b. Please revise your storage temperature statement as follows:

  "Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Store in a dry place and dispense in a child-resistant closure in a tight, light-resistant container as defined in the USP"

  c. For your larger package sizes, please describe how you plan to provide patient information sheets to the patients and indicate how many will be provided with each container size.

  d. Please note that USAN (United States Adopted Names) names (i.e., bupropion hydrochloride extended-release tablets) are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert.

- **CONTAINER:** 60s, 100s, and 500s (100 mg & 150 mg)

  a. See comment (b) under **GENERAL**

  b. Delete "This is a bulk package"

- **PHYSICIAN INSERT**

  1. CLINICAL PHARMACOLOGY

     a. Hepatic

     Please make the following revisions to the second paragraph starting with "The second study showed..... (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION)"

OLD	New
The mean AUC increased by — for hydroxybupropion and — for threo/erythrohydrobupropion.	Change — to "about 1 ½ -fold" Change — to "about 2 ½ -fold"
The median..... and — hours later for threo/erythrohydrobupropion.	Change — hours to "31 hours"

The mean half-lives... [redacted] ... administration). Change [redacted] to "5- and 2-fold"

2. CONTRAINDICATIONS

Add the following statement to the end of the third paragraph starting with, "Bupropion hydrochloride ..... immediate-release formulation of bupropion."

"Bupropion hydrochloride extended-release tablets are contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines)."

3. WARNINGS

a. To the end of the second paragraph starting with "Seizures: Bupropion ..... for therapy with Bupropion hydrochloride extended-release tablets.", add the following sentence.

"Bupropion hydrochloride extended-release tablets should be discontinued and not restarted in patients who experience a seizure while on treatment."

b. Revise the "• Clinical Situations" section as follows:

"Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives (including benzodiazepines); addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin.

c. Revise the "• Concomitant medication" section as follows:

"Many medications (e.g., antipsychotics, antidepressants, theophylline, systemic steroids) are known to lower seizure threshold."

d. Under "• Bupropion Hydrochloride extended-release should be administered...seizure threshold." section, delete the following sentence:

[redacted]

4. PRECAUTIONS

a. "Information for Patients" subsection

i. Add the following sentence next to "As dose is increased during ..... minimize the risk of seizures."

"Patients should be told that bupropion hydrochloride extended-release tablets should be discontinued and not restarted if they experience a seizure while on treatment."

ii. Replace the following statement as follows:

Old	New
[redacted]	Patients should be told that the excessive use or abrupt discontinuation of alcohol or sedatives (including benzodiazepines) may alter the seizure threshold. Some patients have reported lower alcohol tolerance during treatment with bupropion hydrochloride extended-release tablets. Patients should be advised that the consumption of alcohol should be minimized or avoided.

b. Replace the following subsection as follows:

Old	New
[redacted]	**Levodopa and Amantadine:** Limited clinical data suggest a higher incidence of adverse experiences in patients receiving bupropion Concurrently with either levodopa or amantadine Administration of bupropion hydrochloride extended-release tablets to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, using small Initial doses and gradual dose increases.

c. Under "Drugs that Lower Seizure Threshold" subsection, please delete the following sentence:

"[redacted]

5. ADVERSE REACTIONS

a. Under "Hemic and Lymphatic" section, add the following sentence at the end:

"Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.

b. Under "Nervous Systems" section, add term "hallucinations".

6. DOSAGE AND ADMINISTRATION

Under "General Dosing Considerations" section, add the following sentence to the end of the paragraph:

"Bupropion hydrochloride extended-release tablets should be swallowed whole and not crushed, divided, or chewed."

7. HOW SUPPLIED

See comment (b) under **GENERAL**

- **PATIENT PACKAGE INSERT**

Please revise the patient package insert to be the same as the attached reference listed drug's patient package insert, approved October 22, 2002. Replace Wellbutrin SR by "Bupropion hydrochloride extended-release tablets"

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

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes.

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment

APPEARS THIS WAY
ON ORIGINAL

Eon Labs

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
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October 27, 2003

Melaine Shin, R.Ph.
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Food and Drug Administration
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7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF

FPL

- LABELING AMENDMENT -

Re: Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg
ANDA # 75-932

Dear Ms. Shin;

Reference is made to our recent conference call on October 24th, 2003 and to the labeling deficiency letter received on October 23rd, 2003 regarding the Abbreviated New Drug Application for Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg, **ANDA # 75-932**. The deficiency letter requested Eon Labs to make changes to the container label (as per the new USP definition of Controlled Room Temperature of 20 – 25°C), and to the package insert and patient package information (PPI) leaflet in accordance with the currently approved labeling of the reference listed drug, Wellbutrin® Tablets.

As discussed in our conference call, Eon Labs has completed the packaging and labeling of its validation batches in anticipation of the marketing launch of the drug product. The container labels bear the old USP storage legend of 15 – 30°C. Changing container labels at this time would be a burdensome task in that the product would have to be manually re-bulked (over ——— bottles) then re-packaged and re-labeled in new bottles. As agreed by the agency, we will launch the product with the present container labels and will commit to making the changes specified in the deficiency letter at the time of next reprint. Final Printed Labels (FPLs) incorporating the changes will be submitted post approval in a ***Special Supplement – Changes Being Effected - 0 Day***.

With regards to the Package Insert and the PPI leaflet, submitted herein is a **LABELING AMENDMENT** with twelve copies each of FPL incorporating the changes you requested. Also included is a side-by-side comparison to the previously submitted version appropriately highlighted and annotated. Please note that the USP storage legend of the insert was not changed at this time to remain consistent with that on the container label. As per the above commitment, the storage legend of the package insert will be amended at the same time as the container label and will be submitted together in the same supplement.

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OCT 28 2003
OGD/CDER

In response to your general comment c. regarding the PPI leaflets, they will be printed in pads of 20 sheets each. The appropriate number of pads will be supplied with each shipping carton depending on the bottle count and the number of bottles per carton as per the following:

1 PAD = 20 sheets

Dosage strength	60 count (12 btles/carton)	100 count (12 btles/carton)	500 count 12 btles/carton	500 count 6 btles/carton
100 mg	1 pad	1 pad	5 pads	--
150 mg	1 pad	1pad	--	3 pads

The sheets will be provided to the patient by the pharmacist at the time of dispensing.

Please review our labeling amendment at the earliest and if any changes are required, do not hesitate to let me know. We intend to order commercial quantities in the immediate future. Thank you for your attention to this matter.

Sincerely;
Eon Labs, Inc.

Sadie M. Ciganek
Vice President Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Eon Labs

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
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November 3, 2003

Ms. Melaine Shin
Labeling Reviewer
Room E-124
Division of Labeling and Program Support
Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF

- LABELING AMENDMENT –

Re: Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg
ANDA #75-932

Dear Ms. Shin:

Reference is made to our recent conversation of October 31, 2003 regarding Eon Labs' Abbreviated New Drug Application for Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg, **ANDA #75-932**. As requested, additional changes have been made to the Patient Package Information (PPI) leaflet in accordance with the latest approved brand PPI labeling of October 2002.

Submitted herein are twelve copies of Final Printed Labeling (FPL) for the PPI leaflet, together with a side-by-side comparison properly annotated and highlighted to reflect the changes. FPL container labels and inserts were previously submitted in a **LABELING AMENDMENT** dated October 27, 2003.

Please note that the side-by-side comparison of the PPI was performed against the brand label text and **NOT** Eon's previously submitted version as required by the 21 CFR. This was done to expedite the labeling review since the changes made were based directly on the brand labeling and not Eon's previously submitted version. We hope this is acceptable.

If you require further labeling information to complete review of the application, do not hesitate to let me know. I can be reached at (718) 276-8607 x330.

Thank you for your attention to this matter.

Sincerely,
Eon Labs, Inc.

Sadie M. Ciganek
Vice President, Regulatory Affairs

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OGD/CDER

Eon Labs
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November 7, 2003

ORIG AMENDMENT
N/AF

Ms. Melaine Shin
Labeling Reviewer
Room E-124
Division of Labeling and Program Support
Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
7500 Standish Place
Rockville, MD 20855-2773

-LABELING AMENDMENT-

Re: Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg
ANDA # 75-932

Dear Ms. Shin;

Reference is made to our telephone conversation of November 6, 2003 regarding Eon Labs' Abbreviated New Drug Application for Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg, **ANDA # 75-932.** Pursuant to the discussion, Eon Labs intends to introduce only the 100 mg dosage strength to the market place following final approval by the FDA. We will not launch the 150 mg dosage strength until any and all exclusivities have either expired or are no longer valid.

Accordingly, we have amended the insert labeling to remove references to the 150 mg dosage strength in the "Product Description" and "How Supplied" sections. No other changes to the insert labeling were made. With regards to the patient package information (PPI) leaflet, no revision was necessary since neither the 100 mg nor 150 mg dosage strengths were specifically mentioned in the leaflet. Therefore, the last version of the PPI submitted in the November 3rd 2003 **LABELING AMENDMENT** remains in effect.

Submitted herein are twelve (12) copies of Final Printed Labeling (FPL) for the insert labeling with a side-by-side comparison to the previously submitted version to expedite your review. Also submitted is FPL for the PPI leaflets, a duplicate of what was submitted in the November 3rd **LABELING AMENDMENT**. Please be reminded that the container labels for the launch of the 100 mg dosage strength will bear the "old " USP controlled room temperature storage description and that revised container labels with the "new" USP storage legend will be filed post approval in a **Special Supplement – Changes Being Effected – 0 Day** immediately following the launch.

Please review the above and if further information is required to approve this labeling amendment, do not hesitate to let me know. I can be reached at (718) 276-8607 x330.

Thank you for your attention to this matter.

Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs

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Eon Labs
The Pharmacy Drug Company

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227-15 N. Conduit Avenue
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Telephone 718 276-8600
Fax 718 276-1735

ORIG AMENDMENT
N/AF

November 20, 2003

FPL

Mr. Peter Rickman
Director of Labeling and Program Support - Room HFD 610
Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
7500 Standish Place
Rockville, MD 20855-2773

-LABELING AMENDMENT-

Re: Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg
ANDA # 75-932

Dear Mr. Rickman;

Pursuant to my recent conversation on November 20, 2003 with Mr. Peter Richman, FDA's Director of Labeling and Program Support, submitted herein is a **LABELING AMENDMENT** for Bupropion Hydrochloride Extended-Release Tablets, 100 mg and 150 mg, **ANDA 75-932**.

The insert was revised to remove all protected information covered by the M-10 exclusivity for Wellbutrin® SR. The M-10 exclusivity, due to expire on June 11, 2004, provides for information relating to maintenance of an antidepressant for up to one year. Eon Labs certifies that it will not market its Bupropion Hydrochloride Extended-Release Tablets or include in its insert labeling any information relative to the M-10 exclusivity until such time as the exclusivity either expires or is no longer valid.

Submitted herein are twelve (12) copies of final printed labeling (FPL) together with a side-by-side comparison to the previously submitted version appropriately highlighted and annotated with the differences. A summary table of the differences is also provided. Since multiple versions of the insert labeling have already been submitted to the application in the recent weeks, we are re-confirming that the final version submitted in this amendment reflects the following:

1). The insert labeling is for the 100 mg dosage strength only. The 150 mg dosage strength will not be added until the FDA grants final approval for this strength and/or the "180 day" exclusivity for the first-to-file applicant has expired.

2). The current storage legend on both the insert and the container label reflects the old USP definition of CRT. It will be amended to the new USP definition immediately following Eon Labs initial market launch. Revised container labels and inserts will be filed in a "Special Supplement-CBE (0 Day)" once they become available.

If you require additional information to approve the labeling, do not hesitate to let me know. I can be reached at (718) 276-8607 x330. Thank you for your attention to this matter.

Sincerely,
Eon Labs, Inc.
Sadie M. Ciganek
Sadie M. Ciganek
Vice President Regulatory Affairs

RECEIVED
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OGD/CDER