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

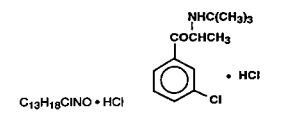
LABELING

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).