CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-913/ S-001, S-002, S-003

Name: Bupropion Hydrochloride Extended-release Tablets USP, 100 mg and 150 mg (Twice-A-Day Dosing)

Sponsor: IMPAX Laboratories, Inc.

Approval Date: March 22, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-913/ S-001, S-002, S-003

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ANDA 75-913/ S-001, S-002, S-003

APPROVAL LETTER

ANDA 75-913/S-001; S-002; S-003

MAR 22 2004

IMPAX Laboratories, Inc.
Attention: Mark C. Shaw
30831 Huntwood Avenue
Hayward, CA 94544

Dear Sir:

This is in reference to your supplemental abbreviated new drug applications dated January 29, 2004, submitted under Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), regarding your abbreviated new drug application (ANDA) for Bupropion Hydrochloride Extended-release Tablets USP, 100 mg and 150 mg (Twice-A-Day Dosing).

Reference is made to your amendments dated February 20, and March 2, 2004, and to your correspondence dated March 19, 2004. Reference is also made to our letter dated January 28, 2004, granting final approval to your Bupropion Hydrochloride Extended-release Tablets USP, 100 mg, and designating your Bupropion Hydrochloride Extended-release Tablets USP, 150 mg, as tentatively approved.

The supplemental applications provide for:

S-001: A change in the desiccant used in the container/closure system for the 100 mg tablet strength;

S-002: A change in the desiccant used in the container/closure system and withdrawal of the proposed ——tablet count package size for the 150 mg tablet strength;

Final approval of your Bupropion Hydrochloride Extended-release Tablets USP, 150 mg; and

S-003: Updated final-printed labeling to include the 150 mg strength.

We have completed the review of these supplemental abbreviated applications and they are approved. Based upon the information you have presented to date, we have concluded that your Bupropion Hydrochloride Extended-release Tablets USP, 150 mg, are safe and effective for use as recommended in the submitted labeling.

The Division of Bioequivalence has determined your Bupropion Hydrochloride Extended-release Tablets USP, 150 mg, (twice-a-day dosing) to be bioequivalent and therapeutically equivalent to the listed drug (Wellbutrin SR® Sustained-Release Tablets, 150 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:

> Dissolution testing should be conducted in 900 mL of water, at 37°C, using USP Apparatus 2 (paddle) at 50 rpm. The test product should meet the following "interim" specifications:
>
> | Time (Hours) | % Dissolved |
> |---|---|
> | 1 | ——— |
> | 2 | ——— |
> | 4 | ——— |
> | 6 | NLT — |
>
> The "interim" dissolution tests 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 supplemental application, Wellbutrin SR® Tablets, 150 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 (the '970 patent)	August 12, 2013
5,427,798 (the '798 patent)	August 12, 2013
5,731,000 (the '000 patent)	August 12, 2013
5,763,493 (the '493 patent)	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 USP, 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 IMPAX Laboratories, Inc. (IMPAX) for infringement of one or more of the patents which were the subjects of the paragraph IV certifications. This action must be brought against IMPAX 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 IMPAX complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for infringement of the '970, '000, or '493 patents was brought against IMPAX within the statutory forty-five day period. You have also informed the agency that with regard to the '798 patent, Glaxo Wellcome, Inc. initiated a patent infringement action against IMPAX in the United States District Court for the Northern District of California (Glaxo Wellcome, Inc. v. IMPAX Laboratories, Inc.), Civil Action No. CA-00-21009. You have also noted that on August 21, 2002, the district court issued an order granting IMPAX's motion for summary judgement of non-infringement, ruling in favor of IMPAX. Furthermore, the Agency recognizes that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act and associated with Civil Action CA-00-21009 for the '798 patent, during which time the FDA was precluded from approving your application, has expired.

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 USP, 150 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 USP, 150 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 for the 150 mg strength. 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.

Sincerely yours,

Robert Lest /for
3/22/2004

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 75-913
Division File
Field Copy
HFD-600/R.West
HFD-330
HFD-205
HFD-600/Orange Book
HFD-600/D.Hare

Endorsements:

HFD-647/B.Wu/3/17/04 3/17/04
HFD-647/S.Rosencrance/3/17/04 3/17/04
HFD-617/T.Hinchliffe/3/17/04 3/17/04
HFD-613/P.Birch/3/17/04 3/18/04
HFD-613/L.Golson/3/17/04 3/18/04

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APPROVAL - 150 MG

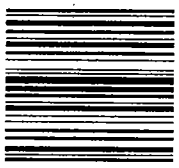
Robert West
3/22/2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-913/ S-001, S-002, S-003

APPROVED LABELING



196-13

Bupropion HCl Extended-Release Tablets

APPROVAL

MAR 2 2 2004

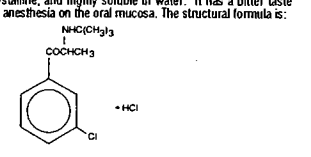
INSERT ENLARGED TO 120% BY FOI STAFF

Bupropion HCl Extended-Release Tablets

Rx only

"Information for the Patient" enclosed.

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



Bupropion hydrochloride extended-release tablets are supplied for oral administration as 100 mg and 150 mg, film-coated, extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: colloidal silicon dioxide, hydroxypropylcellulose, magnesium stearate, and microcrystalline cellulose. The 100 mg tablet also contains FD&C red # 40, FD&C yellow # 5, hypromellose, iron oxide yellow, macrogol, polydextrose, titanium dioxide and triacetin. The 150 mg tablet also contains hypromellose, iron oxide yellow, macrogol, polydextrose, titanium dioxide and triacetin.

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. 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.

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.

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

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. Nevertheless, they may be clinically important because their plasma concentrations are 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.

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.

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

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 that there were 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 ½ fold for hydroxybupropion and about 2 ½ 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, compared to healthy normal volunteers, was revealed.

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, had suggested that the elderly are at increased 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 the 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 is 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 suicide ideation.

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

CONTRAINDICATIONS: Bupropion 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 and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with bupropion.

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

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

- **Dose: At doses of bupropion hydrochloride extended-release 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 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 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 sustained-release formulation of bupropion resulted from the different formulation or the lower dose used. However, as noted above, the immediate-release and sustained-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 seizures 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 in 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 300 mg/day (n=376)	Bupropion hydrochloride extended-release 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 is 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 300 mg/day (n=339)	Bupropion hydrochloride extended-release 400 mg/day (n=112)	Placebo (n=347)
Gain >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 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.

The 100 mg strength of this product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin sensitivity.

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 sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of sustained-released bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS, and placebo, respectively. The majority of these patients had evidence of preexisting hypertension. Three patients (1.2%) treated with the combination of ZYBAN®, and NTS and one patient (0.4%) treated with NTS had study medication discontinued due to hypertension 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 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 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 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: See the tear-off leaflet for information for the Patient.

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

Drug 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 of adverse experiences in patients receiving bupropion concurrently with either levodopa or amantadine. Administration of bupropion 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 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).

Alcohol: In post marketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol intolerance in patients who were drinking alcohol during treatment with bupropion. The consumption of alcohol during treatment with bupropion should be minimized or avoided (also see **CONTRAINDICATIONS**).

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 on labor and delivery in humans is unknown.

Nursing Mothers: Like many other drugs, bupropion and its metabolites are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from bupropion, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

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

Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized 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 sustained-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 Discontinuations Due to Adverse Events in Placebo Controlled Trials

Adverse Event Term	Bupropion hydrochloride extended-release 300 mg/day (n=376)	Bupropion hydrochloride extended-release 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 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 300 mg/day (n=376)	Bupropion hydrochloride extended-release 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%
CNS 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, dysemenorrhea, 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 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 300 mg/day: Anorexia, dry mouth, rash, sweating, tinnitus, and tremor.

Bupropion Hydrochloride Extended-Release 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 sustained-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 sustained-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 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 sustained-release bupropion are included. The extent to which these events may be associated with bupropion hydrochloride extended-release is 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 coadministered 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, 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, hallucinations, 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, deaths 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 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 of bupropion hydrochloride, are yellow, round, convex, film-coated tablets, debossed with "G" on one side and "2442" on the other side.

Bottles of 100 ..... NDC 0115-2442-01
Bottles of 500 ..... NDC 0115-2442-02

Bupropion hydrochloride extended-release tablets, 150 mg of bupropion hydrochloride, are yellow, round, convex, film-coated tablets debossed with "G" on one side and "2444" on the other side.

Bottles of 100 ..... NDC 0115-2444-01

Store at 20-25°C (68-77°F). (See USP Controlled Room Temperature).
Dispense in tightly closed, light-resistant container (USP).

Mfg. by:
IMPAX Laboratories, Inc.
Hayward, CA 94544 USA

Dist. by:
Global Pharmaceuticals
Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124 USA

Rev. 01/2004
196-13

- Original

Lot No.:

Exp. Date

GLOBAL®

NDC 0115-2444-01

buPROPion HCl

Extended-release Tablets

150 mg

WARNING: Do not use in combination with Zyban® or any other medicines that contain bupropion hydrochloride.

Rx only

100 TABLETS

USUAL DOSAGE: See accompanying outsert for complete prescribing information. Dispense in tightly-closed, light-resistant containers with safety closures. Each tablet contains 150 mg of bupropion HCl. Store at 20°-25°C (68°-77°F). (See USP Controlled Room Temperature).

Keep this and all medication out of reach of children.

Zyban® is a registered trademark of Glaxo Wellcome, Inc.

Mfg. by: IMPAX Laboratories, Inc.
Hayward, CA 94544 USA

Dist. by: Global Pharmaceuticals
Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124 USA

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PHARMACIST - DETACH HERE AND GIVE LEAFLET TO PATIENT

Patient Information

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 1000 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 ingredien 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), Pamate® (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 all your medical conditions.** Tell your doctor if you
• are pregnant or plan to become pregnant. It is not known if bupropion can harm the unborn baby.
• are breast feeding. Bupropion passes through your milk It is not known whether bupropion 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

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BY FDI STAFF

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.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-913/ S-001, S-002, S-003

LABELING REVIEW(S)

Supercedes tentative approval summary for the November 14, 2003 submission

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

ANDA Number: 75-913/S003 Dates of Submission: **January 29, 2004**

Applicant's Name: **Impax Pharmaceuticals, Inc**

Established Name: **Bupropion Hydrochloride Extended-release Tablets USP, 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? Yes

Professional Package Insert Labeling:

Satisfactory in FPL as of January 29, 2004 submission (Vol. 11.1, Section V.2; Rev 01/2004: Code 196.13)

Container Labels and Patient Information Sheet Labeling (attached to Container Labels): 100s

Satisfactory in FPL as of November 14, 2003 submission (Vol. 10.1)

Revisions needed post-approval:

The firm has committed to indicate the presence of the patient information sheet on the container label for the pharmacist.

Notify firm that this product is now the subject of a USP monograph. Encourage them to revise the established name to read: Buproprion Hydrochloride Extended-release Tablets USP.

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 #: 10-22-02 (S-029)
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:

APPEARS THIS WAY ON ORIGINAL

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.		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	