CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 077415

Name: Bupropion HCl Extended-release (XL) Tablets, USP 300 mg

Sponsor: IMPAX Laboratories, Inc.

Approval Date: December 15, 2006

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077415

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077415

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-415

DEC 15 2006

IMPAX Laboratories, Inc.
Attention: Mark C. Shaw
Vice President,
Regulatory Affairs and Compliance
30831 Huntwood Avenue
Hayward, CA 94544

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated November 30, 2004, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Bupropion Hydrochloride Extended-release Tablets USP, (XL) 150 mg and 300 mg (Once Daily Dosing).

Reference is also made to your amendments dated June 21 and 29, August 5, September 28, and November 9, 2005; June 5, July 12, July 26, August 4, August 8, August 16, August 18, November 2, and December 14, 2006.

We have completed the review of this ANDA and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your Bupropion Hydrochloride Extended-release Tablets USP, 150 mg, at this time because of the patent issue noted below. Therefore, only your Bupropion Hydrochloride Extended-release Tablets USP, 300 mg, is **approved.** Your Bupropion Hydrochloride Extended-release Tablets USP, (XL) 150 mg is **tentatively approved.**

The reference listed drug (RLD) upon which you have based your ANDA, Wellbutrin XL Extended-release Tablets, 150 mg and 300 mg of GlaxoSmithKline (GSK), is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent Nos. 6,096,341 (the '341 patent) and 6,143,327 (the '327 patent) are both scheduled to expire on October 30, 2018.

Your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Bupropion Hydrochloride Extended-release Tablets USP, (XL) 150 mg and 300 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately unless action is brought against IMPAX Laboratories, Inc. (IMPAX) for infringement of one or more of the patents that were the subjects of paragraph IV certifications. This action must be brought against IMPAX prior to the expiration of 45 days from the date the notice you provided under section 505(j)(2)(B) was received by the NDA/patent holder(s). You notified the agency that litigation was initiated against IMPAX for infringement of the '341 patent in the United States District Court for the Eastern District of Pennsylvania [Bovail Laboratories, Inc. v. Impax Laboratories, Inc., Civil Action No. 05-cv-1085]. This litigation was initiated within the statutory 45-day period with respect to the 150 mg strength; however, it was initiated outside the 45-day period with respect to the 300 mg strength.

I. Approval of Bupropion Hydrochloride Extended-release Tablets USP, 300 mg

The Division of Bioequivalence has determined your Bupropion Hydrochloride Extended-release Tablets USP, (XL) 300 mg to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Wellbutrin XL Extended-release Tablets 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 should be conducted in 900 mL of 0.1 N HCl at 37°C, using USP Apparatus I (basket) at 75 rpm.

The test product should meet the following specifications:

1 hr: (b) (4)
2 hrs:
4 hrs:
8 hrs:
12 hrs

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.

With respect to 180-day generic drug exclusivity, we note that Anchen Pharmaceuticals, Inc. (Anchen) was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification to the '341 and '327 patents. Therefore, Anchen is entitled to the 180-day exclusivity for the 150 mg and 300 mg strengths following the final approval of its ANDA. However, we note that IMPAX and its marketing partner, TEVA Pharmaceuticals, have entered into an agreement with Anchen regarding the relinquishment or selective waiver of exclusivity for the 300 mg strength.

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

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

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

II. Tentative Approval of Bupropion Hydrochloride Extended-release Tablets USP, 150 mg

As noted above, we are unable to grant final approval to your Bupropion Hydrochloride Extended-release Tablets USP, (XL) 150 mg, at this time because of the litigation initiated against IMPAX for infringement of the '341 patent. Your Bupropion Hydrochloride Extended-release Tablets USP, (XL) 150 mg, is therefore **tentatively approved.** This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practices of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

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)

   b. the date the court decides[1] that the '341 patent is invalid or not infringed. See sections 505(j)(5)(B)(iii)(I), (II), and (III) of the Act, or,

   c. the '341 patent has expired, and

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

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as

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[1] This decision may be either a decision of the district court or the court of appeals, whichever court is the first to decide that the patent is invalid or not infringed.

appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED.

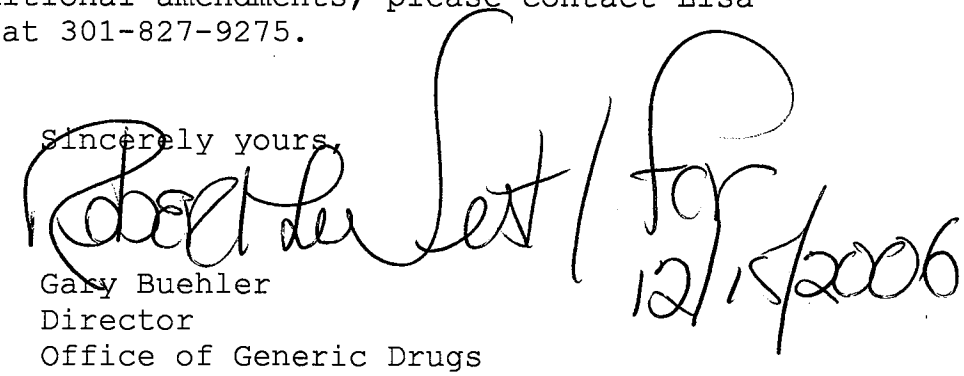
In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product 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 product before the 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 deemed to be approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book."

For further information on the status of this application, or prior to submitting additional amendments, please contact Lisa Kwok, Project Manager, at 301-827-9275.

Sincerely yours,



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

cc: ANDA 77-415
Division File
Field Copy
HFD-013
HFD-610/Orange Book Staff

12/14/06

Approved Electronic Labeling Located at:

\\Cdsesub1\n77415\N_000\2005-11-09\440-02 150 mg 30 ct.pdf
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Endorsements:
HFD-625/A.Srinivasan/ 11/17/06.
HFD-625/S.Liu/ S.H. Liu 11/17/06
HFD-617/L.Kwok/ 11/17/06
HFD-613/S.Park/
HFD-613/L.Golson/

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APPROVAL - 300 mg

TENTATIVE APPROVAL - 150 mg

11/29/06.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077415

LABELING

Bupropion Hydrochloride Extended-release Tablets (XL)

666-03

PRESCRIBING INFORMATION
Bupropion Hydrochloride Extended-release Tablets (XL)

Rx only

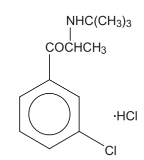
"Patient Information" enclosed.

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of bupropion hydrochloride extended-release tablets or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Bupropion hydrochloride extended-release tablets are not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS: Pediatric Use)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION
Bupropion hydrochloride extended-release tablets (bupropion hydrochloride), an anti depressant 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 $C_{13}H_{18}ClNO{\bullet}HCl$. 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 300-mg, yellow extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: colloidal silicon dioxide, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The film-coating material contains FD&C red #40, FD&C yellow # 5, hypromellose type 2910/ 3cP, 6cP and 50cP, macrogol, polydextrose, titanium dioxide and triacetin. USP drug release test is pending.

CLINICAL PHARMACOLOGY
Pharmacodynamics: Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine and dopamine, and does not inhibit monoamine oxidase or the re-uptake of serotonin. 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 14-day dosing with bupropion hydrochloride extended-release tablets 300 mg once daily to the immediate-release formulation of bupropion at 100 mg 3 times daily, equivalence was demonstrated for peak plasma concentration and area under the curve for bupropion and the 3 metabolites (hydroxybupropion, threohydrobupropion, and erythrohydrobupropion). Additionally, in a study comparing 14-day dosing with bupropion hydrochloride extended-release tablets 300 mg once daily to the sustained-release formulation of bupropion at 150 mg 2 times daily, equivalence was demonstrated for peak plasma concentration and area under the curve for bupropion and the 3 metabolites.

Absorption: Following oral administration of Bupropion hydrochloride extended-release tablets to healthy volunteers, time to peak plasma concentrations for bupropion was approximately 5 hours and food did not affect the C_{max} or AUC of bupropion.

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).

In humans, peak plasma concentrations of hydroxybupropion occur approximately 7 hours after administration of bupropion hydrochloride extended-release tablets. Following administration of bupropion hydrochloride extended-release tablets, peak plasma concentrations of hydroxybupropion are approximately 7 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 13 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, approximately 33 (±10) and 37 (±13) hours, respectively, and steady-state AUCs are 1.4 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 and 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: There is limited information on the pharmacokinetics of bupropion in patients with renal impairment. An inter-study comparison between normal subjects and patients with endstage renal failure demonstrated that the parent drug C_{max} and AUC values were comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3 and 2.8-fold increase, respectively, in AUC for patients with endstage renal failure. The elimination of the major metabolites of bupropion may be reduced by impaired renal function (see PRECAUTIONS: Renal Impairment).

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 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 3 times daily schedule, revealed no relationship between age (18 to 83 years) and plasma concentration of bupropion. A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects. These data suggest there is no prominent effect of age on bupropion concentration; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see PRECAUTIONS: Geriatric Use).

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
Major Depressive Disorder: The efficacy of bupropion as a treatment for major depressive disorder was established with the immediate-release formulation of bupropion in two 4-week, placebo-controlled trials in adult inpatients and in one 6-week, placebo-controlled trial in adult outpatients. In the first study, patients were titrated in a bupropion dose range of 300 to 600 mg/day of the immediate-release formulation on a 3 times daily schedule; 78% of patients received maximum doses of 450 mg/day or less. This trial demonstrated the effectiveness 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 2 fixed doses of the immediate-release formulation of bupropion (300 and 450 mg/day) and placebo. This trial demonstrated the effectiveness of bupropion, but only at the 450-mg/day dose of the immediate-release formulation; 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 bupropion on the HDRS total score, HDRS item 1, the Montgomery-Asberg Depression Rating Scale, the CGI severity score, and the CGI improvement score.
In a longer-term study, outpatients meeting DSM-IV criteria for major depressive disorder, recurrent type, who had responded during an 8-week open trial on bupropion (150 mg twice daily of the sustained-release formulation) were randomized to continuation of their same dose of bupropion or placebo, for up to 44 weeks of observation for relapse. Response during the open phase was defined as CGI Improvement score of 1 (very much improved) or 2 (much improved) for each of the final 3 weeks. Relapse during the double-blind phase was defined as the investigator's judgment that drug treatment was needed for worsening depressive symptoms. Patients receiving continued bupropion treatment experienced significantly lower relapse rates over the subsequent 44 weeks compared to those receiving placebo.

Although there are no independent trials demonstrating the antidepressant effectiveness of bupropion hydrochloride extended-release tablets, studies have demonstrated similar bioavailability of bupropion hydrochloride extended-release tablets to both the immediate-release formulation and to the sustained-release formulation of bupropion under steady-state conditions, i.e., bupropion hydrochloride extended-release tablets 300 mg once daily was shown to have bioavailability that was similar to that of 100 mg 3 times daily of the immediate-release formulation of bupropion and to that of 150 mg 2 times daily of the sustained-release formulation of bupropion, with regard to peak plasma concentration and extent of absorption, for parent drug and metabolites.

INDICATIONS AND USAGE

Major Depressive Disorder: Bupropion hydrochloride extended-release tablets are indicated for the treatment of major depressive disorder.

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

A major depressive episode (DSM-IV) implies the presence of 1) depressed mood or 2) loss of interest or pleasure; in addition, at least 5 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 efficacy of bupropion in maintaining an antidepressant response for up to 44 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial with the sustained-release formulation of bupropion (see CLINICAL TRIALS). Nevertheless, 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 is contraindicated in patients with a seizure disorder.

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

Bupropion hydrochloride extended-release tablets is 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 is 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
Clinical Worsening and Suicide Risk: Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials**. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for bupropion hydrochloride extended-release tablets should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that bupropion hydrochloride extended-release tablets are not approved for use in treating bipolar depression.

Patients should be made aware that bupropion hydrochloride extended-release tablets contain 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, such as bupropion extended-release tablets (SR), the sustained-release formulation or bupropion hydrochloride tablets, the immediate-release formulation.

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.

As bupropion hydrochloride extended-release tablets are bioequivalent to both the immediate-release formulation of bupropion and to the sustained-release formulation of bupropion, the seizure incidence with bupropion hydrochloride extended-release tablets, while not formally evaluated in clinical trials, may be similar to that presented below for the immediate-release and sustained-release formulations of bupropion.

- **Dose: At doses up to 300 mg/day of the sustained-release formulation of bupropion [bupropion extended-release tablets (SR)], the incidence of seizure is approximately 0.1% (1/1,000).**

  Data for the immediate-release formulation of bupropion revealed a seizure incidence of approximately 0.4% (i.e., 13 of 3,200 patients followed prospectively) in patients treated at doses in a range of 300 to 450 mg/day. This seizure incidence (0.4%) may exceed that of some other marketed antidepressants.

  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. The 600 mg dose is twice the usual adult dose and one and one-third the maximum recommended daily dose (450 mg) of bupropion hydrochloride extended-release tablets. This disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.
- **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., anti-psychotics, 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 450 mg,**
- **the rate of incrementation of dose is gradual.**

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 tablets 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 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:*** Increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment, have been associated with treatment with bupropion. Patients in placebo-controlled trials of major depressive disorder with bupropion hydrochloride extended-release tablets (SR), the sustained-release formulation of bupropion, experienced agitation, anxiety, and insomnia as shown in Table 1.

Table 1: Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials of Bupropion Extended-Release Tablets (SR) for Major Depressive Disorder

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

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

Symptoms in these studies 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 sustained-release tablets and 0.8% of patients treated with placebo.

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

Altered Appetite and Weight: In placebo-controlled studies of major depressive disorder using bupropion extended-release tablets (SR), the sustained-release formulation of bupropion, 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 of Bupropion Extended-Release Tablets (SR) for Major Depressive Disorder

Weight Change	Bupropion ER Tablets (SR) 300 mg/day (n=339)	Bupropion ER Tablets (SR) 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.

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.

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 pre-existing hypertension.

Data from a comparative study of the sustained-release formulation of bupropion (ZYBAN® Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of sustained-release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS, and placebo, respectively. The majority of these patients had evidence of pre-existing hypertension. Three patients (1.2%) treated with the combination of ZYBAN and NTS and 1 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 2 patients for exacerbation of baseline hypertension.

Hepatic Impairment: Bupropion hydrochloride extended-release tablets 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 tablets 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: There is limited information on the pharmacokinetics of bupropion in patients with renal impairment. An inter-study comparison between normal subjects and patients with endstage renal failure demonstrated that the parent drug C_{max} and AUC values were comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3 and 2.8-fold increase, respectively, in AUC for patients with endstage renal failure. Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and subsequently excreted by the kidneys. Bupropion hydrochloride extended-release tablets should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered as bupropion and the metabolites of bupropion 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: Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with bupropion hydrochloride extended-release tablets and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers and a Patient Package Insert about using bupropion hydrochloride extended-release tablets will be dispensed by the pharmacist with each new prescription and refill of bupropion hydrochloride extended-release tablets. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and Patient Package Insert, and should assist them in understanding the contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and Patient Package Insert and to obtain answers to any questions they may have. The complete text of the Medication Guide and the Patient Package Insert are provided in tear-off leaflets at the end of this labeling.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking bupropion hydrochloride extended-release tablets.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

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

PHARMACIST DETACH HERE AND GIVE MEDICATION GUIDE TO PATIENT.

Medication Guide
About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves. Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality or being suicidal*.

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies,*** but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your healthcare provider before your child takes an antidepressant.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child. After starting an antidepressant, your child should generally see his or her healthcare provider:

- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your healthcare provider's advice about how often to come back
- More often if problems or questions arise (see Section 3)

You should call your child's healthcare provider between visits if needed.

PHARMACIST-DETACH HERE AND GIVE LEAFLET TO PATIENT.

Patient Information
Bupropion Hydrochloride Extended-Release Tablets (Once Daily)

Read the Patient Information that comes with bupropion hydrochloride extended-release tablets before you start taking bupropion hydrochloride extended-release tablets and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about bupropion hydrochloride extended-release tablets?
There is a chance of having a seizure (convulsion, fit) with bupropion hydrochloride extended-release tablets, especially in people:

- with certain medical problems.
- who take certain medicines.

The chance of having seizures increases with higher doses of bupropion hydrochloride extended-release tablets. For more information, see the sections "Who should not take bupropion hydrochloride extended-release tablets?" and "What should I tell my doctor before using bupropion hydrochloride extended-release tablets?". Tell your doctor about all of your medical conditions and all the medicines you take. **Do not take any other medicines while you are using bupropion hydrochloride extended-release tablets unless your doctor has said it is okay to take them.**

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 is important information I should know and share with my family about taking antidepressants?
Patients and their families should watch out for worsening depression or thoughts of suicide. Also watch out for sudden or severe changes in feelings such as feeling anxious, agitated, panicky, irritable, hostile, aggressive, impulsive, severely restless, overly excited and hyperactive, not being able to sleep, or other unusual changes in behavior. If this happens, especially at the beginning of antidepressant treatment or after a change in dose, call your doctor.

A patient Medication Guide will be provided to you with each prescription of bupropion hydrochloride extended-release tablets entitled "About Using Antidepressants in Children and Teenagers."

Bupropion hydrochloride extended-release tablets have not been studied in children under the age of 18 and are not approved for use in children and teenagers.

What is bupropion hydrochloride extended-release tablets?
Bupropion hydrochloride extended-release tablets is a prescription medicine used to treat adults with a certain type of depression called major depressive disorder.

Who should not take bupropion hydrochloride extended-release tablets?

Do not take bupropion hydrochloride extended-release tablets if you

- have or had a seizure disorder or epilepsy.
- **are taking ZYBAN® (used to help people stop smoking) or any other medicines that contain bupropion hydrochloride, such as bupropion hydrochloride tablets (immediate release) or bupropion hydrochloride sustained-release tablets (SR).** Bupropion is the same active ingredient that is in bupropion hydrochloride extended-release tablets.
- drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- have taken within the last 14 days medicine for depression called a monoamine oxidase inhibitor (MAOI), such as NARDIL® (phenelzine sulfate), PARNATE® (tranylcypromine sulfate), or MARPLAN® (isocarboxazid).
- have or had an eating disorder such as anorexia nervosa or bulimia.
- are allergic to the active ingredient in bupropion hydrochloride extended-release tablets, bupropion, or to any of the inactive ingredients. See the end of this leaflet for a complete list of ingredients in bupropion hydrochloride extended-release tablets.

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

- **Tell your doctor about your medical conditions.** Tell your doctor if you:
  - **are pregnant or plan to become pregnant.** It is not known if bupropion can harm your unborn baby.
  - **are breastfeeding.** Bupropion passes through your milk. It is not known if bupropion can harm your baby.
  - **have liver problems,** especially cirrhosis of the liver.
  - have kidney problems.
  - have an eating disorder, such as anorexia nervosa or bulimia.
  - have had a head injury.
  - have had a seizure (convulsion, fit).
  - have a tumor in your nervous system (brain or spine).
  - have had a heart attack, heart problems, or high blood pressure.
  - are a diabetic taking insulin or other medicines to control your blood sugar.
  - drink a lot of alcohol.
  - abuse prescription medicines or street drugs.
- **Tell your doctor about all the medicines you take**, including prescription and non- prescription medicines, vitamins and herbal supplements. Many medicines increase your chances of having seizures or other serious side effects if you take them while you are using bupropion hydrochloride extended-release tablets.

Bupropion hydrochloride extended-release tablets has not been studied in children under the age of 18 years.

How should I take bupropion hydrochloride extended-release tablets?

- Take bupropion hydrochloride extended-release tablets exactly as prescribed by your doctor.
- **Do not chew, cut, or crush bupropion hydrochloride extended-release tablets.** You must swallow the tablets whole. **Tell your doctor if you cannot swallow medicine tablets.**
- Take bupropion hydrochloride extended-release tablets at the same time each day.
- Take your doses of bupropion hydrochloride extended-release tablets at least 24 hours apart.

Patient Information (cont'd)

- You may take bupropion hydrochloride extended-release tablets with or without food.
- 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 at the regular time. **This is very important.** Too much bupropion hydrochloride extended-release tablets can increase your chance of having a seizure.
- If you take too much bupropion hydrochloride extended-release tablets, or overdose, call your local emergency room or poison control center right away.
- **Do not take any other medicines while using bupropion hydrochloride extended-release tablets unless your doctor has told you it is okay.**
- If you are taking bupropion hydrochloride extended-release tablets for the treatment of major depressive disorder, it may take several weeks for you to feel that bupropion hydrochloride extended-release tablets are working. Once you feel better, it is important to keep taking bupropion hydrochloride extended-release tablets exactly as directed by your doctor. Call your doctor if you do not feel bupropion hydrochloride extended-release tablets are working for you.
- Do not change your dose or stop taking bupropion hydrochloride extended-release tablets without talking with your doctor first.

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

- Do not drink a lot of alcohol 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 chance of having seizures.
- Do not drive a car or use heavy machinery until you know how bupropion hydrochloride extended-release tablets affects you. Bupropion hydrochloride extended-release tablets can impair 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.
- **Severe allergic reactions. Stop bupropion hydrochloride extended-release tablets and 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, chest pain, or have trouble breathing. These could be signs of a serious allergic reaction.
- **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while taking bupropion hydrochloride extended-release tablets, including delusions (believe you are someone else), hallucinations (seeing or hearing things that are not there), paranoia (feeling that people are against you), or feeling confused. If this happens to you, call your doctor.

Common side effects reported in studies of major depressive disorder include weight loss, loss of appetite, dry mouth, skin rash, sweating, ringing in the ears, shakiness, stomach pain, agitation, anxiety, dizziness, trouble sleeping, muscle pain, nausea, fast heartbeat, sore throat, and urinating more often.

If you have nausea, take your medicine with food. If you have trouble sleeping, do not take your medicine too close to bedtime.

Tell your doctor right away about any side effects that bother you.

These are not all the side effects of bupropion hydrochloride extended-release tablets. For a complete list, ask your doctor or pharmacist.

How should I store bupropion hydrochloride extended-release tablets?

- Store bupropion hydrochloride extended-release tablets at room temperature. Store out of direct sunlight. Keep bupropion hydrochloride extended-release tablets in its tightly closed bottle.
- Bupropion hydrochloride extended-release tablets may have an odor.

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.

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

What are the ingredients in bupropion hydrochloride extended-release tablets?
Active ingredient: bupropion hydrochloride.

Inactive ingredients: colloidal silicon dioxide, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The film-coating material contains FD&C red #40, FD&C yellow # 5, hypromellose type 2910/ 3cP, 6cP and 50cP, macrogol, polydextrose, titanium dioxide and triacetin.

Rx only

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Global Pharmaceuticals
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Rev. 08/2006
456-03

Medication Guide (cont'd)

3. You Should Watch for Certain Signs If Your Child is Taking an Antidepressant

Contact your child's healthcare provider ***right away*** if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her healthcare provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®) has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®), sertraline (Zoloft®), fluvoxamine, and clomipramine (Anafranil®).

Your healthcare provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your healthcare provider or pharmacist where to find more information.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

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Rev. 08/2006
456-03

treatment, and that bupropion hydrochloride extended-release tablets should not be used in combination with ZYBAN or any other medications that contain bupropion hydrochloride (such as bupropion hydrochloride extended-release tablets (SR), the sustained-release formulation, and bupropion hydrochloride tablets, the immediate-release formulation).

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 following concomitant administration with other drugs or, alternatively, the effect of concomitant administration of bupropion 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 are substrates or inhibitors of the CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, and cyclophosphamide). In addition, in vitro studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir, ritonavir, and efavirenz inhibit the hydroxylation of bupropion. No clinical studies have been performed to evaluate this finding. 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 tablets of the sustained-release formulation of bupropion 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).

Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of lamotrigine in 12 healthy volunteers.

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 3 times daily to 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism. Nevertheless, there may be the potential for clinically important alterations of blood levels of coadministered drugs.

Drugs Metabolized By Cytochrome P450IID6 (CYP2D6): Many drugs, including most antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme in vitro. In a study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of the CYP2D6 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single dose of 50 mg desipramine increased the C_{max} , AUC, and $t_{1/2}$ of desipramine by an average of approximately 2-, 5-, and 2-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, co-administration 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 hydrochloride extended-release tablets to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, using small initial doses and gradual dose increases.

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

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

Alcohol: In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with bupropion. The consumption of alcohol during treatment with bupropion hydrochloride extended-release tablets 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/day, respectively. These doses are approximately 7 and 2 times the maximum recommended human dose (MRHD), respectively, on a mg/m² basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day (approximately 2 to 7 times the MRHD on a mg/m² 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 (2 to 3 times control mutation rate) in 2 of 5 strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in 1 of 3 in vivo rat bone marrow cytogenetic studies.

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

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. In studies conducted in rats and rabbits, bupropion was administered orally at doses up to 450 and 150 mg/kg/day, respectively (approximately 11 and 7 times the maximum recommended human dose [MRHD], respectively, on a mg/m² basis), during the period of organogenesis. No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately equal to the MRHD on a mg/m² basis) and greater. Decreased fetal weights were seen at 50 mg/kg and greater.

When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately 7 times the MRHD on a mg/m² basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

One study has been conducted in pregnant women. This retrospective, managed-care database study assessed the risk of congenital malformations overall, and cardiovascular malformations specifically, following exposure to bupropion in the first trimester compared to the risk of these malformations following exposure to other antidepressants in the first trimester and bupropion outside of the first trimester. This study included 7,005 infants with antidepressant exposure during pregnancy, 1,213 of whom were exposed to bupropion in the first trimester. The study showed no greater risk for congenital malformations overall, or cardiovascular malformations specifically, following first trimester bupropion exposure compared to exposure to all other antidepressants in the first trimester, or bupropion outside of the first trimester. The results of this study have not been corroborated. Bupropion hydrochloride extended-release tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effect of bupropion hydrochloride extended-release tablets on labor and delivery in humans is unknown.

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

Pediatric Use: Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk). Anyone considering the use of bupropion hydrochloride extended-release tablets in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use: Of the approximately 6,000 patients who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation studies), 275 were ≥65 years old and 47 were ≥75 years old. 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. 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.)
Major Depressive Disorder: Bupropion hydrochloride extended-release tablets have been demonstrated to have similar bioavailability both to the immediate-release formulation of bupropion and to the sustained-release formulation of bupropion (see CLINICAL PHARMACOLOGY). The information included under this subsection is based primarily on data from controlled clinical trials with bupropion hydrochloride extended-release tablets (SR), the sustained-release formulation of bupropion.

Adverse Events Associated With Discontinuation of Treatment Among Patients Treated With Bupropion Hydrochloride Tablets or Bupropion Extended-Release Tablets (SR): In placebo-controlled clinical trials, 9% and 11% of patients treated with 300 and 400 mg/day, respectively, of the sustained-release formulation of bupropion 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 mg/day or 400 mg/day of bupropion extended-release tablets (SR), the sustained-release formulation of bupropion, 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 for Major Depressive Disorder

Adverse Event Term	Bupropion ER Tablets (SR) 300 mg/day (n=376)	Bupropion ER Tablets (SR) 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%

In clinical trials with the immediate-release formulation of bupropion, 10% of patients and volunteers discontinued due to an adverse event. Events resulting in discontinuation, in addition to those listed above for the sustained-release formulation of bupropion, include vomiting, seizures, and sleep disturbances.

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated With Bupropion Hydrochloride Tablets or Bupropion Extended-Release Tablets (SR): Table 4 enumerates treatment-emergent adverse events that occurred among patients treated with 300 and 400 mg/day of the sustained-release formulation of bupropion and with placebo in 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* for Major Depressive Disorder

Body System/ Adverse Event	Bupropion ER Tablets (SR) 300 mg/day (n=376)	Bupropion ER Tablets (SR) 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%

Table 4: Treatment-Emergent Adverse Events In Placebo-Controlled Trials* for Major Depressive Disorder *cont'd*

Body System/ Adverse Event	Bupropion ER Tablets (SR) 300 mg/day (n=376)	Bupropion ER Tablets (SR) 400 mg/day (n=114)	Placebo (n=385)
Special senses			
Tinnitus	6%	6%	2%
Taste perversion	2%	4%	—
Blurred vision or diplopia	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 the sustained-release formulation of bupropion, but equally or more frequently in the placebo group, were: abnormal dreams, accidental injury, acne, appetite increased, back pain, bronchitis, dysmenorrhea, dyspepsia, flatulence, flu syndrome, hypertension, neck pain, respiratory disorder, rhinitis, and tooth disorder.

Incidence based on the number of female patients.

— Hyphen denotes adverse events occurring in greater than 0 but less than 0.5% of patients.

Additional events to those listed in Table 4 that occurred at an incidence of at least 1% in controlled clinical trials of the immediate-release formulation of bupropion (300 to 600 mg/day) and that were numerically more frequent than placebo were: cardiac arrhythmias (5% vs 4%), hypertension (4% vs 2%), hypotension (3% vs 2%), tachycardia (11% vs 9%), appetite increase (4% vs 2%), dyspepsia (3% vs 2%), menstrual complaints (5% vs 1%), akathisia (2% vs 1%), impaired sleep quality (4% vs 2%), sensory disturbance (4% vs 3%), confusion (8% vs 5%), decreased libido (3% vs 2%), hostility (6% vs 4%), auditory disturbance (5% vs 3%), and gustatory disturbance (3% vs 1%).

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 extended-release tablets (SR) and at a rate at least twice the placebo rate are listed below for the 300- and 400-mg/day dose groups.

300 mg/day of Bupropion Extended-Release Tablets (SR): Anorexia, dry mouth, rash, sweating, tinnitus, and tremor.

400 mg/day of Bupropion Extended-Release Tablets (SR): 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 = 1,013), or patients who experienced an adverse event requiring discontinuation of treatment in an open-label surveillance study with the sustained-release formulation of bupropion (n = 3,100). 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 2 patients. Events of major clinical importance are described in the WARNINGS and PRECAUTIONS sections of the labeling.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, while rare events are those occurring in less than 1/1,000 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 tablets 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), aggression, akinesia, aphasia, coma, delirium, delusions, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid ideation, restlessness, 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, increased intraocular pressure, 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 (immediate-release formulation) 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: Overdoses of up to 30 g or more of bupropion have been reported. Seizure was reported in approximately one third of all cases. Other serious reactions reported with overdoses of bupropion alone included hallucinations, loss of consciousness, sinus tachycardia, and ECG changes such as conduction disturbances or arrhythmias. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported mainly when bupropion was part of multiple drug overdoses.

Although most patients recovered without sequelae, deaths associated with overdoses of bupropion alone have been reported rarely in patients ingesting large 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, hemo-perfusion, 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 tablets, hospitalization following suspected overdose should be considered. Based on studies in animals, it is recommended that seizures be treated with intravenous benzodiazepine administration and other supportive measures, as appropriate.

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

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

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

Bupropion hydrochloride extended-release tablets may be taken without regard to meals.

Major Depressive Disorder: Initial Treatment: The usual adult target dose for bupropion hydrochloride extended-release tablets is 300 mg/day, given once daily in the morning. 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 once daily, may be made as early as day 4 of dosing. There should be an interval of at least 24 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 450 mg/day, given as a single dose, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day.

Maintenance Treatment: It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacological therapy beyond response to the acute episode. It is unknown whether or not the dose of bupropion hydrochloride extended-release tablets needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Switching Patients from Bupropion Hydrochloride Tablets or from Bupropion Extended-Release Tablets (SR): When switching patients from bupropion hydrochloride tablets to bupropion hydrochloride extended-release tablets or from bupropion extended-release tablets (SR) to bupropion hydrochloride extended-release tablets, give the same total daily dose when possible. Patients who are currently being treated with bupropion hydrochloride tablets at 300 mg/day (for example, 100 mg 3 times a day) may be switched to bupropion hydrochloride extended-release tablets 300 mg once daily. Patients who are currently being treated with bupropion extended-release tablets (SR) at 300 mg/day (for example, 150 mg twice daily) may be switched to bupropion hydrochloride extended-release tablets 300 mg once daily.

Maintenance Treatment: It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacological therapy beyond response to the acute episode. It is unknown whether or not the dose of bupropion hydrochloride extended-release tablets needed for maintenance treatment is identical to the dose needed to achieve an initial response. 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 tablets should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed 150 mg every other day in these patients. Bupropion hydrochloride extended-release tablets 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 tablets 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, 300 mg of bupropion hydrochloride, are yellow, oval, film-coated tablets, debossed with "682" on one side and plain on the other side.

Bottles of 30	NDC 0115-6822-08
Bottles of 90	NDC 0115-6822-10

Dispense in a tightly-closed, light-resistant container (USP).

Store at 20°-25°C (68°-77°F); excursion permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature]

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

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

Rev. 8/2006
666-03

Bupropion Hydrochloride Extended-release Tablets (XL)

456-03

PHARMACIST DETACH HERE AND GIVE MEDICATION GUIDE TO PATIENT.

Medication Guide
About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves. Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality or being suicidal*.

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies,*** but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your healthcare provider before your child takes an antidepressant.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child. After starting an antidepressant, your child should generally see his or her healthcare provider:

- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your healthcare provider's advice about how often to come back
- More often if problems or questions arise (see Section 3)

You should call your child's healthcare provider between visits if needed.

PHARMACIST-DETACH HERE AND GIVE LEAFLET TO PATIENT.

Patient Information
Bupropion Hydrochloride Extended-Release Tablets (Once Daily)

Read the Patient Information that comes with bupropion hydrochloride extended-release tablets before you start taking bupropion hydrochloride extended-release tablets and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about bupropion hydrochloride extended-release tablets?
There is a chance of having a seizure (convulsion, fit) with bupropion hydrochloride extended-release tablets, especially in people:

- with certain medical problems.
- who take certain medicines.

The chance of having seizures increases with higher doses of bupropion hydrochloride extended-release tablets. For more information, see the sections "Who should not take bupropion hydrochloride extended-release tablets?" and "What should I tell my doctor before using bupropion hydrochloride extended-release tablets?". Tell your doctor about all of your medical conditions and all the medicines you take. **Do not take any other medicines while you are using bupropion hydrochloride extended-release tablets unless your doctor has said it is okay to take them.**

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 is important information I should know and share with my family about taking antidepressants?
Patients and their families should watch out for worsening depression or thoughts of suicide. Also watch out for sudden or severe changes in feelings such as feeling anxious, agitated, panicky, irritable, hostile, aggressive, impulsive, severely restless, overly excited and hyperactive, not being able to sleep, or other unusual changes in behavior. If this happens, especially at the beginning of antidepressant treatment or after a change in dose, call your doctor.

A patient Medication Guide will be provided to you with each prescription of bupropion hydrochloride extended-release tablets entitled "About Using Antidepressants in Children and Teenagers."

Bupropion hydrochloride extended-release tablets have not been studied in children under the age of 18 and are not approved for use in children and teenagers.

What is bupropion hydrochloride extended-release tablets?
Bupropion hydrochloride extended-release tablets is a prescription medicine used to treat adults with a certain type of depression called major depressive disorder.

Who should not take bupropion hydrochloride extended-release tablets?

Do not take bupropion hydrochloride extended-release tablets if you

- have or had a seizure disorder or epilepsy.
- **are taking ZYBAN® (used to help people stop smoking) or any other medicines that contain bupropion hydrochloride, such as bupropion hydrochloride tablets (immediate release) or bupropion hydrochloride sustained-release tablets (SR).** Bupropion is the same active ingredient that is in bupropion hydrochloride extended-release tablets.
- drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- have taken within the last 14 days medicine for depression called a monoamine oxidase inhibitor (MAOI), such as NARDIL® (phenelzine sulfate), PARNATE® (tranylcypromine sulfate), or MARPLAN® (isocarboxazid).
- have or had an eating disorder such as anorexia nervosa or bulimia.
- are allergic to the active ingredient in bupropion hydrochloride extended-release tablets, bupropion, or to any of the inactive ingredients. See the end of this leaflet for a complete list of ingredients in bupropion hydrochloride extended-release tablets.

What should I tell my doctor before using bupropion hydrochloride extended-release tablets?
- **Tell your doctor about your medical conditions.** Tell your doctor if you:
  - **are pregnant or plan to become pregnant.** It is not known if bupropion can harm your unborn baby.
  - **are breastfeeding.** Bupropion passes through your milk. It is not known if bupropion can harm your baby.
  - **have liver problems,** especially cirrhosis of the liver.
  - have kidney problems.
  - have an eating disorder, such as anorexia nervosa or bulimia.
  - have had a head injury.
  - have had a seizure (convulsion, fit).
  - have a tumor in your nervous system (brain or spine).
  - have had a heart attack, heart problems, or high blood pressure.
  - are a diabetic taking insulin or other medicines to control your blood sugar.
  - drink a lot of alcohol.
  - abuse prescription medicines or street drugs.
- **Tell your doctor about all the medicines you take**, including prescription and non- prescription medicines, vitamins and herbal supplements. Many medicines increase your chances of having seizures or other serious side effects if you take them while you are using bupropion hydrochloride extended-release tablets.

Bupropion hydrochloride extended-release tablets has not been studied in children under the age of 18 years.

How should I take bupropion hydrochloride extended-release tablets?
- Take bupropion hydrochloride extended-release tablets exactly as prescribed by your doctor.
- **Do not chew, cut, or crush bupropion hydrochloride extended-release tablets.** You must swallow the tablets whole. **Tell your doctor if you cannot swallow medicine tablets.**
- Take bupropion hydrochloride extended-release tablets at the same time each day.
- Take your doses of bupropion hydrochloride extended-release tablets at least 24 hours apart.

PHARMACIST DETACH HERE AND GIVE MEDICATION GUIDE TO PATIENT.

Medication Guide
About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?
Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:
1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions
Children and teenagers sometimes think about suicide, and many report trying to kill themselves. Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality or being suicidal*.
A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies,*** but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.
For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with
- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide
If any of these are present, make sure you tell your healthcare provider before your child takes an antidepressant.
2. How to Try to Prevent Suicidal Thoughts and Actions
To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.
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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.

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- drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- have taken within the last 14 days medicine for depression called a monoamine oxidase inhibitor (MAOI), such as NARDIL® (phenelzine sulfate), PARNATE® (tranylcypromine sulfate), or MARPLAN® (isocarboxazid).
- have or had an eating disorder such as anorexia nervosa or bulimia.
- are allergic to the active ingredient in bupropion hydrochloride extended-release tablets, bupropion, or to any of the inactive ingredients. See the end of this leaflet for a complete list of ingredients in bupropion hydrochloride extended-release tablets.

What should I tell my doctor before using bupropion hydrochloride extended-release tablets?
- Tell your doctor about your medical conditions. Tell your doctor if you:
  - are pregnant or plan to become pregnant. It is not known if bupropion can harm your unborn baby.
  - are breastfeeding. Bupropion passes through your milk. It is not known if bupropion can harm your baby.
  - have liver problems, especially cirrhosis of the liver.
  - have kidney problems.
  - have an eating disorder, such as anorexia nervosa or bulimia.
  - have had a head injury.
  - have had a seizure (convulsion, fit).
  - have a tumor in your nervous system (brain or spine).
  - have had a heart attack, heart problems, or high blood pressure.
  - are a diabetic taking insulin or other medicines to control your blood sugar.
  - drink a lot of alcohol.
  - abuse prescription medicines or street drugs.
- Tell your doctor about all the medicines you take, including prescription and non- prescription medicines, vitamins and herbal supplements. Many medicines increase your chances of having seizures or other serious side effects if you take them while you are using bupropion hydrochloride extended-release tablets.

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- Take bupropion hydrochloride extended-release tablets at the same time each day.
- Take your doses of bupropion hydrochloride extended-release tablets at least 24 hours apart.

Patient Information (cont'd)

- You may take bupropion hydrochloride extended-release tablets with or without food.
- 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 at the regular time. **This is very important.** Too much bupropion hydrochloride extended-release tablets can increase your chance of having a seizure.
- If you take too much bupropion hydrochloride extended-release tablets, or overdose, call your local emergency room or poison control center right away.
- **Do not take any other medicines while using bupropion hydrochloride extended-release tablets unless your doctor has told you it is okay.**
- If you are taking bupropion hydrochloride extended-release tablets for the treatment of major depressive disorder, it may take several weeks for you to feel that bupropion hydrochloride extended-release tablets are working. Once you feel better, it is important to keep taking bupropion hydrochloride extended-release tablets exactly as directed by your doctor. Call your doctor if you do not feel bupropion hydrochloride extended-release tablets are working for you.
- Do not change your dose or stop taking bupropion hydrochloride extended-release tablets without talking with your doctor first.

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

- Do not drink a lot of alcohol 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 chance of having seizures.
- Do not drive a car or use heavy machinery until you know how bupropion hydrochloride extended-release tablets affects you. Bupropion hydrochloride extended-release tablets can impair 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.
- **Severe allergic reactions. Stop bupropion hydrochloride extended-release tablets and 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, chest pain, or have trouble breathing. These could be signs of a serious allergic reaction.
- **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while taking bupropion hydrochloride extended-release tablets, including delusions (believe you are someone else), hallucinations (seeing or hearing things that are not there), paranoia (feeling that people are against you), or feeling confused. If this happens to you, call your doctor.

Common side effects reported in studies of major depressive disorder include weight loss, loss of appetite, dry mouth, skin rash, sweating, ringing in the ears, shakiness, stomach pain, agitation, anxiety, dizziness, trouble sleeping, muscle pain, nausea, fast heartbeat, sore throat, and urinating more often.

If you have nausea, take your medicine with food. If you have trouble sleeping, do not take your medicine too close to bedtime.

Tell your doctor right away about any side effects that bother you.

These are not all the side effects of bupropion hydrochloride extended-release tablets. For a complete list, ask your doctor or pharmacist.

How should I store bupropion hydrochloride extended-release tablets?

- Store bupropion hydrochloride extended-release tablets at room temperature. Store out of direct sunlight. Keep bupropion hydrochloride extended-release tablets in its tightly closed bottle.
- Bupropion hydrochloride extended-release tablets may have an odor.

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.

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

What are the ingredients in bupropion hydrochloride extended-release tablets?
Active ingredient: bupropion hydrochloride.

Inactive ingredients: colloidal silicon dioxide, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The film-coating material contains FD&C red #40, FD&C yellow # 5, hypromellose type 2910/ 3cP, 6cP and 50cP, macrogol, polydextrose, titanium dioxide and triacetin.

Rx only

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

Dist. by:
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ZYBAN® is a registered trademark of Glaxo SmithKline.

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Marplan® is a registered trademark of Oxford Pharmaceutical Services.

Rev. 08/2006
456-03

Medication Guide (cont'd)

3. You Should Watch for Certain Signs If Your Child is Taking an Antidepressant

Contact your child's healthcare provider ***right away*** if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her healthcare provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®) has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®), sertraline (Zoloft®), fluvoxamine, and clomipramine (Anafranil®).

Your healthcare provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your healthcare provider or pharmacist where to find more information.

Prozac® is a registered trademark of Eli Lilly and Company; Zoloft® is a registered trademark of Pfizer Pharmaceuticals; Anafranil® is a registered trademark of Mallinkrodt Inc.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

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Buproprion Label
Date Art Revised: 11/07/05
P/N: 487-02
Size: 1-1/2" x 4-1/2"; 1/8" radius
Colors: Black, (b) (4)

GLOBAL®

NDC 0115-6822-08

buPROPion HCl

Extended-release Tablets (XL)

300 mg **(Once Daily*)**

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

ATTENTION: Dispense with Medication Guide

Rx only

30 TABLETS

USUAL DOSAGE: *Take one tablet daily or as directed by physician. See accompanying outsert for additional dosing information.
Each extended-release, film-coated tablet contains 300 mg of bupropion HCl.
Contains FD&C Yellow No. 5 (tartrazine) as a color additive.
Store at 20°-25°C (68°-77°F); excursion permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]
Do not use if printed safety seal under cap is broken or missing.
Keep this and all medication out of reach of children.
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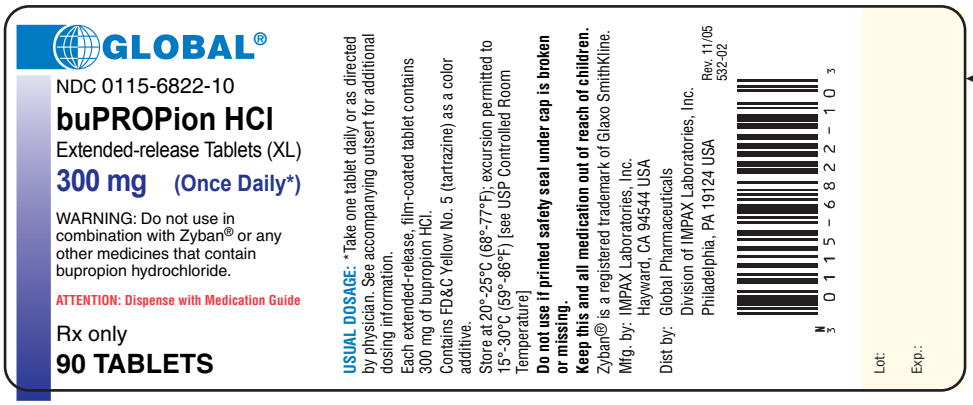
N 3 0 1 1 5 - 6 8 2 2 - 0 8 0

Lot:

Exp.:

Yellow shows no varnish area

Buproprion Label
Date Art Revised: 11/07/05
P/N: 532-02
Size: 2" x 5"; 1/8" radius
Colors: Black, (b) (4)



Yellow shows no varnish area

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077415

LABELING REVIEWS

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

ANDA Number:	77-415
Date of Submissions:	11/30/04 (original submission); 12/28/04 (addition of 300 mg strength)
Applicant's Name:	IMPAX Laboratories, Inc.
Established Name:	Bupropion Hydrochloride Extended-release Tablets USP, (XL) 150 mg and 300 mg (Once Daily)

Labeling Deficiencies

1. CONTAINER (Bottles of 30s):
   a. Principal display panel- revise the established name to read: "buPROPion HCl Extended-release Tablets (XL)" [add "(XL)"]. Please enhance the prominence of "Extended-release Tablets".
   b. Add the following statement to the container label, preferably on the principal display panel: "ATTENTION: Dispense with Medication Guide"
   c. Usual dosage statement: "*Take one tablet daily..." [add "one"]

2. INSERT
   Update your labeling based on the attached approved labeling for the reference listed drug, Wellbutrin XL, approved January 12, 2005.. Refer to the New Correspondence dated January 26, 2005 for additional changes.

3. MEDICATION GUIDE
   Please ensure the Medication Guide is formatted according to 21 CFR 208.20.

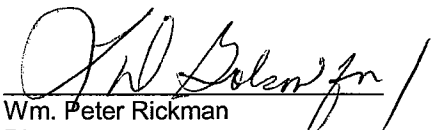
Please revise your labels and labeling, as instructed above, and submit final printed labels and labeling in accord with the electronic labeling rule published December 11, 2003, (68 FR 69009) that requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidance for industry regarding electronic submissions: Providing Regulatory Submissions in Electronic Format — ANDAs (Issued 6/2002) (http://www.fda.gov/cder/guidance/5004fnl.htm). The guidance specifies labeling to be submitted in pdf format. Documents submitted in electronic format should:

- Enable the user to easily view a clear and legible copy of the information
- Enable the user to print each document page by page, as it would have been provided in paper, maintaining fonts, special orientations, table formats, and page numbers
- Include a well-structured table of contents and allow the user to navigate easily through the submission
- Allow the user to copy text, images and data electronically into other common software formats.

To assist in our review, we request that labeling also be submitted in MS Word format.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/cdernew/listserv.html or
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.



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

Attachment: RLD insert labeling

Reference Listed Drug insert labeling removed

FOR THE RECORD:

1. MODEL LABELING
   This review was based on the labeling for Wellbutrin® XL (GlaxoSmithKline; Approved 1-12-05) NDA 21-515/S-009 with the following changes:
   - Per memo from Kim Dettelbach, we will not require generic bupropions to reference a Pregnancy Registry. Therefore, reference to the pregnancy registry has been deleted from Impax's insert labeling.
   - Information regarding the insoluble shell remaining intact in the GI tract has been deleted from Impax's insert labeling since this is specific to the RLD.

2. Bupropion extended release tablets for Wellbutrin XL will contain "(XL)" and "Once Daily" on the labeling to distinguish from the Wellbutrin SR generic products.

3. USP ISSUE: There is a Bupropion Hydrochloride Extended-Release Tablets monograph in USP 28. However, according to the bio review (V:\firmsam\impax\ltrs&rev\77415D1104.doc), the monograph is not for Wellbutrin® XL:
   *"There are three types of Bupropion Hydrochloride Extended-Release Tablets made by GlaxoSmithKline listed as RLD: Wellbutrin® **SR**, Wellbutrin® **XL** and Zyban®. Wellbutrin® SR and Zyban® have same formulation and Wellbutrin® XL has different formulation. This application refers Wellbutrin® **XL** as RLD. The USP listed a dissolution method for Bupropion Hydrochloride Extended-Release Tablets for Wellbutrin® **SR** and Zyban®, but not for Wellbutrin® **XL**. For Wellbutrin® **XL**, there is an FDA-recommended method which is different from the USP method."*

4. PATENTS/EXCLUSIVITIES
   Patent Data – NDA 21-515

Patent Number	Patent Expiration	How Filed	Labeling Impact
6,096,341	October 30, 2018	IV	None
6,143,327	October 30, 2018	IV	None

   Exclusivity Data– NDA 21-515

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
   Impax Laboratories, Inc.
   30831 Huntwood Avenue
   Hayward, CA 94544

6. INACTIVE INGREDIENTS
   The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A3.1, pg. 115 & 119]

Components	**Functions**
Bupropion HCl, USP	Active
Hydroxypropyl cellulose, NF (b) (4)	(b) (4)
Microcrystalline Cellulose, NF (b) (4)	
Lactose Monohydrate, NF (b) (4)	
Colloidal silicon dioxide, NF (b) (4)	
Magnesium Stearate, NF	
(b) (4) *Components of* (b) (4): *Polydextrose* (b) (4) *HPMC 2910/hypromellose 3cp, 6 cp, and 50 cp,* *Titanium Dioxide, USP,* *Macrogol* (b) (4) *NF,* *Triacetin, USP,* ***FD&C Yellow #5*** *FD&C Red #40* *[Vol. A3.1, 1/13/05 fax from* (b) (4)*]*	Coating

   The products contain FD&C Yellow #5. Impax has declared its presence on the container label and insert labeling as required by 21 CFR 201.20.

7. CONTAINER/CLOSURE

Container: white, round, HDPE bottle
Closure: CRC
Impax stated in the June 2005 amendment, that 30-count package will be dispensed to the patients directly, and will not be repackaged by the pharmacist. Thus Impax has updated the packaging configuration to include CRC manufactured by (b) (4)

6. PACKAGING CONFIGURATIONS
   RLD: Bottles of 30s
   ANDA: Bottles of 30s
   (b) (4)

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   RLD: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
   ANDA: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

9. TABLET IMPRINT
   RLD: unscored
   ANDA: The tablet descriptions are satisfactory as seen in the HOW SUPPLIED section.
   - 150 mg: Yellow Film coated, oval tablets, debossed with "681" on one side and plain on the other side.
   - 300 mg: Yellow Film coated, oval tablets, debossed with "682" on one side and plain on the other side.

Date of Review: 7/25/05; revised 7/27/05 Date of Submissions: 11/30/04 and 12/28/04

Primary Reviewer: Ruby Wu (for M.Dillahunt) Date: 7/27/05

Team Leader: Lillie Golson Date: 7/27/05

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cc:

ANDA: 77-415
DUP/DIVISION FILE
HFD-613/RWuforMDillahunt/LGolson (no cc)
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Review

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

ANDA Number: 77-415

Date of Submissions: September 28, 2005

Applicant's Name: IMPAX Laboratories, Inc.

Established Name: Bupropion Hydrochloride Extended-release Tablets USP, (XL)
150 mg and 300 mg (Once Daily)

Proprietary Name: None

Labeling Deficiencies

1. GENERAL

   - Revise the storage temperature to read as follows:

     "Store at 20°-25°C (68°-77°F); excursion permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature]"

2. CONTAINER (Bottles of 30s and 90s):

   - See comment under GENERAL.

   - The "Once Daily" statement should be darker.

3. PACKAGE INSERT/PATIENT INFORMATION SHEET

   - Include the statement "USP drug release test is pending" in the DESCRIPTION section.

   - Under the WARNINGS section, delete the following 6th paragraph:

     "In addition patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment."

4. MEDICATION GUIDE

   - Satisfactory as of September 28, 2005 submission.

Please revise your labels and labeling, as instructed above, and submit in final print in accord with the electronic labeling rule published December 11, 2003, (68 FR 69009) that requires submission of labeling content in electronic format. For additional information, consult the following guidance for industry regarding electronic submissions: Providing Regulatory Submissions in Electronic Format — ANDAs (Issued 6/2002) (http://www.fda.gov/cder/guidance/5004fnl.htm). The guidance specifies labeling to be submitted in pdf format. Documents submitted in electronic format should:

- Enable the user to easily view a clear and legible copy of the information
- Enable the user to print each document page by page, as it would have been provided in paper, maintaining fonts, special orientations, table formats, and page numbers
- Include a well-structured table of contents and allow the user to navigate easily through the submission
- Allow the user to copy text, images and data electronically into other common software formats.

To assist in our review, we request that labeling also be submitted in MS Word format.

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

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

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

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

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

FOR THE RECORD: (Part of this section came from the previous review)

**The previous review was done by Ruby Wu and this submission contains the response to the faxed comments. However, upon review, it was noted that the firm added a paragraph that's not included in the RLD labeling, and I am issuing another NA letter to request them to delete that particular paragraph.

1. The firm used the Tall-Man lettering for the established name as recommended in the Name Differentiation Project.

2. MODEL LABELING

   This review was based on the labeling for Wellbutrin® XL (GlaxoSmithKline; Approved 1-12-05) NDA 21-515/S-009 with the following changes:
   - Per memo from Kim Dettelbach, we will not require generic bupropions to reference a Pregnancy Registry. Therefore, reference to the pregnancy registry has been deleted from Impax's insert labeling.
   - Information regarding the insoluble shell remaining intact in the GI tract has been deleted from Impax's insert labeling since this is specific to the RLD.

3. Bupropion extended release tablets for Wellbutrin XL will contain "(XL)" and "Once Daily" on the labeling to distinguish from the Wellbutrin SR generic products.

4. USP ISSUE: There is a Bupropion Hydrochloride Extended-Release Tablets monograph in USP 28. However, according to the bio review (V:\firmsam\impax\ltrs&rev\77415D1104.doc), the monograph is not for Wellbutrin® XL:

   *"There are three types of Bupropion Hydrochloride Extended-Release Tablets made by GlaxoSmithKline listed as RLD: Wellbutrin® **SR**, Wellbutrin® **XL** and Zyban®. Wellbutrin® SR and Zyban® have same formulation and Wellbutrin® XL has different formulation. This application refers Wellbutrin® **XL** as RLD. The USP listed a dissolution method for Bupropion Hydrochloride Extended-Release Tablets for Wellbutrin® **SR** and Zyban®, but not for Wellbutrin® **XL**. For Wellbutrin® **XL**, there is an FDA-recommended method which is different from the USP method."*

   Per Nhan Tran's email dated 10/24/2005 , since this is an extended release dosage form, the firm does not have to use any of the USP methods if they choose not to. They should put in the Labeling the statement: "USP Drug release Test is pending". After the product is fully approved, he can get the data and convey to the USP for the test assignment.

5. PATENTS/EXCLUSIVITIES
   Patent Data – NDA 21-515

Patent Number	Patent Expiration	How Filed	Labeling Impact
6,096,341	October 30, 2018	IV	None
6,143,327	October 30, 2018	IV	None

   Exclusivity Data– NDA 21-515

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

6. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

   Impax Laboratories, Inc.
   30831 Huntwood Avenue
   Hayward, CA 94544

7. INACTIVE INGREDIENTS

   The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A3.1, pg. 115 & 119]

Components	Functions
Bupropion HCl, USP	Active
Hydroxypropyl cellulose, NF (b) (4)	(b) (4)

Components	Functions
Microcrystalline Cellulose, NF (b) (4)	(b) (4)
Lactose Monohydrate, NF (b) (4)	
Colloidal silicon dioxide, NF (b) (4)	
Magnesium Stearate, NF	
(b) (4) *Components of* (b) (4): *Polydextrose* (b) (4) *HPMC 2910/hypromellose 3cp, 6 cp, and 50 cp,* *Titanium Dioxide, USP,* *Macrogol* (b) (4) *NF,* *Triacetin, USP,* ***FD&C Yellow #5*** *FD&C Red #40* *[Vol. A3.1, 1/13/05 fax from* (b) (4)*]*	Coating

The products contain FD&C Yellow #5. Impax has declared its presence on the container label and insert labeling as required by 21 CFR 201.20.

8. CONTAINER/CLOSURE

Container: white, round, HDPE bottle
Closure: CRC
Impax stated in the June 2005 amendment, that 30-count package will be dispensed to the patients directly, and will not be repackaged by the pharmacist. Thus Impax has updated the packaging configuration to include CRC manufactured by (b) (4)

9. PACKAGING CONFIGURATIONS

RLD: Bottles of 30s
ANDA: Bottles of 30s and 90s

(b) (4)

***There were no labels submitted for review.*

10. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
ANDA: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

11. TABLET IMPRINT (pp. 3413-14 of the original application and pp. 679-80 of the amendment dated Dec 28, 2004)

RLD: unscored
ANDA: The tablet descriptions are satisfactory as seen in the HOW SUPPLIED section.

- 150 mg: Yellow Film coated, oval tablets, debossed with "681" on one side and plain on the other side.
- 300 mg: Yellow Film coated, oval tablets, debossed with "682" on one side and plain on the other side.

Date of Review: October 24, 2005 Date of Submissions: September 28, 2005

Primary Reviewer: Melaine Shin (for M.Dillahunt) Date: 10-31-05

Team Leader: Lillie Golson Date: 10/31/05

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cc:

ANDA: 77-415
DUP/DIVISION FILE
HFD-613/Shinm for MDillahunt/LGolson (no cc)
Review

File Path:V:\FIRMSAM\IMPAX\LTRS&REV\77415.na2.L.doc

Final: October 31, 2005

This AP summary is superceded by AP Summary for 8/16/06 & 8/18/06

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

ANDA Number:	77-415
Date of Submissions:	November 9, 2005
Applicant's Name:	IMPAX Laboratories, Inc.
Established Name:	Bupropion Hydrochloride Extended-release Tablets (XL) 150 mg and 300 mg (Once Daily)
Proprietary Name:	None

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

Do you have 12 Final Printed Labels and Labeling? E-submission

CONTAINER LABELS – Bottles of 30s and 90s

Satisfactory in final print as of November 9, 2005 submission

\\Cdsesub1\n77415\N_000\2005-11-09\440-02 150 mg 30 ct.pdf
\\Cdsesub1\n77415\N_000\2005-11-09\441-02 150 mg 90 ct.pdf
\\Cdsesub1\n77415\N_000\2005-11-09\487-02 300 mg 30 ct.pdf
\\Cdsesub1\n77415\N_000\2005-11-09\532-02 300 mg 90 ct.pdf

PROFESSIONAL PACKAGE INSERT

Satisfactory in final print as of November 9, 2005 submission

\\Cdsesub1\n77415\N_000\2005-11-09\439-02 BPP XL_18x11.pdf

****Please note that there is a citizens petition pending for generics for Wellbutrin XL product.**

REVISIONS NEEDED POST-APPROVAL: Yes. The firm needs to decrease the prominence of net quantity statement relative to the expression of strength.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 21-515

NDA Drug Name: bupropion hydrochloride extended-release tablets (XL)

NDA Firm: GlaxoSmithKline

Date of Approval of NDA Insert and supplement #: Approved 1-12-05: S-009

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

Was this approval based upon an OGD labeling guidance? No

FOR THE RECORD: (Part of this section came from the previous review)

**The previous review was done by Ruby Wu and this submission contains the response to the faxed comments. However, upon review, it was noted that the firm added a paragraph that's not included in the RLD labeling, and I am issuing another NA letter to request them to delete that particular paragraph.

***The firm used the Tall-Man lettering for the established name as recommended in the Name Differentiation Project.

1. MODEL LABELING

This review was based on the labeling for Wellbutrin® XL (GlaxoSmithKline; Approved 1-12-05) NDA 21-515/S-009 with the following changes:

- Per memo from Kim Dettelbach, we will not require generic bupropions to reference a Pregnancy Registry. Therefore, reference to the pregnancy registry has been deleted from Impax's insert labeling.
- Information regarding the insoluble shell remaining intact in the GI tract has been deleted from Impax's insert labeling since this is specific to the RLD.

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3. USP ISSUE: There is a Bupropion Hydrochloride Extended-Release Tablets monograph in USP 28. However, according to the bio review (V:\firmsam\impax\ltrs&rev\77415D1104.doc), the monograph is not for Wellbutrin® XL:

*"There are three types of Bupropion Hydrochloride Extended-Release Tablets made by GlaxoSmithKline listed as RLD: Wellbutrin® **SR**, Wellbutrin® **XL** and Zyban®. Wellbutrin® SR and Zyban® have same formulation and Wellbutrin® XL has different formulation. This application refers Wellbutrin® **XL** as RLD. The USP listed a dissolution method for Bupropion Hydrochloride Extended-Release Tablets for Wellbutrin® **SR** and Zyban®, but not for Wellbutrin® **XL**. For Wellbutrin® **XL**, there is an FDA-recommended method which is different from the USP method."*

Per Nhan Tran's email dated 10/24/2005 , since this is an extended release dosage form, the firm does not have to use any of the USP methods if they choose not to. They should put in the Labeling the statement: "USP Drug release Test is pending". After the product is fully approved, he can get the data and convey to the USP for the test assignment.

5. PATENTS/EXCLUSIVITIES

Patent Data – NDA 21-515

Patent Number	Patent Expiration	How Filed	Labeling Impact
6,096,341	October 30, 2018	IV	None
6,143,327	October 30, 2018	IV	None

Exclusivity Data– NDA 21-515

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

6. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Impax Laboratories, Inc.
30831 Huntwood Avenue
Hayward, CA 94544

7. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the

composition statement. [Vol. A3.1, pg. 115 & 119]

Components	Functions
Bupropion HCl, USP	Active
Hydroxypropyl cellulose, NF (b) (4)	(b) (4)
Microcrystalline Cellulose, NF (b) (4)	
Lactose Monohydrate, NF (b) (4)	
Colloidal silicon dioxide, NF (b) (4)	
Magnesium Stearate, NF	
(b) (4)	Coating
Components of (b) (4):	
Polydextrose (b) (4)	
HPMC 2910/hypromellose 3cp, 6 cp, and 50 cp,	
Titanium Dioxide, USP,	
Macrogol (b) (4) *NF,*	
Triacetin, USP,	
FD&C Yellow #5	
FD&C Red #40	
[Vol. A3.1, 1/13/05 fax from (b) (4)*]*	

The products contain FD&C Yellow #5. Impax has declared its presence on the container label and insert labeling as required by 21 CFR 201.20.

8. CONTAINER/CLOSURE

Container: white, round, HDPE bottle
Closure: CRC
Impax stated in the June 2005 amendment, that 30-count package will be dispensed to the patients directly, and will not be repackaged by the pharmacist. Thus Impax has updated the packaging configuration to include CRC manufactured by (b) (4).

9. PACKAGING CONFIGURATIONS

RLD: Bottles of 30s
ANDA: Bottles of 30s and 90s

(b) (4)

***There were no labels submitted for review.*

10. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

ANDA: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

11. TABLET IMPRINT (pp. 3413-14 of the original application and pp. 679-80 of the amendment dated Dec 28, 2004)

RLD: unscored

ANDA: The tablet descriptions are satisfactory as seen in the HOW SUPPLIED section.

150 mg: Yellow Film coated, oval tablets, debossed with "681" on one side and plain on the other side.

300 mg: Yellow Film coated, oval tablets, debossed with "682" on one side and plain on the other side.

Date of Review: January 9, 2006 Date of Submissions: November 9, 2005

Primary Reviewer: Melaine Shin 1/13/06 Date:

Team Leader: Lillie Golson 1/11/06 Date:

cc: ANDA 77-415
DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)

APPROVAL SUMMARY

File Path: V:\FIRMSAM\IMPAX\LTRS&REV\77415 AP1 Labeling..doc

FINAL: January 9, 2006

THIS REVIEW SUPERSEDES THE APPROVAL SUMMARY FOR THE SUBMISSION DATED 11/9/05
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-415

Date of Submission: July 26, 2006

Applicant's Name: IMPAX Laboratories, Inc.

Established Name: Bupropion Hydrochloride Extended-release Tablets USP, (XL)
150 mg and 300 mg (Once Daily)

Proprietary Name: None

Labeling Deficiencies:

A. GENERAL

Please provide a revised exclusivity statement for the I-497 exclusivity (PREVENTION OF SEASONAL MAJOR DEPRESSIVE EPISODES IN PATIENTS WITH SEASONAL AFFECTIVE DISORDER) expiring June 12, 2009, if you have not already done so.

B. PACKAGE INSERT/PATIENT INFORMATION SHEET

1. CLINICAL PHARMACOLOGY

CLNICAL TRIALS, revise to read; "Major Depressive Disorder: The efficacy of bupropion..."

2. INDICATIONS AND USAGE

First paragraph, revise to read; "Major Depressive Disorder: Bupropion extended-release tablets..."

3. WARNINGS

Add the following as the sixth paragraph;
"In addition patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment."

4. PRECAUTIONS

a. Revise the heading of Table 1 to " Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials of Bupropion extended-release tablets (SR) for Major Depressive Disorder."

b. Revise the heading of Table 2 to "Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials of Bupropion extended-release tablets (SR) for Major Depressive Disorder."

c. Allergic Reactions, your description section indicates that your 300 mg strength contains FD&C yellow #5, however you have not included a warning statement in your precautions section for the 300 mg strength insert.

5. ADVERSE REACTIONS

a. First paragraph, revise to read;

Major Depressive Disorder: Bupropion extended-release tablets have been demonstrated to have similar bioavailability both to the immediate-release formulation of bupropion and to the sustained

release formulation of bupropion (see CLINICAL PHARMACOLOGY). The information included under this subsection is based primarily on data from controlled clinical trials with bupropion extended- release tablets (SR) the sustained-release formulation of bupropion.

b. Revise the heading of the second paragraph as follows;
"Adverse Events Leading to Discontinuation of Treatment With Bupropion or Bupropion extended-release Tablets (SR).

c. Table 3, revise the heading to "Treatment Discontinuation Due to Adverse Events in Placebo-Controlled Trials for Major Depressive Disorder"

d. Fourth paragraph, revise title to "Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated With Bupropion or Bupropion extended-release tablets (SR).

e. Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials, change "Sustained-Release Formulation" to "Bupropion extended-release tablets (SR)".

6. OVERDOSAGE

Human Overdose Experience, revise subsection as follows;

Overdoses of up to 30 g or more of bupropion have been reported. Seizure was reported in approximately one third of all cases. Other serious reactions reported with overdoses of bupropion alone included hallucinations, loss of consciousness, sinus tachycardia, and ECG changes such as conduction disturbances or arrhythmias. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported mainly when bupropion was part of multiple drug overdoses.

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

7. DOSAGE AND ADMINISTRATION

a. Initial Treatment, revise to read; "Major Depressive Disorder: Initial Treatment:"

b. Maintenance Treatment, relocate this subsection to appear after "Increasing the Dosage Above 300 mg/day" subsection.

8. PATIENT INFORMATION SHEET

a. How should I take bupropion extended-release tablets?
Tenth bullet, revise to read; If you are taking bupropion extended-release tablets for the treatment of major depressive disorder, it may take several weeks for you to feel that bupropion extended-release tablets are working. Once you feel better, it is important to keep taking bupropion extended- release tablets exactly as directed by your doctor. Call your doctor if you do not feel bupropion extended-release tablets are working for you.

b. What are possible side effects of bupropion extended-release tablets?
Fifth paragraph, revise as follows; " Common side effects reported in studies of major depressive disorder include weight loss, loss of appetite...."

Please revise your labeling as instructed above and submit in final print. The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2aIG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32.

Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be submitted in PDF and MS Word until the SPL for the RLD is posted on the DailyMed website at

http://dailymed.nlm.nih.gov/dailymed/about.cfm. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Koung Lee at 301-827-7336.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

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

J. Cruz Sanchez for/ L. Golson + Wickman

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

FOR THE RECORD: (Part of this section came from the previous review)

1. The firm used the Tall-Man lettering for the established name as recommended in the Name Differentiation Project.

2. MODEL LABELING

   This review was based on the labeling for Wellbutrin® XL (GlaxoSmithKline; Approved 7-3-06 and 6-12-06) NDA 21-515/S-014 and S-018.

   - S-014 provides for a larger and more prominent font to state the number of times a day that the bupropion formulation should be taken. S-018 was used for the text for the generics
   - Per memo from Kim Dettelbach, we will not require generic bupropions to reference a Pregnancy Registry. Therefore, reference to the pregnancy registry has been deleted from Impax's insert labeling.
   - Information regarding the insoluble shell remaining intact in the GI tract has been deleted from Impax's insert labeling since this is specific to the RLD.

3. Bupropion extended-release tablets for Wellbutrin XL will contain "(XL)" and "Once Daily" on the labeling to distinguish from the Wellbutrin SR generic products.

4. USP ISSUE: There is a Bupropion Hydrochloride Extended-Release Tablets monograph in USP 28. However, according to the bio review (V:\firmsam\impax\ltrs&rev\77415D1104.doc), the monograph is not for Wellbutrin® XL:

   *"There are three types of Bupropion Hydrochloride Extended-Release Tablets made by GlaxoSmithKline listed as RLD: Wellbutrin® **SR**, Wellbutrin® **XL** and Zyban®. Wellbutrin® SR and Zyban® have same formulation and Wellbutrin® XL has different formulation. This application refers Wellbutrin® **XL** as RLD. The USP listed a dissolution method for Bupropion Hydrochloride Extended-Release Tablets for Wellbutrin® **SR** and Zyban®, but not for Wellbutrin® **XL**. For Wellbutrin® **XL**, there is an FDA-recommended method which is different from the USP method."*

   Per Nhan Tran's email dated 10/24/2005 , since this is an extended-release dosage form, the firm does not have to use any of the USP methods if they choose not to. They should put in the Labeling the statement: "USP Drug release Test is pending". After the product is fully approved, he can get the data and convey to the USP for the test assignment.

5. PATENTS/EXCLUSIVITIES
   Patent Data – NDA 21-515

Patent Number	Patent Expiration	How Filed	Labeling Impact
6,096,341	October 30, 2018	IV	None
6,143,327	October 30, 2018	IV	None

   Exclusivity Data– NDA 21-515

Code	Reference	Expiration	Labeling Impact
I-497	REVENTION OF SEASONAL MAJOR DEPRESSIVE EPISODES IN PATIENTS WITH SEASONAL AFFECTIVE DISORDER).	6/12/09	**Not addressed**

6. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

   Impax Laboratories, Inc.
   30831 Huntwood Avenue
   Hayward, CA 94544

7. INACTIVE INGREDIENTS

   The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A3.1, pg. 115 & 119]

Components	**Functions**
Bupropion HCl, USP	Active

Components	Functions
Hydroxypropyl cellulose, NF (b) (4)	(b) (4)
Microcrystalline Cellulose, NF (b) (4)	
Lactose Monohydrate, NF (b) (4)	
Colloidal silicon dioxide, NF (b) (4)	
Magnesium Stearate, NF	
(b) (4) *Components of* (b) (4): *Polydextrose* (b) (4) *HPMC 2910/hypromellose 3cp, 6 cp, and 50 cp,* *Titanium Dioxide, USP,* *Macrogol* (b) (4) *NF,* *Triacetin, USP,* ***FD&C Yellow #5*** *FD&C Red #40* *[Vol. A3.1, 1/13/05 fax from* (b) (4)	Coating

The products contain FD&C Yellow #5. Impax has not declared its presence on the container label and insert labeling as required by 21 CFR 201.20. (See def)

8. CONTAINER/CLOSURE

Container: white, round, HDPE bottle
Closure: CRC
Impax stated in the June 2005 amendment, that 30-count package will be dispensed to the patients directly, and will not be repackaged by the pharmacist. Thus Impax has updated the packaging configuration to include CRC manufactured by (b) (4).

9. PACKAGING CONFIGURATIONS

RLD: Bottles of 30s
ANDA: Bottles of 30s and 90s

(b) (4)

***There were no labels submitted for review.*

10. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
ANDA: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

11. TABLET IMPRINT (pp. 3413-14 of the original application and pp. 679-80 of the amendment dated Dec 28, 2004)

RLD: unscored
ANDA: The tablet descriptions are satisfactory as seen in the HOW SUPPLIED section.

- 150 mg: Yellow Film coated, oval tablets, debossed with "681" on one side and plain on the other side.
- 300 mg: Yellow Film coated, oval tablets, debossed with "682" on one side and plain on the other side.

12. Impax submitted insert labeling with the proposed proprietary name" Budeprion XL" in the July 12, 2006 amendment. Impax has now withdrawn this amendment.

13. Impax has submitted separate inserts for 150 mg and 300 mg anticipating that only one strength may be eligible for full approval.

Date of Review: August 1, 2006 Date of Submission: July 26, 2006

Primary Reviewer: M.Dillahunt Date: 8/7/06

Team Leader: Lillie Golson Date: 8/7/06

cc:

ANDA: 77-415
DUP/DIVISION FILE
HFD-613/ MDillahunt/LGolson (no cc)
Review
V:\FIRMSAM\IMPAX\LTRS&REV\77415.na3.L.doc

****This Approval Summary supersedes the Approval Summary for the submission dated 11/9/2005**

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

ANDA Number: 77-415

Date of Submission: August 16, 2006 and August 18, 2006 (August 10, 2006 submission was withdrawn)

Applicant's Name: IMPAX Laboratories, Inc.

Established Name: Bupropion Hydrochloride Extended-release Tablets USP, (XL)
150 mg and 300 mg (Once Daily)

Proprietary Name: None

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

Do you have 12 Final Printed Labels and Labeling? E-submission

CONTAINER LABELS – Bottles of 30s and 90s for both strengths

Satisfactory in final print as of November 9, 2005 submission

\\Cdsesub1\n77415\N_000\2005-11-09\440-02 150 mg 30 ct.pdf
\\Cdsesub1\n77415\N_000\2005-11-09\441-02 150 mg 90 ct.pdf
\\Cdsesub1\n77415\N_000\2005-11-09\487-02 300 mg 30 ct.pdf
\\Cdsesub1\n77415\N_000\2005-11-09\532-02 300 mg 90 ct.pdf

PROFESSIONAL PACKAGE INSERT

Satisfactory in final print as of August 16, 2006 submission

Package Insert 150 mg: \\Cdsesub1\n77415\N_000\2006-08-16\662-03 150 mg only.pdf
Package Insert 300 mg: \\Cdsesub1\n77415\N_000\2006-08-16\666-03 300 mg only.pdf
Medication Guide and Patient Information: \\Cdsesub1\n77415\N_000\2006-08-16\456-03BPP XL 18x11.pdf

REVISIONS NEEDED POST-APPROVAL: Yes

1. CONTAINER: Please decrease the prominence of the net quantity statement relative to the expression of strength.

2. PACKAGE INSERT for both strengths: ADVERSE REACTIONS - Please revise the heading of the second paragraph as follows:

   Adverse Events Leading to Discontinuation of Treatment With Bupropion Hydrochloride Tablets or Bupropion Hydrochloride Extended- release Tablets (SR)

3. PACKAGE INSERT for 300 mg strength: OVERDOSE, Human Overdose Experience, second paragraph, first sentence - Please delete "rarely".

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 21-515

NDA Drug Name: bupropion hydrochloride extended-release tablets (XL)

NDA Firm: GlaxoSmithKline

Date of Approval of NDA Insert and supplement #: Approved 7-3-2006 (S-014) and 6-12-2006 (S-018) (see detail in the For The Record)

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

Was this approval based upon an OGD labeling guidance? No

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 29	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? If yes, complete this subsection.		x	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		x	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	

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

NOTE AND QUESTION TO THE CHEMIST:

None

FOR THE RECORD:

(Part of this section came from the previous review. Previous reviews were conducted by Ruby Wu, Melaine Shin, and Michelle Dillahunt.)

1. The firm used the Tall-Man lettering for the established name as recommended in the Name Differentiation Project.

2. MODEL LABELING:

   This review was based on the labeling for Wellbutrin® XL by GlaxoSmithKline; NDA 21-515/S-014 and S-018 (Approved 7-3-06 and 6-12-06, respectively)

   - S-014 provides for a larger and more prominent font to state the number of times a day that the bupropion formulation should be taken. S-018 was used for the text for the generics
   - Per memo from Kim Dettelbach, we will not require generic bupropions to reference a Pregnancy Registry. Therefore, reference to the pregnancy registry has been deleted from Impax's insert labeling.
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*"There are three types of Bupropion Hydrochloride Extended-Release Tablets made by GlaxoSmithKline listed as RLD: Wellbutrin® **SR**, Wellbutrin® **XL** and Zyban®. Wellbutrin® SR and Zyban® have same formulation and Wellbutrin® XL has different formulation. This application refers Wellbutrin® **XL** as RLD. The USP listed a dissolution method for Bupropion Hydrochloride Extended-Release Tablets for Wellbutrin® **SR** and Zyban®, but not for Wellbutrin® **XL**. For Wellbutrin® **XL**, there is an FDA-recommended method which is different from the USP method."*

Per Nhan Tran's email dated 10/24/2005 , since this is an extended-release dosage form, the firm does not have to use any of the USP methods if they choose not to. They should put in the Labeling the statement: "USP Drug release Test is pending". After the product is fully approved, he can get the data and convey to the USP for the test assignment.

Insert Labeling contains the statement "USP Drug release test is pending."

5. PATENTS/EXCLUSIVITIES

Patent Data – NDA 21-515

Patent Number	Patent Expiration	How Filed	Labeling Impact
6,096,341	October 30, 2018	IV	None
6,143,327	October 30, 2018	IV	None

Exclusivity Data – NDA 21-515

Code	Reference	Expiration	Labeling Impact
I-497	REVENTION OF SEASONAL MAJOR DEPRESSIVE EPISODES IN PATIENTS WITH SEASONAL AFFECTIVE DISORDER).	June 12, 2009	Carved Out

6. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Impax Laboratories, Inc.
30831 Huntwood Avenue
Hayward, CA 94544

7. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A3.1, pg. 115 & 119]

Components	**Functions**
Bupropion HCl, USP	Active
Hydroxypropyl cellulose, NF (b) (4)	(b) (4)
Microcrystalline Cellulose, NF (b) (4)	
Lactose Monohydrate, NF (b) (4)	
Colloidal silicon dioxide, NF (b) (4)	
Magnesium Stearate, NF	
(b) (4) *Components of (b) (4)* *Polydextrose (b) (4)* *HPMC 2910/hypromellose 3cp, 6 cp, and 50 cp,* *Titanium Dioxide, USP,* *Macrogol (b) (4) NF,* *Triacetin, USP,* ***FD&C Yellow #5*** *FD&C Red #40* *[Vol. A3.1, 1/13/05 fax from (b) (4)]*	Coating

The products contain FD&C Yellow #5. Impax has declared its presence on the container label and insert labeling as required by 21 CFR 201.20.

8. CONTAINER/CLOSURE

Container: white, round, HDPE bottle
Closure: CRC
Impax stated in the June 2005 amendment, that 30-count package will be dispensed to the patients directly, and will not be repackaged by the pharmacist. Thus Impax has updated the packaging configuration to include CRC manufactured by (b) (4)

9. PACKAGING CONFIGURATIONS

RLD: Bottles of 30s
ANDA: Bottles of 30s and 90s

(b) (4)

***There were no labels submitted for review.*

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RLD: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
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ANDA: The tablet descriptions are satisfactory as seen in the HOW SUPPLIED section.

- 150 mg: Yellow Film coated, oval tablets, debossed with "681" on one side and plain on the other side.
- 300 mg: Yellow Film coated, oval tablets, debossed with "682" on one side and plain on the other side.

12. Impax submitted insert labeling with the proposed proprietary name" Budeprion XL" in the July 12, 2006 amendment. Impax has now withdrawn this amendment.

13. Impax has submitted separate inserts for 150 mg and 300 mg anticipating that only one strength may be eligible for full approval.

Date of Review: August 24, 2006

Date of Submission: August 16, 2006 and August 18, 2006 (August 10, 2006 submission was withdrawn)

Primary Reviewer: Sarah Park (for M.Dillahunt) Date: S. Park 8/30/2006

Team Leader: Lillie Golson Date: 8/30/06

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cc:

ANDA: 77-415
DUP/DIVISION FILE
HFD-613/ SPark for MDillahunt/LGolson (no cc)
Review
V:\FIRMSAM\IMPAX\LTRS&REV\77415.ap2.Labeling.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077415

MEDICAL REVIEWS

MEDICAL CONSULTATION

To:	**Parthapratim Chandaroy, Ph.D., DBE/OGD** **Barbara Davit, Ph.D., DBE/OGD**
Re:	**ANDA 77-415**
Drug Product:	**Bupropion Hydrochloride (Hcl) Extended-Release (ER) 150 mg and 300 mg**
Sponsor:	**Impax Laboratories, Inc.**
Reference Drug:	**Wellbutrin XL (bupropion hydrochloride extended release) Tablets, 150 mg** **GlaxoSmithKline N21-515, approved 8/28/03**
Original Submission:	**11/30/04 (amendments 12/28/04, 6/29/05)**
Date of Review:	**October 6, 2006**
Consultant:	**Nancy Chang, M.D.** **Medical Officer, Office of Generic Drugs**
Through:	**Dena Hixon, M.D.** **Associate Director for Medical Affairs, OGD**

Reason for Consult

Impax's Bupropion Hydrochloride ER Tablets differ in formulation from the RLD Wellbutrin XL and also from at least one other ANDA product (Anchen ANDA77-284) in that the Impax product does not have an enteric coating layer for delayed release. This formulation difference has resulted in a different *in vitro* dissolution profile for the Impax product and also a difference in Tmax values found in human single dose BE studies. However, mean elimination half-life values were similar between test and reference products. (Tables below taken from the DBE consult request):

Median (range) T_{max} values for the two bioequivalence studies (units = hours)

	Bupropion		Hydroxybupropion	
	Test	Reference	Test	Reference
Fasting study	3 (1.5-5)	5 (2-12)	10 (4-24)	12 (3-24)
Non-fasting study	3 (1-6)	6 (3-10)	10 (7-24)	12 (8-24)

Mean (%CV) Elimination Half-life values for the two bioequivalence studies (units = hours)

	Bupropion		Hydroxybupropion	
	Test	Reference	Test	Reference
Fasting study	19.0 (48.0)	19.2 (50.2)	24.8 (25.6)	25.0 (22.6)
Non-fasting study	16.4 (49.9)	18.8 (74.1)	22.0 (24.5)	22.5 (25.0)

In Impax's fasting and non-fasting BE trials, the 90% confidence intervals of the geometric mean AUC and Cmax test/reference ratios fell between 80-125% for both bupropion and hydroxybupropion. DBE is requesting a clinical consult to determine if Impax's product is expected to be therapeutically equivalent to the RLD despite the noted difference in Tmax.

Scope

This application has been the subject of internal discussions within OGD, including issues such as the regulatory determination of pharmaceutical equivalence for modified release drugs and the review of product design and in vitro dissolution data.

This scope of this consult will be limited only to the question of the clinical significance of the observed difference in Tmax between the RLD and test products.

Background

Product information and pharmacology

Wellbutrin XL is an extended release formulation of bupropion, an aminoketone antidepressant that weakly inhibits the neuronal uptake of norepinephrine, serotonin and dopamine. It is intended to be dosed once a day, compared to the Wellbutrin SR formulation, which is dosed twice a day, and the immediate release (IR) Wellbutrin tablet, which is dosed 3 times a day. Cmax for the IR and SR formulations is achieved within 2 hours and within 3 hours, respectively. Wellbutrin has a mean elimination half-life of 21 hours after chronic dosing.

WELLBUTRIN XL is contraindicated in patients with a seizure disorder or at higher risk for seizures, as it is associated with a dose-related risk of seizures. Wellbutrin produces dose-related central nervous system stimulation in animals, with convulsions occurring at approximately 10 times the human antidepressant dose.

The initial recommended dose for WELLBUTRIN XL is 150 mg/day with a usual target dose of 300 mg/day and a maximum recommended daily dose of 450 mg/day. The labeling states that patients may be switched from IR and SR formulations of WELLBUTRIN at the same daily dose. Although the labeling for these products state that their formulations are bioequivalent, the SR and IR products are not AB rated to Wellbutrin XL or to each other.

Hydroxybupropion is the major active metabolite of bupropion, and in an antidepressant model in mice, it was found to be half as potent as bupropion, whereas the other two known active metabolites, threohydrobupropion and erythrohydrobupropion, were found to be 5-fold less potent. Hydroxybupropion is

also the only metabolite that shows evidence of presystemic metabolism[1], hence OGD's current recommendation to measure hydroxybupropion levels in addition to the parent drug in the course of BE trials. Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300-450 mg/day.

Regulatory History of Wellbutrin

Wellbutrin (IR) was approved in 1985, followed by the SR formulation in 1996 and the XL formulation in 2003. Wellbutrin XL was originally approved for the treatment of major depression based on 5 BA and BE studies and the results of previous clinical trials of Wellbutrin (IR) in the treatment of major depression. Bioequivalence between the XL and SR formulations was demonstrated at steady state at the same total daily dose in a later supplement. Subsequently, in June 2006, Wellbutrin XL (but not the SR or immediate release formulations) was also approved for the prevention of seasonal major depressive episodes based on three 7-month clinical trials using the Wellbutrin XL formulation. No studies or labeling supplements were submitted to support the seasonal depression indication for the SR or IR formulations.

Zyban (N20711) is an identical formulation to Wellbutrin SR and is approved as an aide in smoking cessation treatment.

Bupropion is also used widely off-label for ADHD in children (Cantwell 1998 J Clin Psych 59(S4):92-4) at various doses and dosing frequencies.

The reliance on PK data for the approval of Wellbutrin XL is documented in the labeling and in the clinical and biopharm reviews of this product. The division had originally recommended that equivalence would need to be demonstrated for Cmax, AUC and Cmin for the parent and all 3 active metabolites. However, upon review of the NDA, the XL formulation was approved even though equivalence in Cmin was not demonstrated for the parent because bioequivalence criteria were met for all of the other parameters:

> Labeling:
> " Although there are no independent trials demonstrating the antidepressant effectiveness of WELLBUTRIN XL, studies have demonstrated similar bioavailability of WELLBUTRIN XL to both the immediate-release formulation and to the sustained-release formulation of bupropion under steady state conditions..."
>
> Reviews:
> "As noted, the pivotal bioequivalence study was a comparision of Wellbutrin IR 100 mg tid with Wellbutrin XL 300 mg qd. Equivalence for Cmax, Cmin, and AUC was shown for all 3 important metabolites, but only for Cmax and AUC for the parent."
>
> "It should be noted that although comparable exposure was demonstrated, there are differences in the shapes of the curves for bupropion in the WELLBUTRIN XL formulation compared with immediate release formulation. The clinical relevance of these differences cannot be predicted based on the pharmacokinetics. However, the comparable exposure and the role of the metabolites in the exposure and pharmacologic activity support the approval of the WELLBUTRIN XL formulation. Of note, for WELLBUTRIN SR, although there were also differences in the shapes of

1 From OGD CP response for 2005P-0498

the plasma concentration curves compared to WELLBUTRIN IR, a clinical trial demonstrated efficacy of WELLBUTRIN SR in maintaining antidepressant response."

Consistent with the reliance on PK data, rather than clinical trial data, to support the approval of the XL product, the labeling describing the safety profile of Wellbutrin XL for the depression indication is based primarily on data from clinical trials of the SR formulation. Estimates of seizure incidence are presented for the IR and SR formulations, but at different dose levels, so that it is not possible to compare seizure incidence for the IR and SR formulations. The XL labeling states the following:

> "As WELLBUTRIN XL is bioequivalent to both the immediate-release formulation of bupropion and to the sustained-release formulation of bupropion, the seizure incidence with WELLBUTRIN XL, while not formally evaluated in clinical trials, may be similar to that ...for the immediate-release and sustained release formulations of bupropion."

The only available direct comparison of adverse events between the IR and XL formulations was found in the BA/BE trials submitted to the NDA for the XL formulation. Based on these data and data from placebo controlled trials of the XL formulation for seasonal affective disorder, the clinical reviewers concluded that the AE profiles of the XL and IR formulations were similar. However, in the BA/BE studies, the actual incidence of AE's was lower in most categories for the XL formulation, suggesting a possible correlation between plasma concentration profile and safety. "Table 2" below is taken from the medical review of NDA 21-515.

Table 2. **Common Adverse Events in WELLBUTRIN XL Bioavailability Studies**

Adverse Event	WELLBUTRIN XL (300 mg) N = 254	Wellbutrin IR (300 mg) N = 95
Headache	9%	11.6%
Constipation	6.7%	13.7%
Nausea	4%	2%
Abdominal pain or discomfort	4%	8.4%
Rash	3.5%	6.3%
Tremor	2%	4.2%
Dizziness	1.6%	5.3%

Similar to Wellbutrin XL, the SR formulation was also originally approved based on bioequivalence studies. A post-approval placebo controlled clinical study demonstrated the efficacy of Wellbutrin SR in maintaining a long term antidepressant response and is the primary basis for safety information on the SR formulation. The mean peak plasma concentration of bupropion is 15% lower with the SR compared to the IR formulation, while the mean trough level is 7% higher with the SR compared to the IR formulation. (Davidson and Connor 1998 J Clin Psych 59(S4):25-31). Despite the paucity of direct comparative data

on safety, some investigators have gone so far as to assert that the SR formulation has a more benign side effect profile compared to the IR formulation (Settle 1998 J Clin Psych 59(S4):32-36); however, even if that assertion is correct, it would be impossible to know to what extent that effect would be attributable to a different rate of rise for SR vs. IR or to the lower Cmax levels for the SR formulation.

As with the XL formulation, labeling and NDA reviews of the SR formulation document the reliance on steady state bioequivalence studies using the same total daily dose for approval of the NDA. Although the drugs were not bioequivalent by usual generic drug standards, the labeling treats the SR and IR drugs as bioequivalent and clinically equivalent formulations:

> Labeling:
> "Thus, at steady state, WELLBUTRIN SR tablets, given twice daily, and the immediate-release formulation of bupropion, given 3 times daily, are essentially bioequivalent for both bupropion and the 3 quantitatively important metabolites.... Although there are not as yet independent trials demonstrating the antidepressant effectiveness of the sustained-release formulation of bupropion, studies have demonstrated the bioequivalence of the immediate-release and sustained-release forms of bupropion under steady-state conditions...with regard to both rate and extent of absorption, for parent drug and metabolites."
>
> Clinical Review:
> "It should be noted that Wellbutrin SR was approved solely on the basis of bioequivalence studies that show equivalence for both Cmax and AUC for all three important metabolites (hydroxy-bupropion, threohydro-bupropion, and erythrohydro-bupropion), **but only for AUC for the parent drug**. That study compared Wellbutrin given on a tid basis and Wellbutrin SR given on a bid basis. We were not troubled by the failure on Cmax for parent drug, since about 90% of the systemic exposure to this compound comes from the metabolites, all of which are active and are believed to be the predominant source of activity for this drug."

In only one part of the label is a suggestion that there might be a clinical difference between SR and IR formulations, although that suggestion is essentially dismissed by later language:

> "At doses up to 300 mg/day of the SR formulation...the incidence of seizure is approximately 0.1%.... Data for the IR formulation revealed a seizure incidence of approximately 0.4% in patients treated at doses in a range of 300 to 450 mg/day... the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day." Labeling for the SR product also states: "It is not possible to know if the lower seizure incidence observed...involving the SR formulation...resulted from the different formulation or the lower dose used. However...the IR and SR 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."
>
> Of note, this language may seem somewhat discordant with the following language in the IR labeling "Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks at fixed dose."

Discussion

The IR, SR and XL formulations of Wellbutrin have roughly equivalent Cmax and AUC values in

bioequivalence trials, although some bioequivalence trials have not met usual generic drug standards for bioequivalence. Nevertheless, these formulations have been labeled as bioequivalent and clinically equivalent formulations, in part based on confirmatory data demonstrating bioequivalence for all 3 active metabolites. As such, safety and efficacy data for these formulations have been used almost interchangeably to describe all three formulations. The Impax product, which has a comparable Cmax and AUC to Wellbutrin XL (and thus presumably to all the Wellbutrin formulations), has a Tmax that is close to that of the SR formulation, and intermediate between the IR and XL formulations. Thus, the clinical range of effects of the Impax product would be expected to be within the range delineated by the line of Wellbutrin products. If there is indeed no difference in safety and efficacy among the Wellbutrin formulations, then the Impax product should also be indistinguishable.

The clinical efficacy of bupropion has been assessed on a time frame of weeks to months, so efficacy is expected to be closely related to steady state levels of bupriopion, which would be most closely related to AUC. If clinically important differences among the formulations might exist related to their differences in Tmax, reflecting differences in the rate of rise of plasma levels, these differences would most likely be evident as differences in safety.

A fundamental difference among the formulations (and between the XL product and the Impax product) is in the rate of rise of plasma levels. Many other drugs, including antidepressants, have been documented to have a greater incidence of adverse events associated with a more rapid rate of release into the systemic circulation (Orbach et al 2005 Clin Rev Allerg Immunol 29(3):173-84; Wermeling 2005 Pharmacother 25(8):1084-94; Polk 1991 J Antimicrob Chemother 27(SB):17-29; Robinson 2003 Clin Ther 25(6):1618-33; Olver 2004 Hum Psychopharmacol 19(1):9-16). However, most if not all of these examples have also been associated with a change in Cmax, so it is difficult to independently assess the contribution of rate of rise to clinical adverse events.

There is very little data available directly comparing the clinical effects of one Wellbutrin formulation compared to another, and therefore it is difficult to address the question of the clinical sameness of the Wellbutrin formulations. The best available information is the safety data from the BA/BE trials comparing Wellbutrin XL and IR, and while those data seem to suggest a possible safety advantage for the XL formulation, they are far from definitive.

The incidence of adverse events reported in the BE studies for the Impax product was similar between the test and reference products; however, the total number of adverse events reported was small (15 in test groups, 14 in reference groups, with 74 total study subjects).

Even weaker evidence comes from the analysis of seizure incidence in labeling. The most serious adverse event associated with bupropion is seizures. Within the approved dosing range, a 4-fold difference in the incidence of seizures was reported between the SR and IR formulations. While this has been taken by some authors to mean that the SR formulation is less likely to provoke seizures compared to the IR formulation (Stahl 1998 J Clin Psych 59(S4):5-14), it is impossible to determine the relative contributions of dose, rate of rise, and Cmax to this apparent difference in seizure rates, because the two groups differed by all 3 variables. In addition, the different incidence rates were reported across different trials, not within trials, so that other unidentified variables may have also contributed to this apparent difference.

Another area where a clinical effect of different release rates and plasma concentration profiles is theoretically possible is in the off-label treatment of ADHD. Some authors have reported differences in efficacy during the course of the day during treatment with methylphenidate. These differences in efficacy were correlated with changes in plasma concentrations of methylphenidate during the course of the day. However, there is insufficient data at present to determine the safety or efficacy of bupropion for this use, much less whether or

not bupropion might exhibit a similar concentration-effect relationship during the daily course of treatment.

Conclusions

At present, there are no available data demonstrating clinically meaningful differences among the immediate and modified release formulations of Wellbutrin or between the Wellbutrin products and the proposed Impax product.

Existing regulatory precedent in bupropion NDA reviews has not placed any significance on the rate of rise in serum concentrations of the drug. Indeed, even formulations that would not have met the usual generic standards for bioequivalence and that have widely disparate concentration-time profiles have been treated as bioequivalent formulations in labeling. Therefore, although we can not be completely assured that the Impax and Wellbutrin products will not be clinically different, approval of the Impax product as a therapeutically equivalent generic would be consistent with existing regulatory precedent and the use of these products in clinical practice.

CC: Division File
HFD-600/Nancy Chang
HFD-600/Dena Hixon
HFD-650

Saved in:
V:\FIRMSAM\Impax\CONTROLS\77415C1104.mor
V:\DIVISION\ClinicalTeam\Drug Files\bupropion\77415C1104.mor

Printed in final on: October 10, 2006

Endorsements: (final with dates)

HFD-600/Nancy Chang _____ October 6, 2006

HFD-600/Dena Hixon _____ October 6, 2006

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Nancy Chang
10/6/2006 01:14:28 PM
MEDICAL OFFICER

Dena Hixon
10/10/2006 03:11:56 PM
MEDICAL OFFICER

ADDENDUM

MEDICAL CONSULTATION

To:	**Parthapratim Chandaroy, Ph.D., DBE/OGD** **Barbara Davit, Ph.D., DBE/OGD**
Re:	**ANDA 77-415**
Drug Product:	**Bupropion Hydrochloride (Hcl) Extended-Release (ER)** **150 mg and 300 mg**
Sponsor:	**Impax Laboratories, Inc.**
Reference Drug:	**Wellbutrin XL (bupropion hydrochloride extended release) Tablets, 150 mg** **GlaxoSmithKline N21-515, approved 8/28/03**
Original Submission:	**11/30/04 (amendments 12/28/04, 6/29/05)**
Date of Review:	**December 13, 2006**
Consultant:	**Nancy Chang, M.D.** **Medical Officer, Office of Generic Drugs**
Through:	**Dena Hixon, M.D.** **Associate Director for Medical Affairs, OGD**

This addendum is to clarify the last sentence of the consult for ANDA 77-415 for generic bupropion HCl extended-release tablets. (Medical Consultation, Date of Review: October 6, 2006). We concluded in this consult that there was no reasonable basis upon which to conclude that the observed differences in Tmax between the RLD and test products were clinically significant.

The last sentence of the consult reads: "Therefore, although we can not be completely assured that the Impax and Wellbutrin products will not be clinically different, approval of the Impax product as a therapeutically equivalent generic would be consistent with existing regulatory precedent and the use of these products in clinical practice."

This sentence should read: "Approval of the Impax product as a therapeutically equivalent generic drug to Wellbutrin XL would be consistent with (among other things) existing regulatory precedent and the use of these products in clinical practice. We can reasonably expect that the Impax product and Wellbutrin XL would have the same clinical effect when administered to patients under the conditions for use prescribed, recommended, or suggested in the labeling. Based on the current, relevant scientific evidence, there is no reasonable basis upon which to reasonably conclude otherwise."

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Nancy Chang
12/13/2006 01:23:41 PM
MEDICAL OFFICER

addendum to bupropion medical consult as recommended by Sonal Vaid

Robert L. West
12/13/2006 01:41:39 PM
CSO
for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077415

CHEMISTRY REVIEWS

ANDA 77-415

Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg

Impax Laboratories Inc.

Aloka Srinivasan, Ph.D.

Division of Chemistry III
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-415

2. REVIEW #: 1

3. REVIEW DATE: March 28, 2005

4. REVIEWER: Aloka Srinivasan, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Firm	
Original	Nov 30, 2004
Major Amendment	Dec 28, 2004
Minor Amendment	Jan 12, 2005
Agency	
Acceptable for Filing	Dec 1, 2004
Date of Filing	Jan 13, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Impax Laboratories, Inc.
Address:	30831 Huntwood Avenue Hayward, CA 94544
Representative:	Mark C. Shaw
Telephone:	(510)-476-2018
Fax:	(510)-476-2091

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Wellbutrin XL

b) Non-Proprietary Name (USAN): Bupropion Hydrochloride Extended-Release Tablets

9. LEGAL BASIS FOR SUBMISSION:

In their application, Impax has stated the following:

a. The basis for Impax Pharmaceuticals' proposed ANDA for Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg is the approved, referenced listed drug, Wellbutrin XL Tablets, 150 mg and 300 mg manufactured by SmithKline Beecham, subject of NDA No. 21-515.

b. Impax has claimed the Paragraph IV certification for the following US patents listed for Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg in this ANDA application:

US Patent #	Expiration Date
6096341	Oct 30, 2018
6143327	Oct 30, 2018

c. Impax has claimed on p. 9 of Vol. 3.1 that to the best of their knowledge, that exclusivity M-10 has expired on June 11, 2004.

10. PHARMACOL. CATEGORY: Antidepressant

11. DOSAGE FORM: Extended-Release Tablets

12. STRENGTH/POTENCY: 150 mg and 300 mg

13. ROUTE OF ADMINISTRATION: Oral Administration

14. Rx/OTC DISPENSED: _X_Rx ___OTC

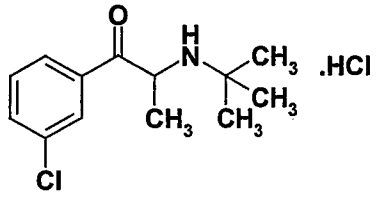
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Buproprion Hydrochloride



Chemical Name:	(±)-1-(3-Chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanione hydrochloride
Molecular Formula:	$C_{13}H_{18}ClNO \cdot HCl$
Molecular Weight:	276.21
CAS:	31677-93-7

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	1/10/2005	Reviewer: Bing Wu
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application

5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
ANDA	76-711	Bupropion HCl ER Tablets, 200 mg (Impax), approved on 12/03/04

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 77-415

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The firm needs to address the minor deficiencies related drug substance, drug product, and analytical methods.

Not Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

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 diethylpropione; 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.

Bupropion hydrochloride extended-release tablets are supplied for oral administration as 150-mg and 300-mg, yellow extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: colloidal silicon dioxide, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The film-coating material contains FD&C red #40, FD&C yellow # 5, hypromellose type 2910/ 3cP, 6cP and 50cP, macrogol, polydextrose, titanium dioxide and triacetin.

B. Description of How the Drug Product is Intended to be Used

The usual adult target dose for bupropion hydrochloride extended-release tablets is 300 mg/day, given once daily in the morning. 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 once daily, may be made as early as day 4 of dosing. There should be an interval of at least 24 hours between successive doses.

The maximum daily dosage is 450 mg.

C. Basis for Approvability or Not-Approval Recommendation

ANDA 77-415 has the following deficiencies:

- The inconsistencies in the drug substance COA needs to be clarified.
- [redacted] (b) (4) for the package of 30s needs to be justified.
- In-process controls are inadequate.
- Analytical Methods are inadequate.
- A second identification test needs to be added in the drug product release specification.
- Bioequivalance and drug release review is pending
- Labeling review is pending
- EER is pending.

III. Administrative

A. Reviewer's Signature Aloka Srinivasan 5/16/05

B. Endorsement Block

Endorsements (Draft and Final with Dates)

Aloka Srinivasan, Ph.D./Chemistry Reviewer /5/6/05 Aloka Srinivasan 5/16/05
Shing H. Liu, Ph.D../Team Leader/5/9/05 S.H.Liu 5/16/05
Lisa Kim, Pharm. D./Project Manager/

C. CC Block

ANDA 77-415
DIV FILE
Field Cop

File: V:\FIRMSAM\IMPAX\LTRS&REV\77415.REV1.doc

The current document is the review of the following submissions related to ANDA 77-415:

- Impax's Original Application dated 11 Nov, 2004, for Bupropion HCl Extended-Release Tablets, 150 mg. This document will be referred to as the **original application** throughout this review.

- Impax's major amendment dated 28 Dec, 2004, for addition of new strength, Bupropion HCl Extended-Release Tablets, 300 mg. This document will be referred to as **Amendment 1** throughout review.

- Impax's minor amendment dated 12 Jan, 2005, provides the quantitative composition of the excipient, [redacted] (b) (4), and the labeling for the 500 count configuration. This document will be referred to as **Amendment 2** throughout this review.

Following this page 27 pages withheld in full (b)(4)-CCI/TS

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS
N/A

32. LABELING: Acceptable as of 23 March, 2005. Reviewer: J. Grace

33. ESTABLISHMENT INSPECTION

34. BIOEQUIVALENCE: Pending Review

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
The firm has requested a categorical exclusion from the requirement of an Environmental Assessment Statement in accordance with 21 CFR 25.31(a) on p. 3617 of the original application and p. 927 of Amendment 1.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-415

APPLICANT: Impax, Inc.

DRUG PRODUCT: Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

4.

(b) (4)

5.

6.

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

1. Please provide any additional room temperature stability data accrued till date.

2. The bioequivalence information that you have provided is currently under review. After completion of bioequivalence review, the deficiencies if any, will be communicated to you under a separate cover.

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

4. Please be aware that the Labeling deficiencies, if any, must be resolved prior to approval of the ANDA.

5. Please acknowledge that in the event of any dispute, the USP methods will be deemed the official methods.

Sincerely yours,

for 5/16/05

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

CHEMISTRY REVIEW

Chemistry Assessment Section

cc: ANDA 77-415
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/ASrinivasan, Ph.D./Chemistry Reviewer/ 5/6/05 Aloka Srinivasan 5/16/05
HFD-630/SLiu, Ph.D./Team Leader/5/9/05 S.H. Liu 5/16/05
HFD-617/SPark, R.Ph../Project Manager/ C. Kiester for 5/11/05

F/T by: EW 5/13/05

V:\FIRMSAM\IMPAX\LTRS&REV\77415.REV1.doc

TYPE OF LETTER: NOT APPROVABLE – TELEPHONE AMENDMENT

ANDA 77-415

Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg

Impax Laboratories Inc.

Aloka Srinivasan, Ph.D.

Division of Chemistry III
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-415

2. REVIEW #: 2

3. REVIEW DATE: July 16, 2005

4. REVIEWER: Aloka Srinivasan, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Firm	
Original	Nov 30, 2004
Major Amendment	Dec 28, 2004
Minor Amendment	Jan 12, 2005
Agency	
Acceptable for Filing	Dec 1, 2004
Date of Filing	Jan 13, 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	June 21, 2005
Telephone Amendment	August 5, 2005
Minor Amendment	June 5, 2005
Telephone Amendment	November 2, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Impax Laboratories, Inc.
Address:	30831 Huntwood Avenue Hayward, CA 94544
Representative:	Mark C. Shaw
Telephone:	(510)-476-2018

Fax: (510)-476-2091

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Wellbutrin XL

b) Non-Proprietary Name (USAN): Bupropion Hydrochloride Extended-Release Tablets

9. LEGAL BASIS FOR SUBMISSION:

In their application, Impax has stated the following:

a. The basis for Impax Pharmaceuticals' proposed ANDA for Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg is the approved, referenced listed drug, Wellbutrin XL Tablets, 150 mg and 300 mg manufactured by SmithKline Beecham, subject of NDA No. 21-515.

b. Impax has claimed the Paragraph IV certification for the following US patents listed for Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg in this ANDA application:

US Patent #	Expiration Date
6096341	Oct 30, 2018
6143327	Oct 30, 2018

c. Impax has claimed on p. 9 of Vol. 3.1 that to the best of their knowledge, that exclusivity M-10 has expired on June 11, 2004.

10. PHARMACOL. CATEGORY: Antidepressant

11. DOSAGE FORM: Extended-Release Tablets

12. STRENGTH/POTENCY: 150 mg and 300 mg

13. ROUTE OF ADMINISTRATION: Oral Administration

14. Rx/OTC DISPENSED: _X_Rx ___OTC

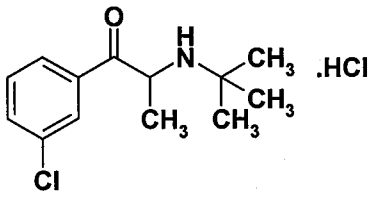
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Buproprion Hydrochloride



Chemical Name:	(±)-1-(3-Chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanione hydrochloride
Molecular Formula:	$C_{13}H_{18}ClNO \cdot HCl$
Molecular Weight:	276.21
CAS:	31677-93-7

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	5/18/2005	Reviewer: Ashley Ham
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review

4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	12/13/05	J. D Ambrogio
Methods Validation	N/A		
Labeling	Acceptable	8/30/06	S. Park
Bioequivalence	Acceptable	8/24/05	B. V. Li
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 77-415

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

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 diethylpropione; 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.

Bupropion hydrochloride extended-release tablets are supplied for oral administration as 150-mg and 300-mg, yellow extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: colloidal silicon dioxide, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The film-coating material contains FD&C red #40, FD&C yellow # 5, hypromellose type 2910/ 3cP, 6cP and 50cP, macrogol, polydextrose, titanium dioxide and triacetin.

B. Description of How the Drug Product is Intended to be Used

The usual adult target dose for bupropion hydrochloride extended-release tablets is 300 mg/day, given once daily in the morning. 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 once daily, may be made as early as day 4 of dosing. There should be an interval of at least 24 hours between successive doses.

The maximum daily dosage is 450 mg.

C. Basis for Approvability or Not-Approval Recommendation

ANDA 77-415 has the following deficiencies:

- CMC is approvable
- Dissolution is acceptable
- Bioequivalance review is acceptable
- Labeling review is acceptable
- EER is acceptable

III. Administrative

A. Reviewer's Signature ALS 11/17/06

B. Endorsement Block

Endorsements (Draft and Final with Dates)

Aloka Srinivasan, Ph.D./Chemistry Reviewer / ALS 11/17/06.
Shing H. Liu, Ph.D../Team Leader/ S.H. Liu 11/17/06
Lisa Kwok, Pharm. D./Project Manager/ 11/17/06

C. CC Block
ANDA 77-415
DIV FILE
Field Copy

Following this page, 16 pages withheld in full (b)(4)-CCI/TS

(b) (4)

[redacted]

30. MICROBIOLOGY
N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS
N/A

32. LABELING: Acceptable as of 8/30/06

33. ESTABLISHMENT INSPECTION: EER Acceptable as of 12/13/05

34. BIOEQUIVALENCE: Acceptable as of 8/24/05

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Satisfactory in Review Cycle 1

cc: ANDA 77-415
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/ASrinivasan, Ph.D./Chemistry Reviewer/ Moka Srinivasan 11/17/06.
HFD-630/SLiu, Ph.D./Team Leader/ S.H. Liu 11/17/06
HFD-617/LKwok, Pharm.D./Project Manager/ LKwok 11/17/06

F/T by: LK 10/19/06

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TYPE OF LETTER: APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077415

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	77-415
Drug Product Name	Bupropion Hydrochloride Extended-Release Tablets
Strength	150 mg, 300 mg
Applicant Name	Impax Laboratories, Inc.
Submission Date(s)	Nov. 30, 2004 and Dec 28, 2004
First Generic	No
Reviewer	Bing V. Li, Ph.D.
File Location	V:\firmsam\impax\ltrs&rev\77415D1104.doc
Clinical Site	Gateway Medical Research, Inc.
Analytical Site	(b) (4)

EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There are three types of Bupropion Hydrochloride Extended-Release Tablets made by GlaxoSmithKline listed as RLD: Wellbutrin® **SR**, Wellbutrin® **XL** and Zyban®. Wellbutrin® SR and Zyban® have same formulation and Wellbutrin® XL has different formulation. This application refers Wellbutrin® **XL** as RLD. The USP listed a dissolution method for Bupropion Hydrochloride Extended-Release Tablets for Wellbutrin® **SR** and Zyban®, but not for Wellbutrin® **XL**. For Wellbutrin® **XL**, there is an FDA-recommended method which is different from the USP method. The firm conducted its dissolution testing using the FDA method. The firm also conducted its dissolution testing in three other different media. (DI water, acetate buffer, pH 4.5, and simulated intestinal fluid without enzyme, pH 6.8). The firm's dissolution testing with the FDA method is acceptable. The firm proposed dissolution specifications for the 150 mg ER tablet but did not proposed any specifications for the 300 mg ER tablet. The firm's proposed specifications are not acceptable. The DBE proposes different specifications which the both ER tablets meet at the L1 level. The firm should acknowledge the FDA-recommended method and the current proposed specifications (1hr: (b) (4)%, 2hrs: (b) (4)%, 4hrs: (b) (4)%, 8hrs: (b) (4)%, 12hrs: NLT (b) (4)% dissolved). The dissolution testing portion is **incomplete**.

The DBE will review the fasted and fed BE studies and waiver requests at a later date.

FDA-recommended METHOD: (for Wellbutrin® XL)

Medium	0.1 N HCl
Volume	900 mL
Temperature	37°C ± 5°C
Apparatus	USP Apparatus 1 (Basket)
Rotational Speed	75 rpm
Specification	2 hours: (b) (4) 4 hours: 8 hours: 16 hours

USP METHOD: (for Zyban® and Wellbutrin® SR)

Medium	Water
Volume	900 mL
Temperature	37°C ± 5°C
Apparatus	USP apparatus 2 (paddles)
Rotational Speed	50 rpm
Specification	1 h: between 25% and 45 % 4 h: between 60% and 85 % 8 h: NLT 80%

Source of Method:

- USP-NF
- NDA 21-515, CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

Reviewer's Comments on the dissolution method listed above:

Though not specified, the USP dissolution method is for Wellbutrin® **SR,** and Zyban® and not for Wellbutrin® **XL.** The reasons are as follows (facts collected from NDA 21-515 review):

1. Wellbutrin® XL tablet floated to the top when tested in using USP apparatus 2 (paddle). Therefore, paddle in USP method is not applicable.
2. Wellbutrin® XL released very slow in water, (b) (4) % drug was released in 16 hours. Therefore, water used in USP method is not applicable.

Relevant OGD Dissolution History:

1. Three types of Bupropion HCl ER Tablets have been approved as RLDs which is summarized as below:

NDA	Name	Strengths	RLD
20-358	Wellbutrin® SR	50 mg, 100 mg, 150 mg and 200 mg	150 mg
20-711	Zyban®	150 mg	150 mg

21-515	Wellbutrin® XL	150 mg, 300 mg	150 mg

2. The 150 mg Wellbutrin® SR and 150 mg Zyban® tablets have the same formulation, but Wellbutrin® XL has a different formulation. Wellbutrin® is an antidepressant and Zyban® is a smoking cessation aid.

3. In the past, Impax has submitted three applications for its Bupropion HCl ER Tablets:

   - ANDA 75-913 was submitted for the Bupropion HCl ER Tablets 100 mg and 150 mg, referencing Wellbutrin SR® Tablets. The dissolution testing with the **USP method** was acceptable and the firm proposed specifications were also acceptable (1 hour: (b) (4)%, 2 hours: (b) (4)%, 4 hours: (b) (4)%, 6 hours: (b) (4)%)

   - ANDA 76-711 was submitted for the Bupropion HCl ER Tablet, 200 mg, referencing Wellbutrin® SR 200 mg. The dissolution testing with the **USP method** was acceptable and the firm's specifications, as listed above, were also accepted.

   - ANDA 75-914, was submitted for the Bupropion HCl ER Tablet, 150 mg, referencing Zyban® 150 mg. The dissolution testing with the **USP method** was acceptable and the firm's specifications, as listed above, were also accepted.

4. In the current submission (ANDA 77-415), Impax is applying for the Bupropion HCl ER Tablets, 150 mg and 300 mg, referencing Wellbutrin® **XL**. The dissolution was conducted using the FDA-recommended method.

5. In addition, OGD has approved various methods and specifications for the generic version of Wellbutrin® SR and Zyban® in the past. A brief summary is as follows:

ANDA	Firm	Submission date	Method	Specification	RLD
77-475	Abrika	Dec. 22, 2004	water, 900 ml, 50 rpm, apparatus 1 (basket)	NA	Zyban®
76-834	Geneva PTC	August 28, 2003	USP	1 hour: (b) (4) 3 hours: 8 hours:	Zyban®
75-932/SCS-004	Eon Labs, Inc.	January 21, 2004	900 mL of 0.1 N HCl, pH 1.5, USP Apparatus I (Basket), 50 rpm	1hour: 25% - 50% 2hours: 40% - 65% 4hours: 65% - 90% 6hours: NLT 80%	Wellbutrin® SR
76-711	Impax Laboratories	May 14, 2004 June 11, 2004	USP	1 hour: 30-55% 2 hours: 50-75%	Wellbutrin® SR, 200 mg

		(Telephone Amendment)		4 hours: 70-90% 6 hours: NLT 80%	
(b) (4)					Zyban® Wellbutrin® SR
(b) (4)					Wellbutrin® SR and Zyban®
75-914 75-913	Impax Pharmaceuticals, Inc.	April 3, 2003 May 16, 2001 June 22, 2000, Aug. 25, 2000	USP	1 hour: 30-55% 2 hours: 50-75% 4 hours: 70-90% 6 hours: NLT 80%	Wellbutrin® SR and Zyban®
(b) (4)					Wellbutrin® SR
00-278	(b) (4)	July 12, 2000	USP	NA	
75-932	Eon Labs Manufacturing, Inc	07/26/00	0.1 N HCl, pH 1.5 900 ml USP Apparatus 1, baskets, 50 RPM	1 hour: 25-50% 2 hour: 40-65% 4 hour: 65-90% 6 hour: NLT 80%	Wellbutrin® SR

Table 1 Comparative Dissolution Data

The firm has conducted the dissolution testing using the following four methods:

Please note that the dissolution testing data were submitted on two different dates. The 150 mg ER tablet has comparative dissolution data while the 300 mg ER tablet has comparative dissolution data plus data for the 150 mg test ER tablet. The dissolution testing data for the 150 mg test ER tablet submitted on two dates are identical.

Method 1: RLD method:

Source of Method:	FDA
Medium:	0.1 N HCl
Volume:	900 mL, 37 °C ± 5°C
Apparatus:	USP apparatus 1 (basket) at 75 rpm
Firm proposed specification:	1hr: (b) (4)
Only for the 150 mg ER tablet	2hrs: %
	4hrs: %
	8hrs: %
	12hrs: (b) (4) % dissolved

Dissolution Data in 0.1 N HCl: (11-30-2004)

Sampling Time (min)	Impax's Bupropion Hydrochloride ER Tablets, Strength: 150 mg, Lot No. R04035-500, Reference: V1.11, p 2972, Firm's reference: LO1207, pp.45-49			GlaxoSmithKline Wellbutrin® XL Tablets, Strength: 150 mg, Lot No. 04C003P, Reference: V1.11, p 2972, Firm's reference: CY1159, pp.66-71		
	Mean%	%CV	Range%	Mean%	%CV	Range%
60	25	1.9	(b) (4)	0	0	(b) (4)
120	38	2.1		2	1.6	
240	56	2.6		24	5.7	
360	70	2.6		51	5.3	
480	80	2.8		73	4.7	
720	93	2.5		92	1.8	

Dissolution Data in 0.1 N HCl: (12-28-2004)

Sampling Time (min)	Impax's Bupropion Hydrochloride ER Tablets, Strength: 150 mg, Lot No. R04035-500, Reference: V3.1, p 0093, Firm's reference: JC1217, pp.71-76			GlaxoSmithKline Wellbutrin® XL Tablets, Strength: 300 mg, Lot No. 03K021P, Reference: V3.1, p 0097, Firm's reference: CY1159, pp.63-65			Impax's Bupropion Hydrochloride ER Tablets, Strength: 300 mg, Lot No. R04041-180, Reference: V3.1, p 0093, Firm's reference: CY1159, pp.87-91		
	Mean %	%CV	Range%	Mean %	%CV	Range%	Mean%	%CV	Range%
60	25	1.9	(b) (4)	1	0.5	(b) (4)	22	0.7	(b) (4)
120	38	2.1		8	4.1		32	1.1	
240	56	2.6		32	6.4		48	1.3	
360	70	2.6		53	5.9		60	1.5	
480	80	2.8		71	4.8		70	1.8	
720	93	2.5		90	2.2		84	2.3	

Method 2:

Source of Method:	Firm
Medium:	water
Volume:	900 mL, 37 °C ± 5°C
Apparatus:	USP apparatus 1 (basket) at 75 rpm

Dissolution Data in DI Water: (11-30-2004)

Sampling Time (min)	Impax's Bupropion Hydrochloride ER Tablets, Strength: 150 mg Lot No. R04035-500 Reference: V1.11, p 2971 Firm's reference: JC1217, pp.71-76			GlaxoSmithKline Wellbutrin® XL Tablets, Strength: 150 mg Lot No. 04C003P Reference: V1.11, p 2971 Firm's reference: CY1159, pp.42-44		
	Mean%	%CV	Range%	Mean%	%CV	Range%
60	27	2.5	(b) (4)	0	0.0	(b) (4)
120	40	2.9		1	0.2	
240	58	2.4		5	2.7	
360	72	2.4		16	2.6	
480	80	2.1		26	2.9	
720	88	1.8		46	4.2	

Dissolution Data in DI Water: (12-28-2004)

Sampling Time (min)	Impax's Bupropion Hydrochloride ER Tablets, Strength: 150 mg Lot No. R04035-500 Reference: V3.1, p 0094 Firm's reference: JC1217, pp.71-76			GlaxoSmithKline Wellbutrin® XL Tablets, Strength: 300 mg Lot No. 03K021P Reference: V3.1, p 0098 Firm's reference: CY1159, pp.50-54			Impax's Bupropion Hydrochloride ER Tablets, Strength: 300 mg* Lot No. R04041-180 Reference: V3.1, p 0094 Firm's reference: CY1159, pp.37-41, YC917, pp67-69		
	Mean %	%CV	Range%	Mean %	%CV	Range%	Mean%	%CV	Range%
60	27	2.5	(b) (4)	1	0.8	(b) (4)	19	5.9	(b) (4)
120	40	2.9		1	0.6		35	0.7	
240	58	2.4		8	3.2		51	1.0	
360	72	2.4		17	4.4		62	1.1	
480	80	2.1		26	6.1		71	1.2	
720	88	1.8		45	9.1		82	1.5	

*results obtained from 18 tablets.

Method 3:

Source of Method:	Firm
Medium:	pH4.5, Acetate Buffer
Volume:	900 mL, 37 °C ± 5°C
Apparatus:	USP apparatus 1 (basket) at 75 rpm

Dissolution Data in pH 4.5, Acetate Buffer: (11-30-2004)

Sampling Time (min)	Impax's Bupropion Hydrochloride ER Tablets, Strength: 150 mg Lot No. R04035-500 Reference: V1.11, p 2973 Firm's reference: JC1217, pp.77-80			GlaxoSmithKline Wellbutrin® XL Tablets, Strength: 150 mg Lot No. 04C003P Reference: V1.11, p 2973 Firm's reference: JC1217, pp.81-84		
	Mean%	%CV	Range%	Mean%	%CV	Range%
60	29	1.7	(b) (4)	0	0.2	(b) (4)
120	43	2.3		0	0.0	
240	63	2.6		1	0.7	
360	77	2.5		8	2.9	
480	87	2.4		17	4.3	
720	98	2.0		34	6.5	

Dissolution Data in pH 4.5, Acetate Buffer: (12-28-2004)

Sampling Time (min)	Impax's Bupropion Hydrochloride ER Tablets, Strength: 150 mg Lot No. R04035-500 Reference: V3.1, p 0095 Firm's reference: JC1217, pp.71-76			GlaxoSmithKline Wellbutrin® XL Tablets, Strength: 300 mg Lot No. 03K021P Reference: V3.1, p 0099 Firm's reference: CY1159, pp.55-59			Impax's Bupropion Hydrochloride ER Tablets, Strength: 300 mg Lot No. R04041-180 Reference: V3.1, p 0095 Firm's reference: CY1159, pp.45-49		
	Mean %	%CV	Range%	Mean %	%CV	Range%	Mean%	%CV	Range%
60	29	1.7	(b) (4)	0	0.1	(b) (4)	22	1.1	(b) (4)
120	43	2.3		1	0.9		35	0.7	
240	63	2.6		6	4.5		52	1.0	
360	77	2.5		15	7.3		64	1.2	
480	87	2.4		25	9.5		74	1.3	
720	98	2.0		44	12.6		87	1.7	

Method 4:

Source of Method:	Firm
Medium:	pH~6.8, Simulated Intestinal Fluid
Volume:	900 mL, 37 °C ± 5°C
Apparatus:	USP apparatus 1 (basket) at 75 rpm

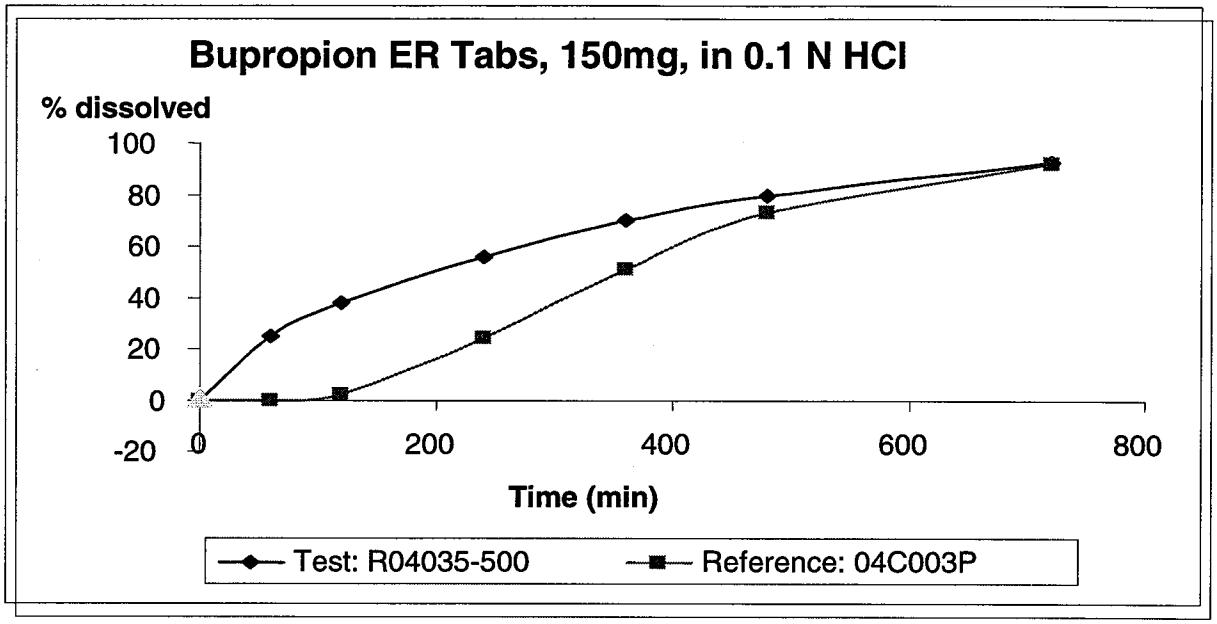
Dissolution Data in pH~6.8, Simulated Intestinal Fluid: (11-30-2004)

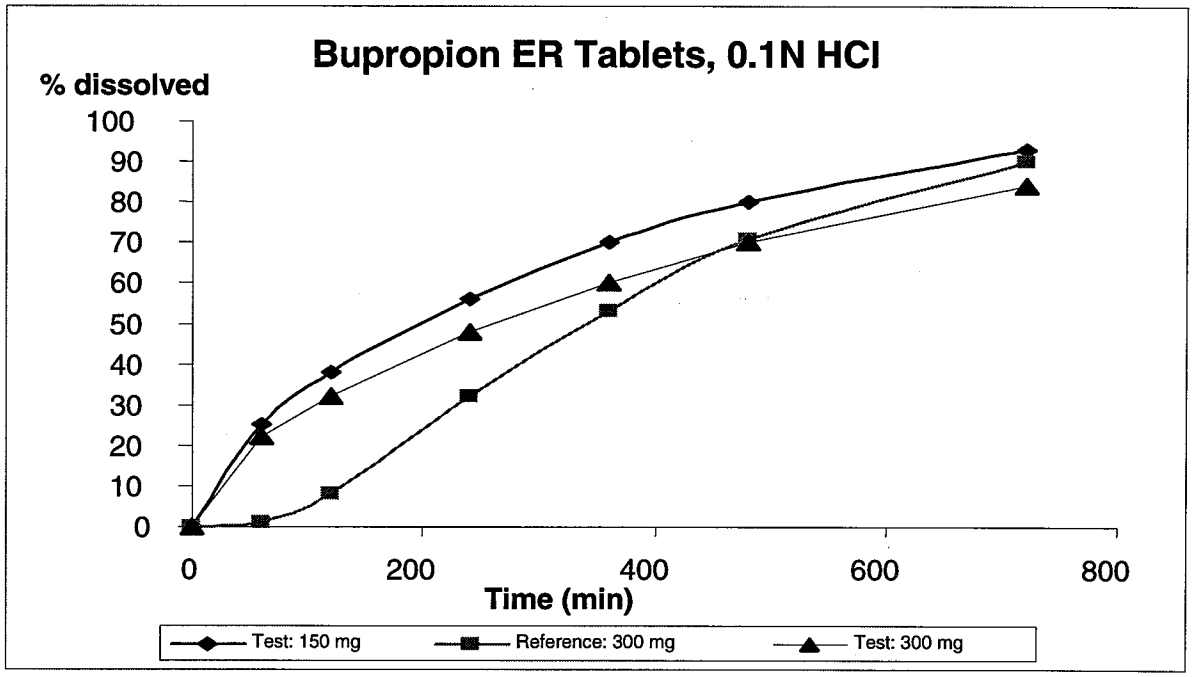
Sampling Time (min)	Impax's Bupropion Hydrochloride ER Tablets, Strength: 150 mg, Lot No. R04035-500, Reference: V1.11, p 2974, Firm's reference: ST1241, pp.26-30			GlaxoSmithKline Wellbutrin® XL Tablets, Strength: 150 mg, Lot No. 04C003P, Reference: V1.11, p 2974, Firm's reference: CY1159, pp.75-79		
	Mean%	%CV	Range%	Mean%	%CV	Range%
60	21	1.3	(b) (4)	20	1.2	(b) (4)
120	35	2.8		38	1.4	
240	48	2.8		65	1.3	
360	59	3.1		81	1.8	
480	65	2.9		86	1.9	
720	67	2.4		90	1.9	

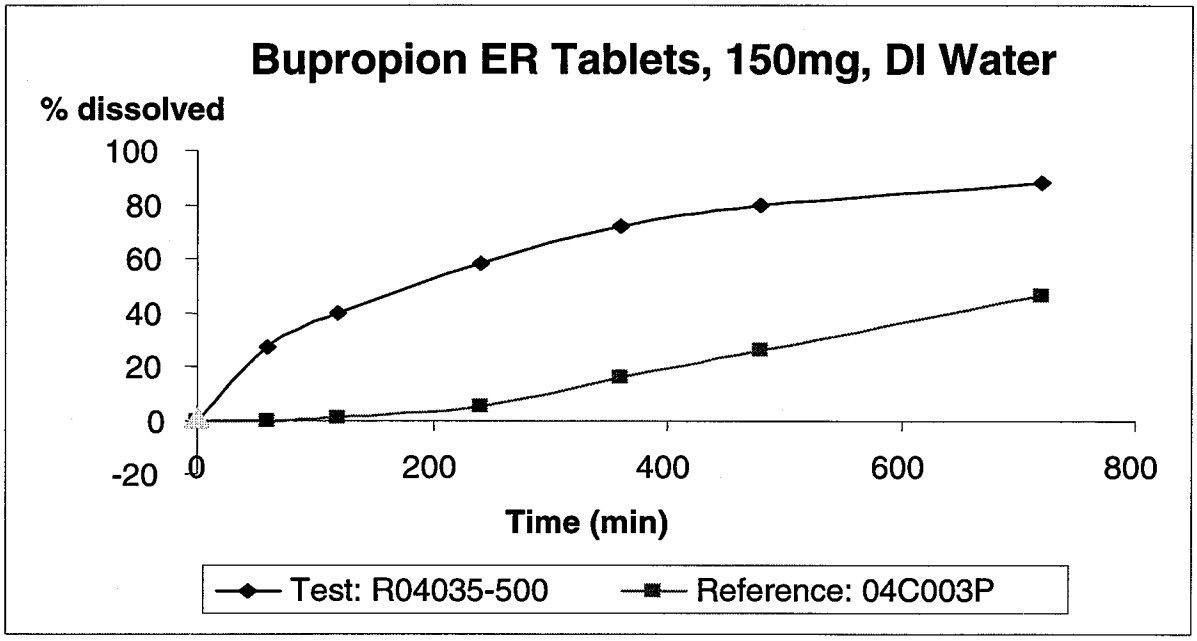
Dissolution Data in pH~6.8, Simulated Intestinal Fluid: (12-28-2004)

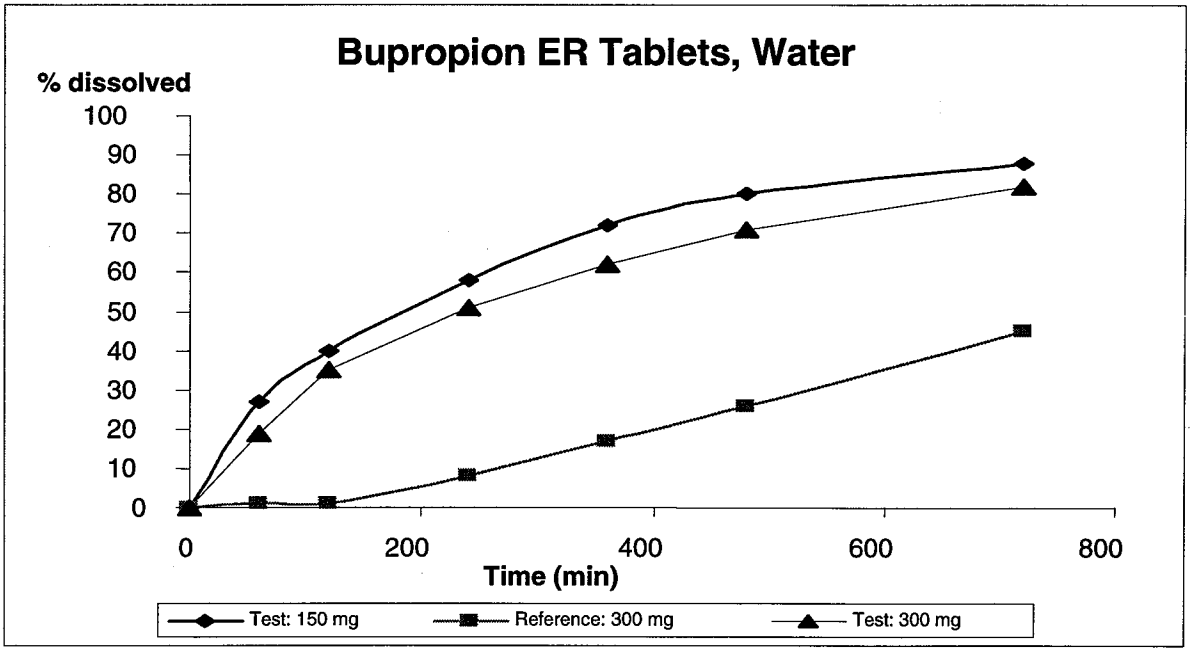
Sampling Time (min)	Impax's Bupropion Hydrochloride ER Tablets, Strength: 150 mg, Lot No. R04035-500, Reference: V3.1, p 0096, Firm's reference: ST1241, pp.26-30			GlaxoSmithKline Wellbutrin® XL Tablets, Strength: 300 mg, Lot No. 03K021P, Reference: V3.1, p 0100, Firm's reference: CY1159, pp.80-82			Impax's Bupropion Hydrochloride ER Tablets, Strength: 300 mg, Lot No. R04041-180, Reference: V3.1, p 0096, Firm's reference: CY1159, pp.72-74		
	Mean %	%CV	Range%	Mean %	%CV	Range%	Mean%	%CV	Range%
60	21	1.3	(b) (4)	20	0.5	(b) (4)	22	0.4	(b) (4)
120	35	2.8		38	0.8		31	0.7	
240	48	2.8		59	1.6		43	1.0	
360	59	3.1		74	2.3		52	1.2	
480	65	2.9		84	2.5		58	1.5	
720	67	2.4		92	1.9		64	1.7	

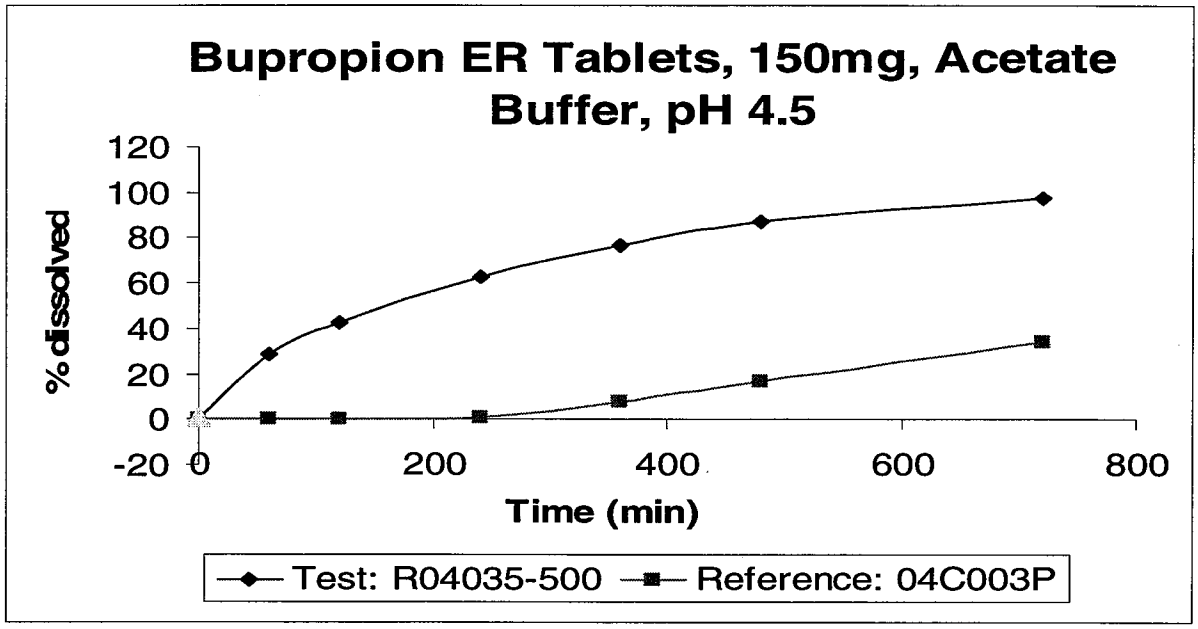
Figure 1. Dissolution Comparison.

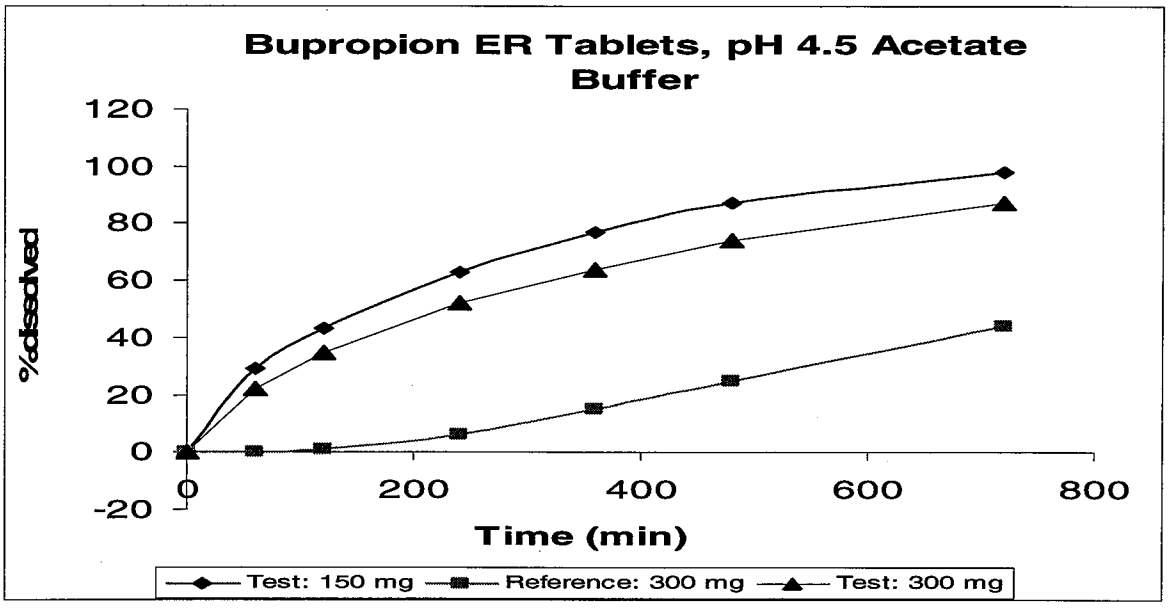


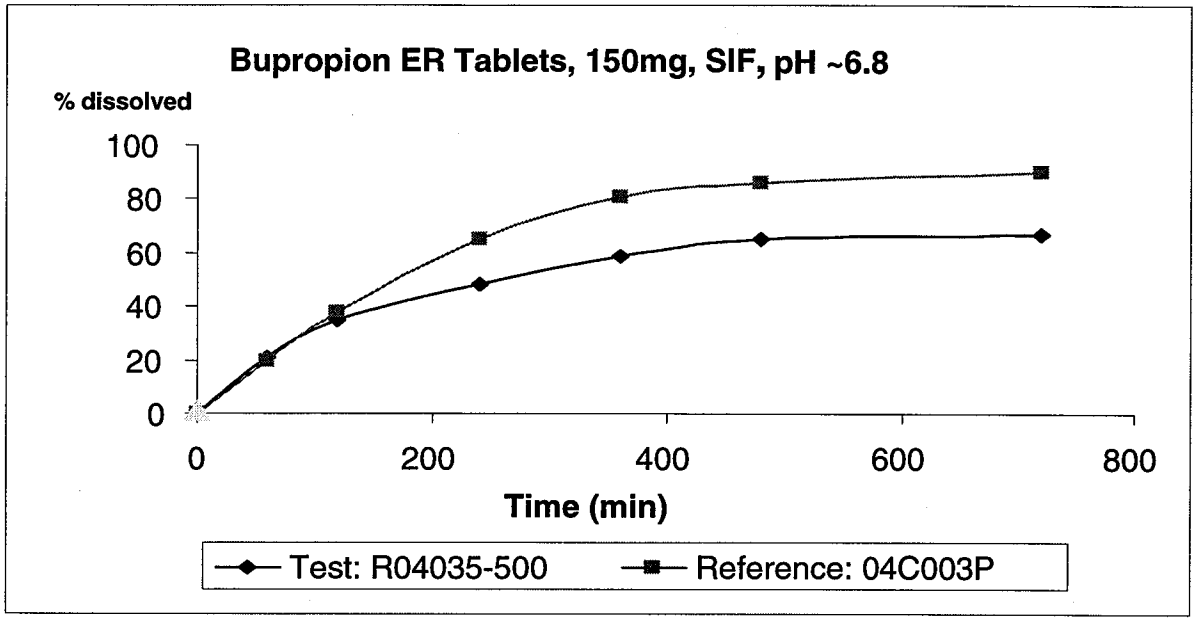



Bupropion ER Tablets, 150mg, DI Water
% dissolved
100
80
60
40
20
0
-20
0
200
400
600
800
Time (min)
Test: R04035-500
Reference: 04C003P


Bupropion ER Tablets, Water
% dissolved
100
90
80
70
60
50
40
30
20
10
0
0
200
400
600
800
Time (min)
Test: 150 mg
Reference: 300 mg
Test: 300 mg


Bupropion ER Tablets, 150mg, Acetate Buffer, pH 4.5
% dissolved
120
100
80
60
40
20
0
-20
0
200
400
600
800
Time (min)
Test: R04035-500
Reference: 04C003P


Bupropion ER Tablets, pH 4.5 Acetate Buffer
%dissolved
120
100
80
60
40
20
0
-20
0
200
400
600
800
Time (min)
Test: 150 mg
Reference: 300 mg
Test: 300 mg


Bupropion ER Tablets, 150mg, SIF, pH ~6.8
% dissolved
100
80
60
40
20
0
0
200
400
600
800
Time (min)
Test: R04035-500
Reference: 04C003P

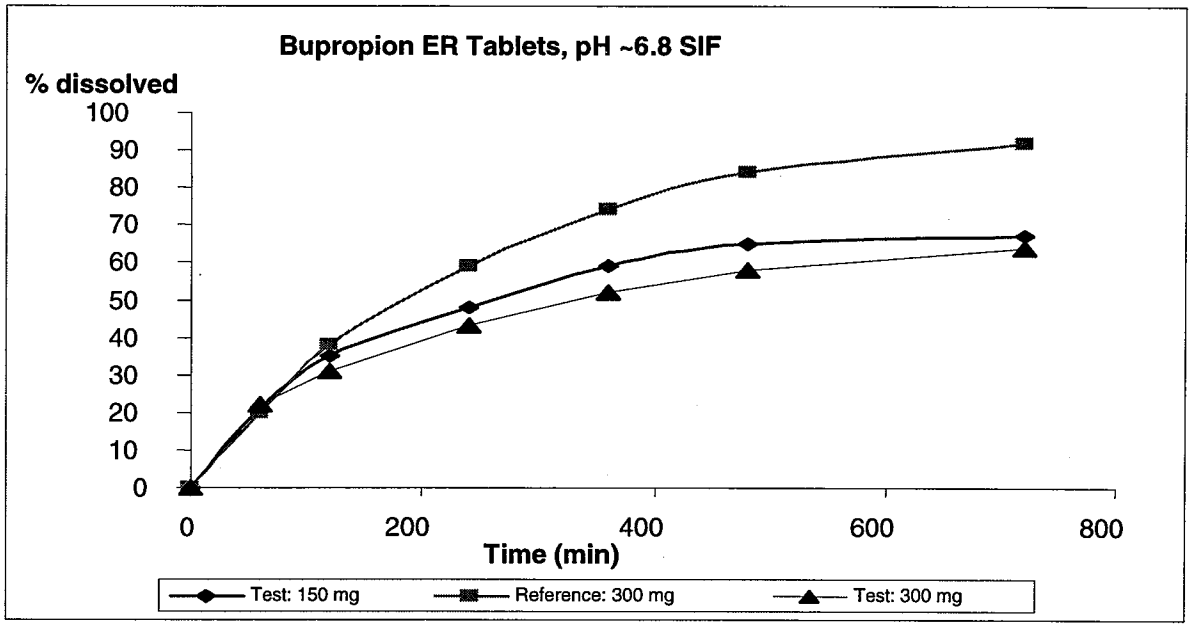
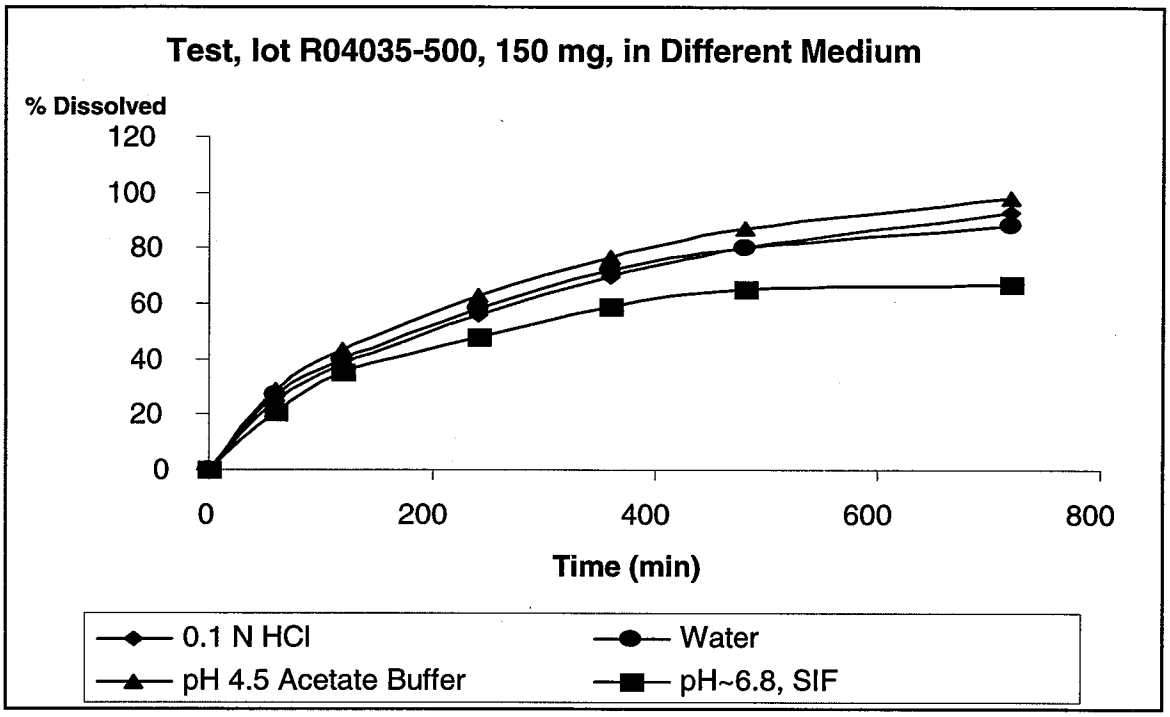

Bupropion ER Tablets, pH ~6.8 SIF
% dissolved
100
90
80
70
60
50
40
30
20
10
0
0
200
400
600
800
Time (min)
Test: 150 mg
Reference: 300 mg
Test: 300 mg

Figure 2: Effect of Dissolution medium on the dissolution profiles for both test and reference 150 mg ER tablets.



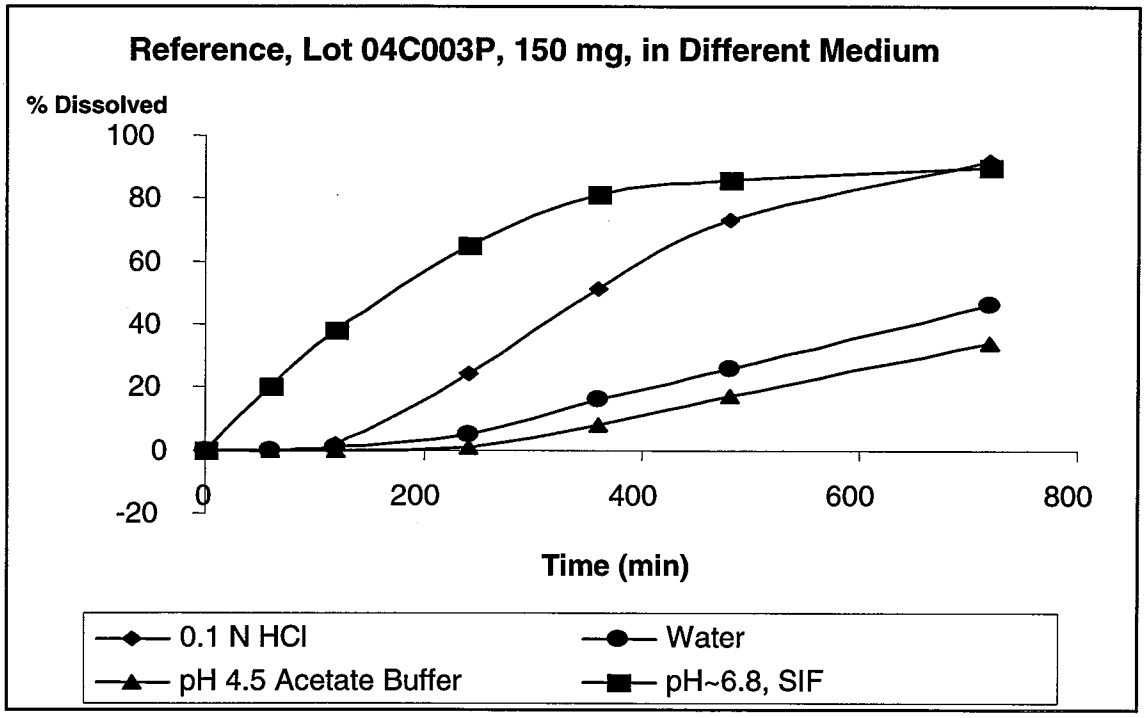
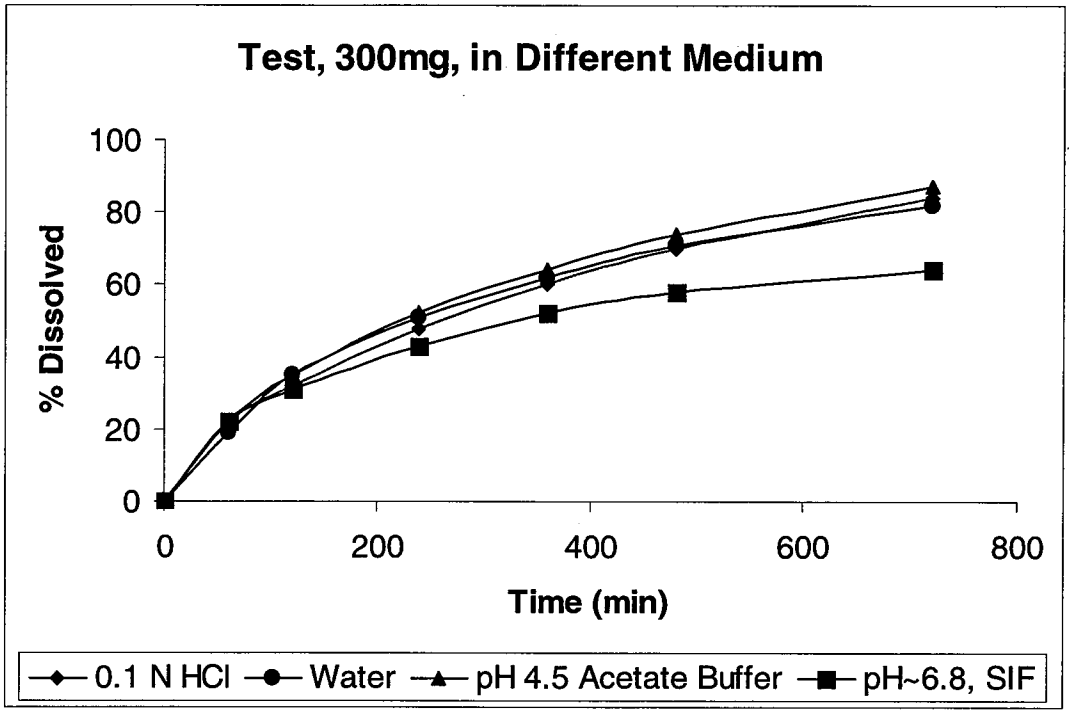


Figure 2: Effect of Dissolution medium on the dissolution profiles for both test and reference 300 mg ER tablets.



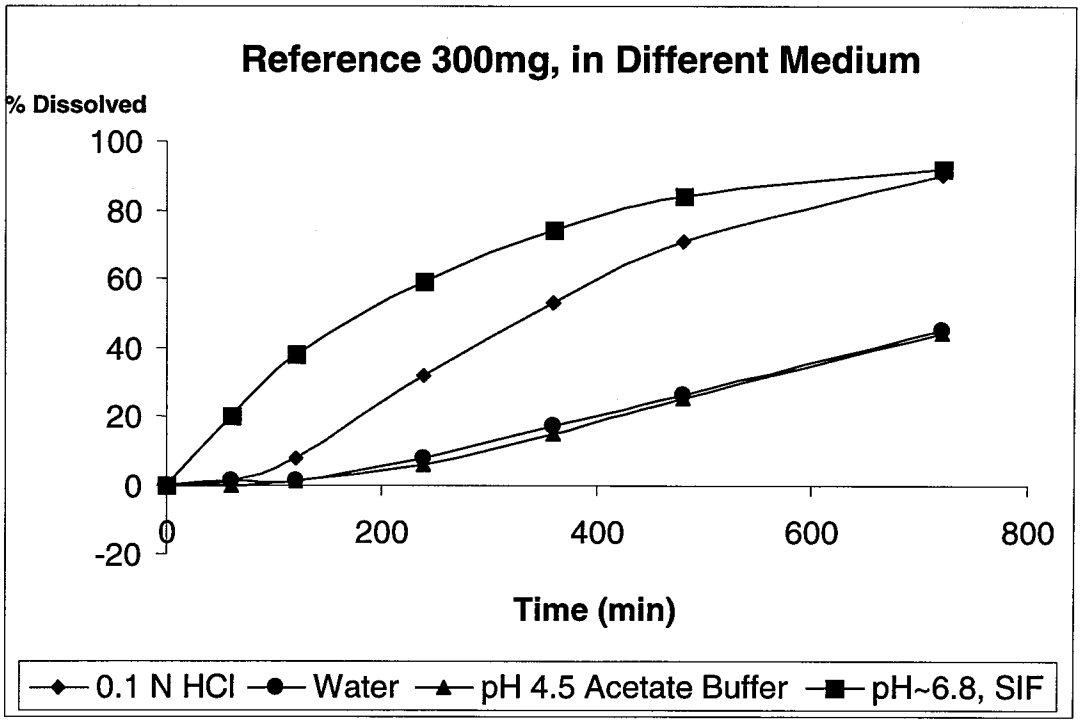


Table 2. F2 calculation (calculated by the reviewer):

Product	Product	Dissolution Medium	F2
Impax's Bupropion hydrochloride ER tablets, 150 mg, Lot No. R04035-500	GSK's Wellbutrin® XL, Lot No. 04C003P	In 0.1 N HCl	31.29
		In DI water	16.71
		In pH 4.5 acetate buffer	11.77
		In pH 6.8 SIF	38.32

Product	Product	Dissolution Medium	F2 (Firm's)	F2 (Reviewer calculated)
Impax's Bupropion hydrochloride ER tablets, 300 mg Lot # R04041	Impax's Bupropion hydrochloride ER tablets, 150 mg Lot # 04035	In 0.1 N HCl	55	55
		In DI water	56	56
		In pH 4.5 acetate buffer	48	48
		In pH 6.8 SIF	65	65
	GSK's Wellbutrin® XL, 300 mg Lot No. 03K021P	In 0.1 N HCl	NA	41
		In DI water	NA	21
		In pH 4.5 acetate buffer	NA	19
		In pH 6.8 SIF	NA	36

Comments on the Dissolution:

1. FOR THE TEST PRODUCTS:

- The dissolution profiles of the 150 mg ER tablet in 0.1 N HCl, water and acetate buffer pH 4.5 are similar while that in SIF pH 6.8 is similar but slower.
- The dissolution profiles of the 300 mg tablet in 0.1 N HCl, water and acetate buffer pH 4.5 are similar while that in SIF pH 6.8 is similar but slower.
- The dissolution profile of the 150 mg ER tablet is similar to the dissolution profile of the 300 mg ER tablet in all 4 media.
- **Suitable medium: 0.1 N HCl same as the FDA recommended medium**

2. FOR THE REFERENCE PRODUCTS:

- The dissolution profiles of the 150 mg ER tablet in 0.1 N HCl, water, acetate buffer pH 4.5 and SIF pH 6.8 are not similar and the profile in pH 6.8 is faster than the profiles in other 3 media.
- The dissolution profiles of the 300 mg ER tablet in 0.1 N HCl, water, acetate buffer pH 4.5 and SIF pH 6.8 are not similar and the profile at pH 6.8 is faster than the profiles in other 3 media.
- The dissolution profile of the 150 mg ER tablet is similar to the dissolution profile of the 300 mg ER tablet in all 4 media.
- **Suitable medium: SIF pH 6.8 not same as the FDA recommended medium (0.1 N HCl).**

3. FOR THE TEST AND REFERENCE COMPARISON:

- The dissolution profile of the test 150 mg ER tablet is not similar to the dissolution profile of the reference 150 mg ER tablet in all 4 media.
- The dissolution profile of the test 300mg ER tablet is not similar to the dissolution profile of the reference 300 mg ER tablet in all 4 media.

4. The reviewer checked the Impax's BE study results on the 150 mg ER tablet and found that the 90% CI of the PK parameters meet the 80% to 125% criteria. In spite of the dissimilarity in dissolution profiles the test 150 mg ER tablet is bioequivalent to the 150 mg Wellbutrin® XL tablet.

5. Based on the overall evaluation of the 150 mg and 300 mg dissolution data, as well as the BE results, the DBE recommends the current dissolution testing method (900 ml of 0.1 N HCl with basket at 75 rpm). The DBE recommends the following specifications which are different from the specification proposed by the firm.

1hr: (b) (4)
2hrs: %
4hrs: %
8hrs: %
12hrs: (b) (4) % dissolved

6. With this review of the multiple media dissolution data, Impax's 300 mg ER tablet has met the dissolution requirement toward the waiver-eligibility. The proportional similarity of the formulations (150 mg ER tablet vs. 300 ER tablet) and bioequivalence studies will be reviewed later.

Table 3 SAS Transport Files

Are the SAS files located in the EDR? (Yes/No)	
Fasting BE Study	
Plasma Data	Yes
PK data	Yes
Fed BE Study	
Plasma Data	Yes
PK Data	Yes

DEFICIENCY COMMENTS:

1. There is no USP method for this product, but there is an FDA-recommended method. The firm's dissolution testing with the FDA-recommended method is acceptable. But the firm proposed specification is not acceptable. The firm should accept the FDA-recommended method and the following current proposed specifications

   1hr: (b) (4)%
   2hrs: %
   4hrs: %
   8hrs: %
   12hrs: (b) (4)% dissolved

2. There is a discrepancy in two applications in the notebook referenced for the 150 mg (lot R04035-500) dissolution data. In the original application the referenced notebook for 150 mg bupropion hydrochloride extended-release tablets dissolution data is "LO 1207, pp 45-49" (orange jacket v 1.11, p 2972), whereas the same data in the amendment application cited "JC1217, pp. 71-76" as the referenced notebook. (Orange jacket v 3.1, p 0093). The firm needs to clarify which one is the correct referenced notebook for 150 mg bupropion.

3. In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data summary, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could provide this information for any other applications pending in the Division and in applications to be submitted in the future.

RECOMMENDATIONS:

The dissolution testing conducted by Impax Laboratories, Inc., comparing its test products, Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg, with its the reference products, GlaxoSmithKline's Wellbutrin® XL, 150 mg and 300 mg respectively, is **incomplete.** The firm's dissolution testing with the FDA-recommended method is acceptable, but the firm proposed specification is not acceptable. The firm needs to accept the FDA-recommended method and the current proposed specification (1hr: (b) (4)%, 2hrs: (b) (4)%, 4hrs: (b) (4)%, 8hrs: (b) (4)%, 12hrs: (b) (4)% dissolved).

05/31/05

Reviewer Bing V. Li, Ph.D
Team # I
Division of Bioequivalence
Office of Generic Drugs

5/31/2005

Team Leader Shriniwas Nerurkar, Ph.D.
Team # I
Division of Bioequivalence
Office of Generic Drugs

5/31/05

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drug

ANDA No.	77-415
Drug Product Name	Bupropion Hydrochloride Extended-Release Tablets
Strength	150 mg
Applicant Name	Impax Laboratories, Inc.
Submission Date(s)	Nov. 30, 2004
First Generic	No
Reviewer	Bing V. Li, Ph.D.
File Location	V:\firmsam\impax\ltrs&rev\77415D1104.doc
Clinical Site	Gateway Medical Research, Inc.
Analytical Site	(b) (4)

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-415 APPLICANT: Impax Laboratories, Inc.

DRUG PRODUCT: Bupropion Hydrochloride Extended-Release Tablets, 150 mg

The Division of Bioequivalence has completed its review of the dissolution testing portion and has the following deficiencies:

1. The dissolution testing comparing your test product, Bupropion Hydrochloride Extended-Release Tablets, 150 mg, with the reference product, GlaxoSmithKline's Wellbutrin® XL, 150 mg, is **incomplete.** Your proposed specification is not acceptable. The DBE requests you to accept FDA-recommended dissolution method and specification as follows:

Medium	0.1 N HCl
Volume	900 mL
Temperature	37°C ± 5°C
Apparatus	USP Apparatus 1 (Basket)
Rotational Speed	75 rpm
Specification	1hr: (b) (4)
	2hrs: %
	4hrs: %
	8hrs: %
	12hrs: (b) (4) % dissolved

2. In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could provide this information for any other applications pending in the Division and in applications to be submitted in the future.

3. In addition, there is a discrepancy in two applications in the notebook referenced for the 150 mg (lot R04035-500) dissolution data. In the original application the referenced notebook for 150 mg bupropion hydrochloride extended-release tablets dissolution data is "LO 1207, pp 45-49" (orange jacket v 1.11, p 2972), whereas the same data in the amendment application cited "JC1217, pp. 71-76" as the referenced notebook. (Orange jacket v 3.1, p 0093) You need to clarify which one is the correct referenced notebook for 150 mg bupropion hydrochloride extended-release tablets dissolution study.

Sincerely yours,

/s/ Barbara M. Davit

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

CC: ANDA 77-415
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-650/BLi BL 05/31/05
HFD-650/SNerurkar
HFD-650/D.P. Conner BMD 5/31/05

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Printed in final on

BIOEQUIVALENCE - incomplete

Submission date: Nov. 30, 2004
Dec. 28, 2004

[NOTE: The *in vitro* testing is incomplete. The fasting and fed BE studies and waiver request are pending review.]

1. DISSOLUTION (Dissolution Data)

Strength: 150 mg, 300 mg
X **Outcome: IC**

Outcome Decisions: IC-incomplete
WinBio Comments: IC.

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-415
Drug Product Name	Bupropion Hydrochloride Extended-Release Tablets
Strength	150 mg, 300 mg
Applicant Name	Impax Laboratories, Inc.
Submission Date(s)	Nov. 30, 2004 and Dec 28, 2004 Amendment June 29, 2005
First Generic	No
Reviewer	Bing V. Li, Ph.D.
File Location	V:\firmsam\impax\ltrs&rev\77415A0605.doc
Clinical Site	Gateway Medical Research, Inc.
Analytical Site	(b) (4)

I. Executive Summary

This is a review of the amendment of dissolution testing data only.

Impax Laboratories, Inc. submitted dissolution testing in its original application using FDA-recommended method. The DBE found it incomplete pending to the firm's acceptance to the FDA-recommended dissolution specification (1hr: (b) (4)%, 2hrs: (b) (4) (b) (4)%, 4hrs: (b) (4)%, 8hrs: (b) (4)%, 12hrs: (b) (4)%). The firm submitted this amendment and accepted the FDA recommended specification. The firm also addressed two other comments that the reviewers commented. The firm's responses are acceptable. **The dissolution testing portion is complete.**

II. Table of Contents

III. Submission Summary

A. Relevant Dissolution Information

See the dissolution review of the original submission of the study. (V:\firmsam\impax\ltrs&rev\77415D1104.doc).

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1

C. Review of Submission

Deficiency 1: *You should accept the FDA-recommended method and the following current proposed specifications as follows:*

1hr: (b) (4)
2hrs:
4hrs:
8hrs:
12hrs: *dissolved*

Firm's Response:

IMPAX accepts the dissolution conditions and specifications.

Reviewer's Comments: The firm's response to deficiency 1 is acceptable.

Deficiency 2: *In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data summary, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could provide this*

information for any other applications pending in the Division and in applications to be submitted in the future.

Firm's Response: The study summaries are provided in hard copies as well as electronic format on the enclosed CD-ROM (EDR).

Reviewer's Comment: The firm's response to the deficiency 2 is acceptable.

Deficiency 3: *There is a discrepancy in two applications in the notebook referenced for the 150 mg (lot R04035-500) dissolution data. In the original application the referenced notebook for 150 mg bupropion hydrochloride extended-release tablets dissolution data is "LO 1207, pp 45-49" (orange jacket v 1.11, p 2972), whereas the same data in the amendment application cited "JC1217, pp. 71-76" as the referenced notebook. (Orange jacket v 3.1, p 0093). You need to clarify which one is the correct referenced notebook for 150 mg bupropion.*

Firm's Response: An error was made in referencing the notebook number and pages on the amendment application (Orange jacket v 3.1, p 0093). The correct notebook reference should be "LO 1207, pp 45-49". Please refer to Attachment 3 for the corrected dissolution data sheet.

Reviewer's Comment: The firm's response to the deficiency 3 is acceptable.

D. Comments

The dissolution testing is complete.

E. Recommendations

The dissolution testing conducted by Impax Laboratories, Inc., comparing its test products, Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg, with its the reference products, GlaxoSmithKline's Wellbutrin® XL, 150 mg and 300 mg respectively, is **acceptable.**

Bing V. Li 7/11/05

Bing V. Li
Reviewer, Branch I
Division of Bioequivalence

Date

Shriniwas G. Nerurkar 7/11/2005

Shriniwas G. Nerurkar
Group Leader, Branch I
Division of Bioequivalence

Date

Barbara M. Davit 7/14/05

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

Date

ANDA No.	77-415
Drug Product Name	Bupropion Hydrochloride Extended-Release Tablets
Strength	150 mg, 300 mg
Applicant Name	Impax Laboratories, Inc.
Submission Date(s)	Nov. 30, 2004 and Dec 28, 2004 Amendment June 29, 2005
First Generic	No
Reviewer	Bing V. Li, Ph.D.
File Location	V:\firmsam\impax\ltrs&rev\77415A0605.doc
Clinical Site	Gateway Medical Research, Inc.
Analytical Site	(b) (4)

BIOEQUIVALENCE COMMENTS

ANDA: 77-415

APPLICANT: Impax Laboratories, Inc.

DRUG PRODUCT: Bupropion Hydrochloride Extended-Release Tablets, 150 mg, 300 mg

The Division of Bioequivalence has completed its review of the dissolution testing portion and has the following comments:

The dissolution testing comparing your test products, Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg, with the reference products, GlaxoSmithKline's Wellbutrin® XL, 150 mg and 300 mg respectively, is acceptable. The DBE acknowledges that you conduct the FDA-recommended method and specifications as follows:

Medium	0.1 N HCl
Volume	900 mL
Temperature	37°C ± 5°C
Apparatus	USP Apparatus 1 (Basket)
Rotational Speed	75 rpm
Specification	1hr: (b) (4)
	2hrs:
	4hrs:
	8hrs:
	12hrs: dissolved

Sincerely yours,

for Barbara M. Davit

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

CC: ANDA 77-415
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ Reviewer
HFD/650/ Project Manager

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Endorsements: (Final with Dates)
HFD-650/BLi BL 7/11/05
HFD-650/SNerurkar
HFD-650/D.P. Conner 7/11/05 7/11/05

DISSOLUTION - ~~Incomplete~~ Acceptable Submission date: 06/29/2005

[NOTE: The *in vitro* dissolution testing is acceptable]

1. DISSOLUTION (Dissolution Data)
Strength: 150 mg and 300 mg

X **Outcome: AC**

Outcome Decisions: AC– Acceptable
WinBio Comments: AC

CC: ANDA 77-415
ANDA DUPLICATE
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HFD-650/ Bio Drug File
HFD-650/ Reviewer
HFD/650/ Project Manager

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7/11/05

Endorsements: (Final with Dates)
HFD-650/BLi
HFD-650/SNerurkar
HFD-650/D.P. Conner 7/14/05

BL 7/11/05

DISSOLUTION - ~~Incomplete~~ Acceptable

Submission date: 06/29/2005

[NOTE: The *in vitro* dissolution testing is acceptable]

1. DISSOLUTION (Dissolution Data)
Strength: 150 mg and 300 mg

Outcome: AC

Outcome Decisions: AC– Acceptable
WinBio Comments: AC

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-415
Drug Product Name	Bupropion Hydrochloride Extended Release Tablets
Strength	150 mg and 300 mg
Applicant Name	Impax Laboratories, Inc.
Address	30831 Huntwood Avenue Hayward, CA 94544
Submission Date(s)	November 30, 2004
Amendment Date(s)	December 28, 2004 (new 300 mg strength), June 29, 2005 (Dissolution)
Reviewer	Parthapratim Chandaroy, Ph.D.
First Generic	No
File Location	V:\FIRMSAM\IMPAX\LTRS&REV\77415N1104.doc

Executive Summary

The firm submitted single-dose fasting and non-fasting *in vivo* bioequivalence (BE) studies comparing its test product Bupropion Hydrochloride Extended Release Tablets, 150 mg to the reference listed drug (RLD) WELLBUTRIN XL® (bupropion hydrochloride extended release) Tablets, 150 mg (GlaxoSmithKline). The firm also submitted comparative *in vitro* dissolution data for the test and reference products, 150 mg and 300 mg strengths.

The design for the fasting BE study is a two-way, crossover design in healthy subjects (n=36). The non-fasting BE study is also a two-way, crossover design in healthy subjects (n=38). Statistical analyses of the plasma concentration data for bupropion and hydroxybupropion for both studies demonstrate bioequivalence.

For the fasting BE study, bupropion results (point estimate, 90% CI) are: $\ln AUC_{0-t}$ of 98, 91.94-104.37; $\ln AUC_{\infty}$ of 98, 92.10-103.88; $\ln C_{max}$ of 89, 80.26-98.15. Hydroxybupropion results (point estimate, 90% CI) are: $\ln AUC_{0-t}$ of 102, 95.29-109.60; $\ln AUC_{\infty}$ of 103, 95.98-109.62; $\ln C_{max}$ of 106, 98.32-113.71.

For the non-fasting BE study, bupropion results (point estimate, 90% CI) are: $\ln AUC_{0-t}$ of 108, 101.44-115.36; $\ln AUC_{\infty}$ of 107, 100.44-113.74; $\ln C_{max}$ of 110, 103.20-117.96. Hydroxybupropion results (point estimate, 90% CI) are: $\ln AUC_{0-t}$ of 108, 99.33-116.40; $\ln AUC_{\infty}$ of 107, 98.79-115.96; $\ln C_{max}$ of 117, 108.86-124.70.

The firm also conducted dissolution testing on its Bupropion Hydrochloride Extended Release Tablets, 150 mg and 300 mg. The test products meet the FDA dissolution specifications. The firm has accepted the DBE's recommended method and specifications. The application is acceptable with no deficiencies.

Table of Contents

Submission Summary

A. Drug Product Information

Test Product	Bupropion Hydrochloride Extended Release Tablets, 150 mg and 300 mg
Reference Product	WELLBUTRIN XL® (bupropion hydrochloride) Tablets, 150 mg and 300 mg
RLD Manufacturer	SmithKline Beecham[1]
NDA No.	21-515
RLD Approval Date	08/28/2003
Indication	WELLBUTRIN XL® (bupropion hydrochloride) is indicated for the treatment of major depressive disorder.

[1] Electronic Orange Book (2005) entry for WELLBUTRIN XL®

B. PK/PD Information[2]

Bioavailability	In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 μg/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.
Food Effect	In a study with healthy volunteers, food did not affect the C_{max} or AUC of bupropion.
T_{max}	Approximately 5 hours (bupropion) and 7 hours (all three metabolites)
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.
Excretion	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.
Half-life	21 (±9) hours (bupropion); 20 (±5) hours (hydroxybupropion); 33 (±10) hours (erythrohydrobupropion); 37 (±13) hours (threohydrobupropion)
Relevant OGD or DBE History	Currently, there are ten[3] generic bupropion hydrochloride extended release tablets of different strengths available in the market from three different companies. The RLD for these drugs is WELLBUTRIN SR® or ZYBAN® (same formulation). In the past, IMPAX has submitted three applications for its Bupropion Hydrochloride Extended Release Tablets: • ANDA 75-913 was submitted for Bupropion HCl ER Tablets, 100 mg and 150 mg, with WELLBUTRIN SR® Tablets as RLD. The dissolution testing with the **USP method** was acceptable and the firm proposed specifications were also acceptable (1 hour: (b) (4)%, 2 hours: (b) (4)%, 4 hours: (b) (4)%, 6 hours:

[2] PDR® (Physician's desk reference) electronic version entry for WELLBUTRIN XL®
[3] Electronic orange book (2005) entry for Bupropion Hydrochloride

	(b) (4)%) • ANDA 76-711 was submitted for the Bupropion HCl ER Tablet, 200 mg, with WELLBUTRIN SR® Tablets, 200 mg, as RLD. The dissolution testing with the **USP method** was acceptable and the firm's specifications, as listed above, were also acceptable. • ANDA 75-914, was submitted for the Bupropion HCl ER Tablet, 150 mg, with ZYBAN® Tablets, 150 mg, as RLD. The dissolution testing with the **USP method** was acceptable and the firm's specifications, as listed above, were also acceptable. The extended release drug WELLBUTRIN XL® (from SmithKline Beecham) was approved on August 28, 2003. The DBE has reviewed the following documents for bupropion hydrochloride extended release tablets, with WELLBUTRIN XL® as the RLD: ANDA: • 77-284 (Anchen; submission date 9/21/04) Dissolution: • 77-284 (Anchen; submission date 9/23/04) • 77-285 (Abrika; submission date 9/23/04) • 77-415 (Impax; submission date 11/30/04 and 12/28/04) Controlled Documents: • 05-0339 ((b) (4) submission date 3/10/05)
Agency Guidance	BA/BE General Guidance
Drug Specific Issues (if any)	Current DBE recommendations for demonstration of bioequivalence of Bupropion Hydrochloride Extended Release Tablets, 150 mg and 300 mg (with WELLBUTRIN XL® Tablets as the RLD) are as follows: 1. A single-dose, two-way crossover fasting *in-vivo* bioequivalence study comparing Bupropion Hydrochloride Extended Release Tablets, 150 mg, to the reference listed drug (RLD), Wellbutrin XL® (Bupropion Hydrochloride Extended Release) Tablets, 150 mg. Due to safety concerns, studies using the 300 mg dose are not recommended. 2. A single-dose, two-way crossover fed *in-vivo* bioequivalence study comparing Bupropion Hydrochloride Extended Release Tablets, 150 mg, to the RLD. 3. Measure plasma concentrations of the parent drug bupropion and metabolite hydroxybupropion; 4. Waiver of *in vivo* bioequivalence study requirements for the 300 mg strengths may be granted provide the conditions of 21 CFR

	§320.22(d)(2) are met. 5. Conduct comparative dissolution testing using 12 dosage units of the test and reference products using the following FDA method: Medium: 0.1 N HCl at 37°C ± 0.5°C Volume: 900 mL Apparatus: 1 (Basket) Rotational speed: 75 rpm Sampling time: 1, 2, 4, 6 and 8 hours and until at least 80% of the labeled content is dissolved.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	---
In vitro dissolution	Yes	2
Waiver requests	Yes	1
BCS Waivers	No	---
Vasoconstrictor Studies	No	---
Clinical Endpoints	No	---
Failed Studies	No	---
Amendments	No	---

D. Pre-Study Bioanalytical Method Validation

	Parent
Analyte name	Bupropion
Internal Standard	(b) (4)
Method description	LC/MS/MS (solid-phase extraction method)
QC range	2 ng/mL to 160 ng/mL
Standard curve range	1 ng/mL to 200 ng/mL
Limit of quantitation	1.00 ng/mL
Average recovery of Drug (%)	91.3%
Average Recovery of Int. Std (%)	92.2%
QC Intraday precision range (%CV)	1.71% to 5.79%
QC Intraday accuracy range (%)	98.5% to 107%
QC Interday precision range (%CV)	2.28% to 5.29%
QC Interday accuracy range (%)	101% to 102%
Bench-top stability (hrs)	6 hours at room temperature (RT)
Stock stability (days)	94 days at 4°C
Processed stability (hrs)	48 hours at RT
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	56 days at -80°C
Dilution integrity	10-fold (precision 3.18%, accuracy 98.8%)
Specificity	Acceptable
SOPs submitted	Yes
Bioanalytical method is acceptable	Yes
20% Validation Chromatograms included (Y/N)	Yes
Random or Serial Selection of Chromatogram	Serial

	Metabolite
Analyte name	Hydroxybupropion
Internal Standard	(b) (4)
Method description	LC/MS/MS (solid-phase extraction method)
QC range	10 ng/mL to 800 ng/mL
Standard curve range	5 ng/mL to 1000 ng/mL
Limit of quantitation	5.00 ng/mL
Average recovery of Drug (%)	95.0%
Average Recovery of Int. Std (%)	92.0%
QC Intraday precision range (%CV)	0.62% to 2.48%
QC Intraday accuracy range (%)	101% to 112%
QC Interday precision range (%CV)	2.56% to 4.63%
QC Interday accuracy range (%)	104% to 106%
Bench-top stability (hrs)	6 hours at RT
Stock stability (days)	31 days at 4°C
Processed stability (hrs)	48 hours at RT
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	56 days at -80°C
Dilution integrity	10-fold (precision 6.45%, accuracy 101%)
Specificity	Acceptable
SOPs submitted	Yes
Bioanalytical method is acceptable	Yes
20% Validation Chromatograms included (Y/N)	Yes
Random or Serial Selection of Chromatogram	Serial

Comments on Pre-Study Bioanalytical Method Validation:
The pre-study bioanalytical method validation is **acceptable**.

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	04168
Study Design	Open label, randomized, single-dose, two-treatment, two-period, two-sequence crossover study under fasting conditions.
No. of subjects enrolled	40
No. of subjects completing	36
No. of subjects analyzed	36
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 22 Female: 14
Test product	Bupropion Hydrochloride Extended Release Tablets
Reference product	WELLBUTRIN XL® (bupropion hydrochloride) Tablets
Strength tested	150 mg tablet
Dose	1 x 150 mg tablet with approximately 240 mL of water under fasting conditions.

Summary of Statistical Analysis (n=36) for Bupropion		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	98	91.94-104.37
AUC_{∞}	98	92.10-103.88
C_{max}	89	80.26-98.15

Summary of Statistical Analysis (n=36) for Hydroxybupropion		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	102	95.29-109.60
AUC_{∞}	103	95.98-109.62
C_{max}	106	98.32-113.71

Reanalysis of Bupropion Study Samples Additional information in Appendix: Table 6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic Repeats	0	0	0.00	0.00	0	0	0.00	0.00
Sample conc.>ULOQ*	3	3	0.19	0.19	3	3	0.19	0.19
Total	**3**	**3**	**0.19**	**0.19**	**3**	**3**	**0.19**	**0.19**

Total number of samples assayed = 1573
* ULOQ: Upper Limit of Quantitation

Did use of recalculated plasma concentration data change study outcome? No. All reassays were performed for analytical reasons and the reviewer agrees with the outcome of the reanalyses. There were no pharmacokinetic repeats and no recalculations were performed.

2. Single-dose Fed Bioequivalence Study

Study Summary, Fed Bioequivalence Study	
Study No.	04169
Study Design	Open label, randomized, single-dose, two-treatment, two-period, two-sequence crossover study under fed conditions.
No. of subjects enrolled	40
No. of subjects completing	38
No. of subjects analyzed	38
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 23 Female: 15
Test product	Bupropion Hydrochloride Extended Release Tablets
Reference product	WELLBUTRIN XL® (bupropion hydrochloride) Tablets
Strength tested	150 mg tablet
Dose	1 x 150 mg tablet with approximately 240 mL of water under fed conditions.

Summary of Statistical Analysis (n=38) for Bupropion		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	108	101.44-115.36
AUC_{∞}	107	100.44-113.74
C_{max}	110	103.20-117.96

Summary of Statistical Analysis (n=38) for Hydroxybupropion		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	108	99.33-116.40
AUC_{∞}	107	98.79-115.96
C_{max}	117	108.86-124.70

Reanalysis of Study Samples Additional information in Appendix: Table 17								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic Repeats	0	0	0.00	0.00	0	0	0.00	0.00
Pre-dose sample conc. > 40% of LLOQ*	2	0	0.12	0.00	1	0	0.06	0.00
Total	**2**	**0**	**0.12**	**0.00**	**1**	**0**	**0.06**	**0.00**

Total number of samples assayed = 1667

* LLOQ: Lower Limit of Quantitation

Did use of recalculated plasma concentration data change study outcome? No. All reassays were performed for analytical reasons and the reviewer agrees with the outcome of the reanalyses. There were no pharmacokinetic repeats and no recalculations were performed.

F. Formulation

Location in appendix	**Table 23**, Page 33
Are inactive ingredients within IIG limits?	No
If no, list ingredients outside of limits	Hydroxypropyl cellulose
If a tablet, is the product scored?	No
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test?	N/A
Is the formulation acceptable?	Yes (See details in Appendix: section .D, page 43)
If not acceptable, why?	N/A

G. In Vitro Dissolution

The comparative dissolution testing results for the test and reference products were submitted and found acceptable in the amendment dated June 29, 2005[4]. The firm has accepted the DBE's recommended method and specifications.

H. Waiver Request(s)

Strengths for which waivers are requested	300 mg
Regulation cited	21 CFR §320.22(d)(2)
Proportional to strength tested *in vivo*?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	Yes
If not then why?	N/A

[4] Dissolution review (done on May 31, 2005; V:\firmsam\impax\ltrs&rev\77415D1104.doc) and dissolution amendment (done on July 19, 2005; V:\firmsam\impax\ltrs&rev\77415A0605.doc) was done by Bing Li.

I. Deficiency Comments

None

J. Recommendations

1. The single-dose, fasting bioequivalence study (#04168) conducted by IMPAX Laboratories, Inc. on its Bupropion Hydrochloride Extended Release Tablets, 150 mg (Lot # R04035-30), comparing it to GlaxoSmithKline's WELLBUTRIN XL® (bupropion hydrochloride) Tablets, 150 mg (Lot # 04D024P), is **acceptable**.

2. The single-dose, non-fasting bioequivalence study (#04169) conducted by IMPAX Laboratories, Inc. on its Bupropion Hydrochloride Extended Release Tablets, 150 mg (Lot # R04035-30), comparing it to GlaxoSmithKline's WELLBUTRIN XL® (bupropion hydrochloride) Tablets, 150 mg (Lot # 04D024P), is **acceptable**.

3. The *in vitro* dissolution testing conducted by IMPAX Laboratories, Inc. on its Bupropion Hydrochloride Extended Release Tablets, 150 mg and 300 mg, is **acceptable**.

   The dissolution testing should be conducted in 900 mL of 0.1 N HCl at 37°C, using USP Apparatus I (basket) at 75 rpm. The test product should meet the following specification:

   1 hr: (b) (4)%
   2 hrs: %
   4 hrs: %
   8 hrs: %
   12 hrs: (b) (4)% *dissolved*

   The firm has acknowledged the FDA dissolution method and specifications in an amendment submitted on June 29, 2005.

4. The formulation of the 300 mg strength is proportional to the 150 mg strength of the test product which underwent acceptable *in vivo* bioequivalence testing. The waiver request for the 300 mg strength is **granted.**

   The firm should be informed of the above recommendations.

Parthapratim Chandaroy 8/24/05
Parthapratim Chandaroy, Ph.D. Reviewer, Branch V Date

Moheb H. Makary 8/24/05
Moheb H. Makary, Ph.D. Acting Team Leader, Branch V Date

Dale P. Conner 8/24/05
Dale P. Conner, Pharm.D. Date
Director, Division of Bioequivalence
Office of Generic Drugs

Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a). Study Design

Study Information	
Study Number	04168
Study Title	A Randomized, Two-Way Crossover, Single Dose, Open Label Study to Evaluate Bioequivalence of a Test Tablet Formulation of Extended-Release Bupropion HCl (150 mg), Compared to an Equivalent Dose of a Commercially Available Reference Drug Product (Wellbutrin XL™, GlaxoSmithKline) in 40 Fasted, Healthy, Adult Subjects.
Clinical Site	Gateway Medical Research, Inc. 400 Fountain Lakes Blvd. St. Charles, MO 63301
Principal Investigator	Walter A. Parham, M.D.
Study/Dosing Dates	Period 1: August 24, 2004 Period 2: September 14, 2004
Analytical Site	(b) (4)
Analytical Director	(b) (6) Ph.D.
Analysis Dates	September 27 to October 2, 2004
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	39

Comment: The firm submitted long-term storage (freezer) stability data, obtained from samples stored at -80°C for **56** days, in the Analytical Method Validation Report (Vol. C1.1, page 219, TABLE 1).

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Bupropion HCl ER Tablets	WELLBUTRIN XL® Tablets
Manufacturer	IMPAX Laboratories, Inc.	GlaxoSmithKline
Batch/Lot No.	R04035-30	04D024P
Manufacture Date	8/10/2004	N/A
Expiration Date	N/A	8/2005
Strength	150 mg	150 mg
Dosage Form	Extended Release Tablet	Extended Release Tablet
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	97.2%	98.7%
Content Uniformity (mean, %CV)	99.0% (1.5%)	99.3% (1.1%)
Formulation	See Appendix (**Table 23**)	N/A
Dose Administered	1 x 150 mg with 240 mL of water under fasting conditions	1 x 150 mg with 240 mL of water under fasting conditions
Route of Administration	Oral	Oral

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	21 days
Randomization Scheme	AB: 1, 6, 7, 9, 13, 14, 16, 18, 20, 21, 22, 25, 26, 27, 28, 31, 33, 34, 36, 40 BA: 2, 3, 4, 5, 8, 10, 11, 12, 15, 17, 19, 23, 24, 29, 30, 32, 35, 37, 38, 39
Blood Sampling Times	0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60, 72, 96, 120, and 144 hours post-dose.
Blood Volume Collected/Sample	7 mL
Blood Sample Processing/Storage	Blood samples were collected in tubes containing EDTA, and chilled in an ice water bath/Kryorack® while awaiting centrifugation. Samples were centrifuged at 3400 rpm for 15 minutes at 4°C, and the resultant plasma from each tube was decanted into an individual pre-labeled polypropylene tube containing 25 µL 4N HCl. Samples were stored at -20°C until analysis.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	At least 10 hours pre-dose until 4 hours post-dose.
Length of Confinement	At least 10 hours pre-dose until 24 hours post-dose.
Safety Monitoring	A 12-lead electrocardiogram and tests (including several blood tests and urine analysis) were done at screening. Vital signs (sitting blood pressure and pulse rate) were monitored at the time 0 (baseline), 3, 5, 8, and 24 hours post-dose.

Comments on Study Design:

- The study design is **acceptable**.

b). Clinical Results

Table 1 Demographics of Study Subjects (n=36)

Age		Body Mass Index		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	75.0
Mean	34.9	Mean	25.4	18-40	63.9	Male	61.1	African American	19.4
SD	11.3	SD	3.0	41-64	36.1	Female	38.9	Hispanic	2.8
Range	18-58	Range	19.3-31.4	65-75	0			Asian	0
				>75	0			Others	2.8

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
4	Subject dropped due to positive pregnancy test	I	N/A
7	Subject dropped due to positive pregnancy test	I	N/A
28	Subject dropped due to adverse events	I	N/A
38	Subject dropped due to positive urine drug of abuse test	Before II	N/A

Table 3 Study of Adverse Events

Adverse Events	# in Test Group	# in Reference Group
Body as a Whole		
Achiness	1	0
Dizziness	1	1
Fever	1	0
Headache	1	2
Hot Flash	0	1
Lightheadedness	0	1
Migraine Headache	0	1
Tiredness	1	0
Gastrointestinal		
Abdominal Cramping	1	1
Diarrhea	1	0
Nausea	1	1
Respiratory		
Sore Throat	2	0
Abnormal Urinalysis	1	0
Total	**11**	**8**

Table 4 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sampling deviations: sample drawn late/early	several	several

Comments on Dropouts/Adverse Events/Protocol Deviations:

- There were 19 adverse events experienced by 7 subjects. Except one "severe" migraine headache, all were categorized as "mild" or "moderate" in severity. Some were considered "possibly related" or "probably related" to the study treatments, while

majority of them were considered as "unrelated" or "remotely related": abnormal urinalysis, headache, lightheadedness, dizziness, hot flash, nausea, migraine headache, sore throat, fever, achiness, and tiredness. No pharmacologic interventions were required, except for subject # 28, who was removed from the study due to adverse events (sore throat, fever, achiness, tiredness) experienced and the need for concomitant medication therapy.

- Blood draw deviations were as high as 12 hours (at 72 hour time point). Blood draw deviations outside the predetermined deviation window were corrected to reflect the actual time of collection prior to the pharmacokinetic analysis. Thus, these deviations did not influence the outcome of the study.
- Subject Nos. 4 and 7 were removed from the study during period I because of positive pregnancy test. Subject #28 was removed from the study during period I because of adverse events. Subject #38 was removed from the study at the check-in of period II because of positive urine drugs of abuse test.
- **The adverse events and protocol deviations did not compromise the integrity of the study.**

c). Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Bupropion						
QC Conc. (ng/mL)	2	20	160				
Inter day Precision (%CV)	6.34	5.99	3.51				
Inter day Accuracy (%)	103	101	108				
Cal. Standards Conc. (ng/mL)	1	2	5	10	20	50	200
Inter day Precision (%CV)	11.0	4.57	5.03	5.34	5.96	2.06	1.61
Inter day Accuracy (%)	101	103	97.0	98.2	102	98.2	101
Linearity Range (range of R^2)	0.9986-1.0000						

	Hydroxybupropion						
QC Conc. (ng/mL)	10	100	800				
Inter day Precision (%CV)	8.35	6.23	4.75				
Inter day Accuracy (%)	100	90.0	106				
Cal. Standards Conc. (ng/mL)	5	10	25	50	100	250	1000
Inter day Precision (%CV)	8.54	4.04	4.65	4.12	6.35	1.27	0.928
Inter day Accuracy (%)	104	105	102	95.2	90.6	102	101
Linearity Range (range of R^2)	0.9994-1.0000						

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:
For both analytes and internal standard, there were no interfering peaks. Peak shape and baseline formation were satisfactory for both analytes and internal standard.

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
000-04005M.0	6/29/2004	Standard operating procedure for an LC/MS/MS method for the determination of bupropion and hydroxybupropion in human EDTA plasma samples spiked with hydrochloric acid.

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

- There were a total of 6 sample repeat assays in the study, representing 0.38% of the total study assays. All repeat assays were performed for analytical reasons.
- The analytical method and data are **acceptable**.

d). Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations for Bupropion are presented in **Table 11** and **Figure 1**.

Bupropion						
Parameter	**Units**	**Test**		**Reference**		**T/R**
		Mean	%CV	Mean	% CV	
AUC_{0-t}	ng/mL x hr	691.14	37.94	703.62	38.37	0.98
AUC_{∞}	ng/mL x hr	728.23	37.30	742.58	37.50	0.98
C_{max}	ng/mL	70.14	76.29	79.87	72.84	0.88
T_{max}	hr	2.79	35.40	5.00	30.98	0.56
K_e	hr^{-1}	0.05	49.59	0.05	46.10	1.00
$T_{1/2}$	hr	19.03	47.97	19.19	50.17	0.99

Hydroxybupropion						
Parameter	**Units**	**Test**		**Reference**		**T/R**
		Mean	%CV	Mean	% CV	
AUC_{0-t}	ng/mL x hr	11875.41	41.54	11622.55	37.51	1.02
AUC_{∞}	ng/mL x hr	12307.10	40.55	12036.85	37.67	1.02
C_{max}	ng/mL	265.61	35.50	253.72	36.19	1.05
T_{max}	hr	10.00	55.34	13.28	44.74	0.75
K_e	hr^{-1}	0.03	21.04	0.03	21.34	1.01
$T_{1/2}$	hr	24.81	25.55	24.96	22.61	0.99

Table 9 Least Square Geometric Means and 90% Confidence Intervals (n=36)

Bupropion				
Parameter	**Test**	**Reference**	**T/R**	**90% CI**
AUC_{0-t}	649.23	662.76	0.98	91.94-104.37
AUC_{∞}	685.23	700.55	0.98	92.10-103.88
C_{max}	61.88	69.72	0.89	80.26-98.15

Hydroxybupropion				
Parameter	**Test**	**Reference**	**T/R**	**90% CI**
AUC_{0-t}	10971.83	10736.01	1.02	95.29-109.60
AUC_{∞}	11430.80	11143.67	1.03	95.98-109.62
C_{max}	249.58	236.04	1.06	98.32-113.71

Table 10 Additional Study Information

Root mean square error, AUC_{0-t}	**0.159008**
Root mean square error, AUC_{∞}	**0.150904**
Root mean square error, C_{max}	**0.252414**
K_{el} and $AUC_{0-\infty}$ determined for how many subjects?	**36 (test); 36 (reference)**
Do you agree or disagree with firm's decision?	**Agree**
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	**None**
-first measurable drug concentration as C_{max}	**None**
Were the subjects dosed as more than one group?	**No**

Comments on Pharmacokinetic Analysis:

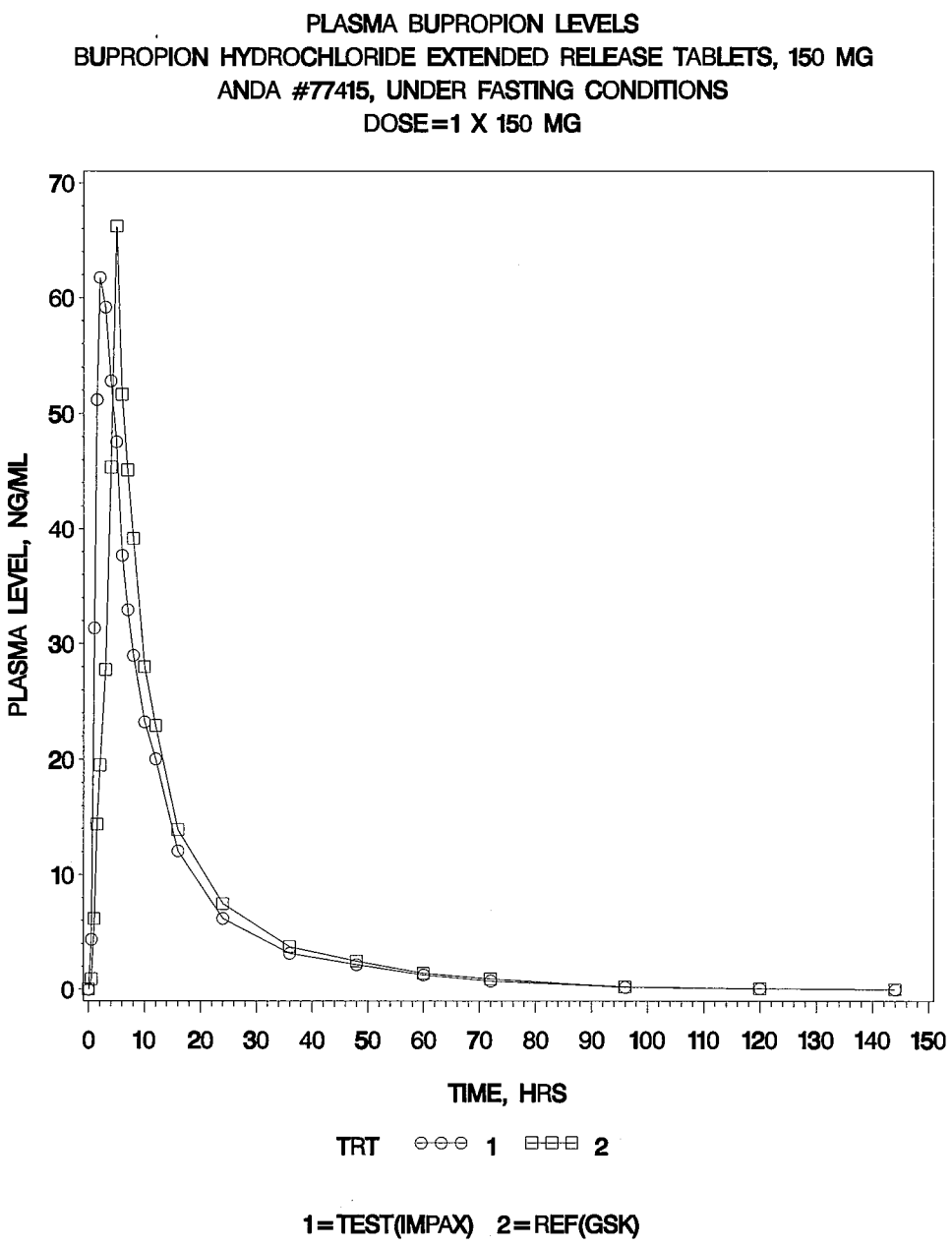
- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with the firm's calculations.
- The 90% confidence intervals for ln-transformed AUC_{0-t}, AUC_{∞}, and C_{max} are within the acceptable limits of 80-125%.
- Subjects were dosed as one group.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: The single-dose fasting study is **acceptable**.

Table 11 Mean Bupropion Plasma Concentrations (ng/mL), Single-Dose Fasting Bioequivalence Study

Time (Hr)	Test (n=36)		Reference (n=36)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	N/A	0.00	N/A	N/A
0.5	4.35	117.80	0.89	484.56	4.89
1	31.36	74.32	6.16	451.80	5.09
1.5	51.18	109.57	14.37	444.42	3.56
2	61.75	90.87	19.51	330.71	3.17
3	59.17	53.62	27.74	142.50	2.13
4	52.81	40.17	45.35	69.29	1.16
5	47.54	33.21	66.22	41.65	0.72
6	37.69	33.48	51.65	38.70	0.73
7	32.95	34.43	45.10	41.01	0.73
8	28.97	35.05	39.15	37.79	0.74
10	23.22	34.52	27.97	36.83	0.83
12	20.03	28.10	22.90	39.91	0.87
16	12.07	27.08	13.90	37.07	0.87
24	6.18	32.91	7.47	34.11	0.83
36	3.14	40.86	3.71	41.21	0.84
48	2.16	55.32	2.47	45.80	0.87
60	1.27	94.67	1.41	70.80	0.90
72	0.74	125.81	0.92	99.56	0.81
96	0.20	292.19	0.21	262.82	0.92
120	0.07	406.11	0.07	419.24	1.07
144	0.00	.	0.00	.	.

Figure 1 Mean Bupropion Plasma Concentrations, Single dose, Fasting Bioequivalence Study



2. Single-dose Fed Bioequivalence Study

a). Study Design

Study Information	
Study Number	04169
Study Title	A Randomized, Two-Way Crossover, Single Dose, Open Label Study to Evaluate Bioequivalence of a Test Tablet Formulation of Extended-Release Bupropion HCl (150 mg), Compared to an Equivalent Dose of a Commercially Available Reference Drug Product (Wellbutrin XL™, GlaxoSmithKline) in 40 Fed, Healthy, Adult Subjects.
Clinical Site	Same as fasting study.
Principal Investigator	Irwin Plisco, M.D.
Study/Dosing Dates	Period 1: September 18, 2004 Period 2: October 9, 2004
Analytical Site	(b) (4)
Analytical Director	(b) (6) Ph.D.
Analysis Dates	October 21 to October 29, 2004
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	41

Comment: The firm submitted long-term storage (freezer) stability data, obtained from samples stored at -80°C for **56** days, in the Analytical Method Validation Report (Vol. C1.1, page 219, TABLE 1).

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Bupropion HCl ER Tablets	WELLBUTRIN XL® Tablets
Manufacturer	IMPAX Laboratories, Inc.	GlaxoSmithKline
Batch/Lot No.	R04035-30	04D024P
Manufacture Date	8/10/2004	N/A
Expiration Date	N/A	8/2005
Strength	150 mg	150 mg
Dosage Form	Extended Release Tablet	Extended Release Tablet
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	97.2%	98.7%
Content Uniformity (mean, %CV)	99.0% (1.5%)	99.3% (1.1%)
Formulation	See Appendix (**Table 23**)	N/A
Dose Administered	1 x 150 mg with 240 mL of water at under fed conditions	1 x 150 mg with 240 mL of water under fed conditions
Route of Administration	Oral	Oral

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	21 days
Randomization Scheme	AB: 1, 3, 5, 7, 8, 10, 11, 14, 15, 17, 20, 21, 22, 24, 25, 27, 30, 35, 36, 39 BA: 2, 4, 6, 9, 12, 13, 16, 18, 19, 23, 26, 28, 29, 31, 32, 33, 34, 37, 38, 40
Blood Sampling Times	0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60, 72, 96, 120, and 144 hours post-dose.
Blood Volume Collected/Sample	7 mL
Blood Sample Processing/Storage	Same as fasting study.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See **Table** 12
Length of Fasting before Meal	At least 10 hours of fasting before being served with a standard high-fat breakfast. Subjects fasted for 4 hours post-dose.
Length of Confinement	Same as fasting study
Safety Monitoring	Same as fasting study
Standard FDA Meal Used?	Yes
If no, then meal is listed in table below	N/A

Comments on Study Design:

- The study design is **acceptable**.

b). Clinical Results

Table 12 Demographics of Study Subjects (n=38)

Age		**Body Mass Index**		**Age Groups**		**Gender**		**Race**	
				Range	**%**	**Sex**	**%**	**Category**	**%**
				<18	0			Caucasian	63.2
Mean	27.5	Mean	26.1	18-40	89.5	Male	60.5	African American	31.6
SD	9.8	SD	3.3	41-64	10.5	Female	39.5	Hispanic	2.6
Range	18-62	Range	17.7-32.4	65-75	0			Asian	2.6
				>75	0			Others	0

Table 13 Dropout Information

Subject No	Reason	Period	Replaced?
13	Subject removed from the study due to positive urine drug of abuse test	Before II	N/A
31	Subject withdrawn from the study due to personal reasons	Before II	N/A

Table 14 Study of Adverse Events

Adverse Events	# in Test Group	# in Reference Group
Body as a Whole		
Diaphoresis	1	0
Dizziness	0	1
Headache	2	2
Cardiovascular		
Syncope	1	0
Gastrointestinal		
Nausea	0	2
Respiratory		
Sore Throat	0	1
Total	**4**	**6**

Table 15 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Blood sampling deviations: sample drawn late/early	several	several

Comments on Dropouts/Adverse Events/Protocol Deviations:

- There were 10 adverse events experienced by 5 subjects. All were categorized as "mild" in severity, except one "severe" event (syncope). Most were considered "possibly related" to the study treatments, while two of them were considered as "unrelated": nausea and sore throat. No pharmacologic interventions were required.
- Blood draw deviations were as high as 400 minutes (at 120 hour time point). Blood draw deviations outside the predetermined deviation window were corrected to reflect the actual time of collection prior to the pharmacokinetic analysis. Thus, these deviations did not influence the outcome of the study.
- Subject #13 was removed from the study at the check-in of period II because of positive urine drugs of abuse test. Subject #31 elected to withdraw from the study before period II due to personal reasons.
- **The adverse events and protocol deviations did not compromise the integrity of the study.**

c). Bioanalytical Results

Table 16 Assay Quality Control – Within Study

	Bupropion						
QC Conc. (ng/mL)	2	20	160				
Inter day Precision (%CV)	11.5	9.85	8.52				
Inter day Accuracy (%)	102	99.5	101				
Cal. Standards Conc. (ng/mL)	1	2	5	10	20	50	200
Inter day Precision (%CV)	11.5	6.34	6.74	5.71	7.51	5.22	2.75
Inter day Accuracy (%)	97.5	103	98.2	98.1	103	103	99.5
Linearity Range (range of R^2)	0.9948-0.9997						

	Hydroxybupropion						
QC Conc. (ng/mL)	10	100	800				
Inter day Precision (%CV)	9.02	5.34	8.62				
Inter day Accuracy (%)	94.1	106	101				
Cal. Standards Conc. (ng/mL)	5	10	25	50	100	250	1000
Inter day Precision (%CV)	8.87	6.52	6.37	3.93	5.65	4.15	3.19
Inter day Accuracy (%)	94.0	97.0	98.0	104	106	103	98.6
Linearity Range (range of R^2)	0.9904-1.0000						

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:
For both analytes and internal standard, there were no interfering peaks. Peak shape and baseline formation were satisfactory for both analytes and internal standard.

Table 17 SOP's dealing with analytical repeats of study sample

SOP No.	Date of SOP	SOP Title
000-04005M.0	6/29/2004	Standard operating procedure for an LC/MS/MS method for the determination of bupropion and hydroxybupropion in human EDTA plasma samples spiked with hydrochloric acid.

Table 18 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

- There were a total of 2 sample repeat assays in the study, representing 0.12% of the total study assays. All repeat assays were performed for analytical reasons.
- The analytical method and data are **acceptable**.

d). Pharmacokinetic Results

Table 19 Arithmetic Mean Pharmacokinetic Parameters

Note: Mean Bupropion plasma concentrations are presented in **Table 22** and **Figure 2.**

Bupropion						
Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC_{0-t}	ng/mL x hr	883.91	32.59	818.33	32.88	1.08
AUC_{∞}	ng/mL x hr	916.32	32.31	858.81	32.61	1.07
C_{max}	ng/mL	82.72	28.04	75.58	30.62	1.09
T_{max}	hr	3.32	37.67	6.21	24.02	0.53
K_e	hr^{-1}	0.05	49.61	0.05	53.32	1.04
$T_{1/2}$	hr	16.37	49.85	18.75	74.06	0.87

Hydroxybupropion						
Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC_{0-t}	ng/mL x hr	13564.98	44.41	12864.41	46.36	1.05
AUC_{∞}	ng/mL x hr	13937.36	44.35	13280.61	46.24	1.05
C_{max}	ng/mL	319.95	39.34	279.49	44.06	1.14
T_{max}	hr	10.61	33.65	13.79	39.29	0.77
K_e	hr^{-1}	0.03	23.93	0.03	28.85	1.01
$T_{1/2}$	hr	21.99	24.53	22.49	24.98	0.98

Table 20 Least Square Geometric Means and 90% Confidence Intervals (n=38)

Bupropion				
Parameter	Test	Reference	T/R	90% CI
AUC_{0-t}	841.81	778.20	1.08	101.44-115.36
AUC_{∞}	873.36	817.11	1.07	100.44-113.74
C_{max}	80.06	72.57	1.10	103.20-117.96

Hydroxybupropion				
Parameter	Test	Reference	T/R	90% CI
AUC_{0-t}	12280.98	11421.65	1.08	99.33-116.40
AUC_{∞}	12636.34	11806.15	1.07	98.79-115.96
C_{max}	298.85	256.50	1.17	108.86-124.70

Table 21 Additional Study Information

Root mean square error, AUC_{0-t}	0.165818
Root mean square error, AUC_{∞}	0.160370
Root mean square error, C_{max}	0.172345
K_{el} and $AUC_{0-\infty}$ determined for how many subjects?	38 (test); 38 (reference)
Do you agree or disagree with firm's decision?	Agree
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as C_{max}	None
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic Analysis:

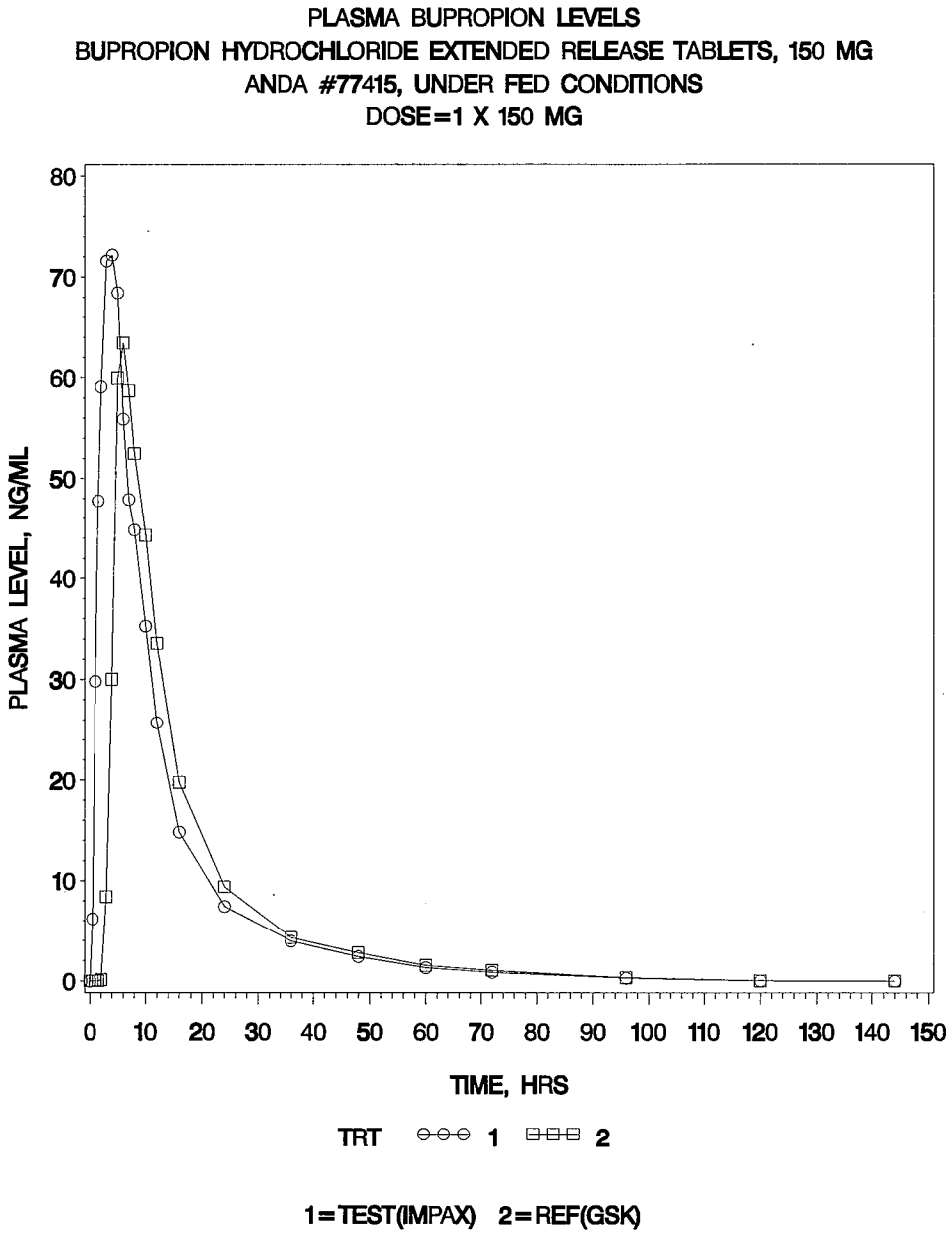
- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with the firm's calculations.
- The 90% confidence intervals for ln-transformed AUC_{0-t}, AUC_{∞}, and C_{max} are within the acceptable limits of 80-125%.
- Subjects were dosed as one group.

Summary and Conclusions, Single-Dose Fed Bioequivalence Study: The single-dose fed study is **acceptable**.

Table 22 Mean Bupropion Plasma Concentrations (ng/mL), Single-Dose Fed Bioequivalence Study

Time (Hr)	Test (n=38)		Reference (n=38)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	.	0.00	.	.
0.5	6.19	113.74	0.00	.	.
1	29.82	76.10	0.00	.	.
1.5	47.75	54.65	0.00	.	.
2	59.11	45.28	0.12	349.06	478.96
3	71.59	36.74	8.39	140.05	8.53
4	72.18	28.05	30.01	68.52	2.41
5	68.44	30.26	59.95	45.05	1.14
6	55.89	34.80	63.44	42.18	0.88
7	47.89	30.61	58.71	36.04	0.82
8	44.83	34.20	52.46	35.99	0.85
10	35.27	36.13	44.29	42.39	0.80
12	25.69	32.73	33.56	42.07	0.77
16	14.84	33.27	19.77	37.35	0.75
24	7.42	42.26	9.37	36.66	0.79
36	3.97	51.43	4.30	48.41	0.92
48	2.42	72.95	2.80	61.84	0.86
60	1.33	99.07	1.55	89.05	0.86
72	0.87	120.89	1.05	110.93	0.83
96	0.29	199.32	0.34	203.41	0.85
120	0.03	616.44	0.03	616.44	0.99
144	0.00	.	0.00	.	.

Figure 2 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



B. Formulation

Table 23 Formulation Data

INGREDIENT	FUNCTION	AMOUNT PER TABLET			
		150 mg		300 mg	
		(mg)	(%)	(mg)	(%)
Cores					
Bupropion Hydrochloride, USP	Active	150.0	37.71	300.0	37.71
Hydroxypropyl Cellulose, NF		(b) (4)			
Microcrystalline Cellulose, NF					
Lactose Monohydrate, NF					
Colloidal Silicon Dioxide, NF					
Magnesium Stearate, NF					
Coating					
(b) (4)	(b) (4)	(b) (4)			
(b) (4)					
Total Fill Weight		**397.8**	**100.0**	**795.6**	**100.0**

* Above IIG limit - See details in Appendix: section D, page 43

(b) (4)

C. Dissolution Data

Method 1: FDA Recommended method:

Source of Method:	FDA
Medium:	0.1 N HCl
Volume:	900 mL, 37°C ± 0.5°C
Apparatus:	USP apparatus 1 (basket) at 75 rpm
FDA specifications:	1 hr: (b) (4)%
	2 hrs: %
	4 hrs: %
	8 hrs: %
	12 hrs: (b) (4)% dissolved

The firm has accepted the DBE's recommended method and specifications (amendment dated June 29, 2005).

Table 24 Dissolution Data[5] in 0.1 N HCl: (11-30-2004)[6]

Sampling Time (min)	Impax's Bupropion Hydrochloride ER Tablets, Strength: 150 mg, Lot No. R04035-500 (Reference: C1.11, p 2972)			GlaxoSmithKline's WELLBUTRIN® XL Tablets, Strength: 150 mg, Lot No. 04C003P (Reference: C1.11, p 2972)		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
60	25	1.9	(b) (4)	0	0	(b) (4)
120	38	2.1		2	1.6	
240	56	2.6		24	5.7	
360	70	2.6		51	5.3	
480	80	2.8		73	4.7	
720	93	2.5		92	1.8	

Table 25 Dissolution Data in 0.1 N HCl: (12-28-2004)[7]

Sampling Time (min)	Impax's Bupropion Hydrochloride ER Tablets, Strength: 150 mg Lot No. R04035-500 (Reference: C3.1, p 0093)			GlaxoSmithKline's WELLBUTRIN® XL Tablets, Strength: 300 mg Lot No. 03K021P (Reference: C3.1, p 0097)			Impax's Bupropion Hydrochloride ER Tablets, Strength: 300 mg Lot No. R04041-180 (Reference: C3.1, p 0093)		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
60	25	1.9	(b) (4)	1	0.5	(b) (4)	22	0.7	(b) (4)
120	38	2.1		8	4.1		32	1.1	
240	56	2.6		32	6.4		48	1.3	
360	70	2.6		53	5.9		60	1.5	
480	80	2.8		71	4.8		70	1.8	
720	93	2.5		90	2.2		84	2.3	

[5] Dissolution review of ANDA 77-415 (V:\firmsam\impax\ltrs&rev\77415D1104.doc) done by Bing V. Li, Ph.D. on May 31, 2005

[6] Original ANDA 77-415 submission date (November 30, 2004)

[7] Amendment to ANDA 77-415 submitted for the new 300 mg strength (December 28, 2004)

Method 2:

Source of Method: Firm
Medium: de-ionized water
Volume: 900 mL, 37°C ± 0.5°C
Apparatus: USP apparatus 1 (basket) at 75 rpm

Table 26 Dissolution Data in DI Water: (11-30-2004)

Sampling Time (min)	Impax's Bupropion Hydrochloride ER Tablets, Strength: 150 mg, Lot No. R04035-500 (Reference: C1.11, p 2971)			GlaxoSmithKline's WELLBUTRIN® XL Tablets, Strength: 150 mg, Lot No. 04C003P (Reference: C1.11, p 2971)		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
60	27	2.5	(b) (4)	0	0.0	(b) (4)
120	40	2.9		1	0.2	
240	58	2.4		5	2.7	
360	72	2.4		16	2.6	
480	80	2.1		26	2.9	
720	88	1.8		46	4.2	

Table 27 Dissolution Data in DI Water: (12-28-2004)

Sampling Time (min)	Impax's Bupropion Hydrochloride ER Tablets, Strength: 150 mg, Lot No. R04035-500 (Reference: C3.1, p 0094)			GlaxoSmithKline's WELLBUTRIN® XL Tablets, Strength: 300 mg, Lot No. 03K021P (Reference: C3.1, p 0098)			Impax's Bupropion Hydrochloride ER Tablets, Strength: 300 mg*, Lot No. R04041-180 (Reference: C3.1, p 0094)		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
60	27	2.5	(b) (4)	1	0.8	(b) (4)	19	5.9	(b) (4)
120	40	2.9		1	0.6		35	0.7	
240	58	2.4		8	3.2		51	1.0	
360	72	2.4		17	4.4		62	1.1	
480	80	2.1		26	6.1		71	1.2	
720	88	1.8		45	9.1		82	1.5	

*results obtained from 18 tablets.

Method 3:

Source of Method: Firm
Medium: pH4.5, Acetate Buffer
Volume: 900 mL, 37°C ± 0.5°C
Apparatus: USP apparatus 1 (basket) at 75 rpm

Table 28 Dissolution Data in pH 4.5, Acetate Buffer: (11-30-2004)

Sampling Time (min)	Impax's Bupropion Hydrochloride ER Tablets, Strength: 150 mg, Lot No. R04035-500 (Reference: C1.11, p 2973)			GlaxoSmithKline's WELLBUTRIN® XL Tablets, Strength: 150 mg, Lot No. 04C003P (Reference: C1.11, p 2973)		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
60	29	1.7	(b) (4)	0	0.2	(b) (4)
120	43	2.3		0	0.0	
240	63	2.6		1	0.7	
360	77	2.5		8	2.9	
480	87	2.4		17	4.3	
720	98	2.0		34	6.5	

Table 29 Dissolution Data in pH 4.5, Acetate Buffer: (12-28-2004)

Sampling Time (min)	Impax's Bupropion Hydrochloride ER Tablets, Strength: 150 mg, Lot No. R04035-500 (Reference: C3.1, p 0095)			GlaxoSmithKline's WELLBUTRIN® XL Tablets, Strength: 300 mg, Lot No. 03K021P (Reference: C3.1, p 0099)			Impax's Bupropion Hydrochloride ER Tablets, Strength: 300 mg, Lot No. R04041-180 (Reference: C3.1, p 0095)		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
60	29	1.7	(b) (4)	0	0.1	(b) (4)	22	1.1	(b) (4)
120	43	2.3		1	0.9		35	0.7	
240	63	2.6		6	4.5		52	1.0	
360	77	2.5		15	7.3		64	1.2	
480	87	2.4		25	9.5		74	1.3	
720	98	2.0		44	12.6		87	1.7	

Method 4:

Source of Method:	Firm
Medium:	pH~6.8, Simulated Intestinal Fluid
Volume:	900 mL, 37 °C ± 5°C
Apparatus:	USP apparatus 1 (basket) at 75 rpm

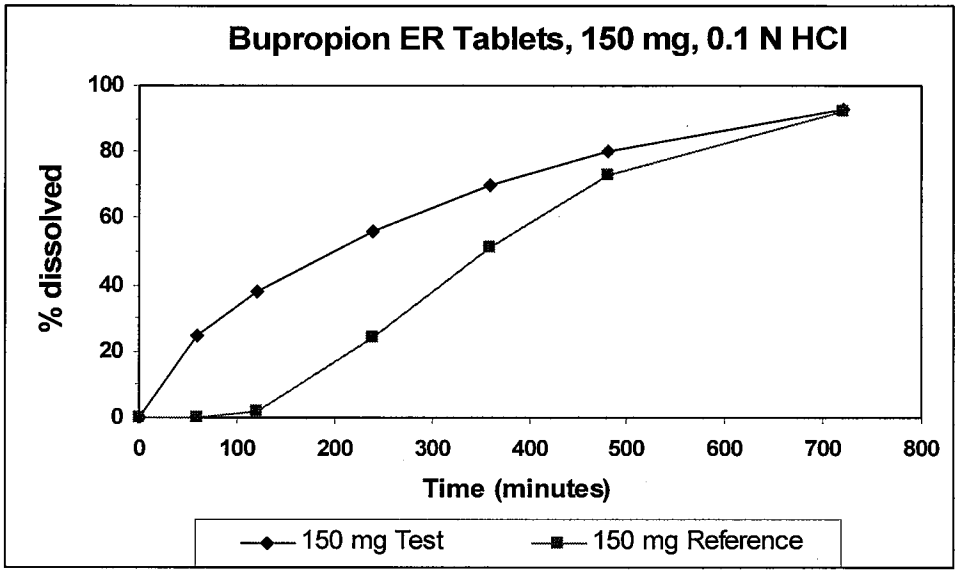
Table 30 Dissolution Data in pH~6.8, Simulated Intestinal Fluid: (11-30-2004)

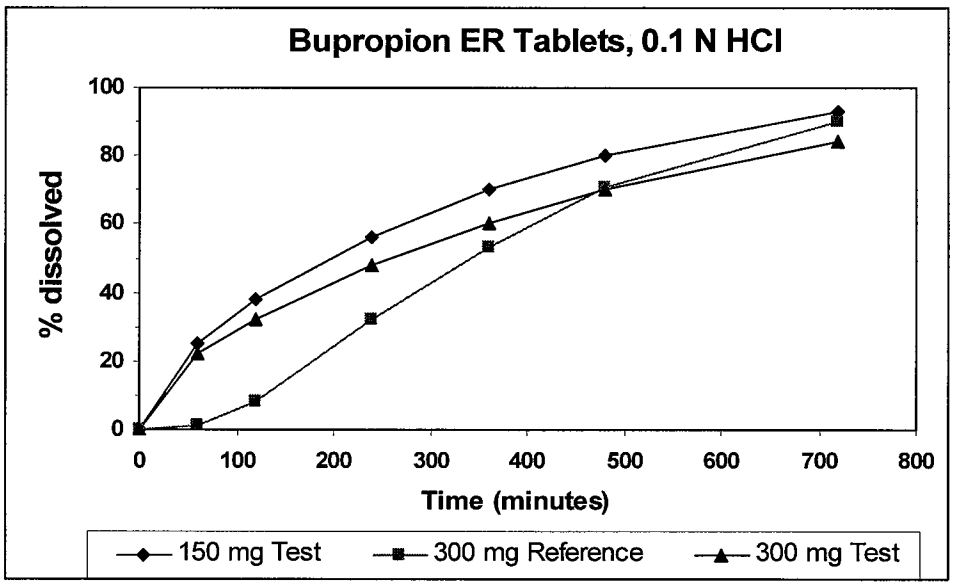
Sampling Time (min)	Impax's Bupropion Hydrochloride ER Tablets, Strength: 150 mg, Lot No. R04035-500 (Reference: C1.11, p 2974)			GlaxoSmithKline's WELLBUTRIN® XL Tablets, Strength: 150 mg, Lot No. 04C003P (Reference: C1.11, p 2974)		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
60	21	1.3	(b) (4)	20	1.2	(b) (4)
120	35	2.8		38	1.4	
240	48	2.8		65	1.3	
360	59	3.1		81	1.8	
480	65	2.9		86	1.9	
720	67	2.4		90	1.9	

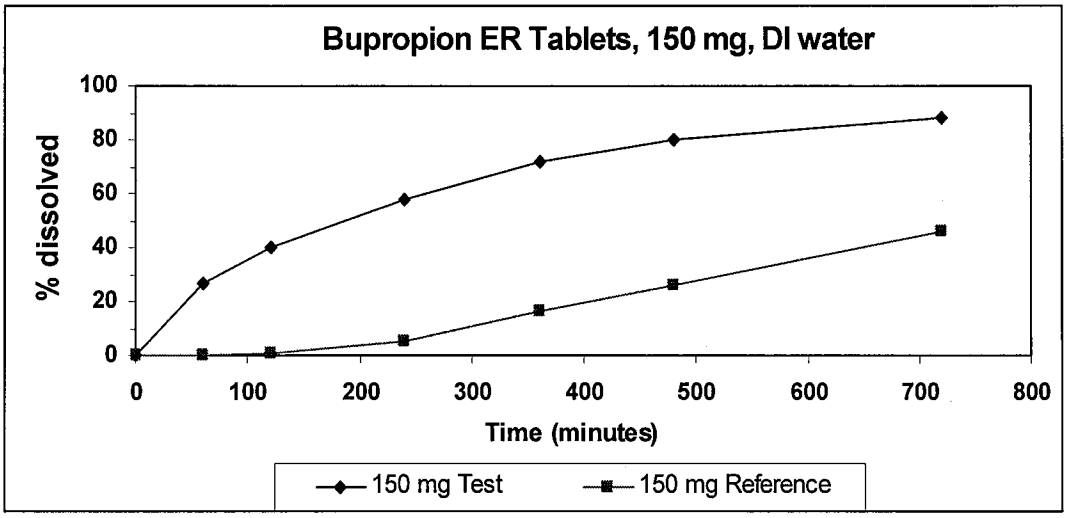
Table 31 Dissolution Data in pH~6.8, Simulated Intestinal Fluid: (12-28-2004)

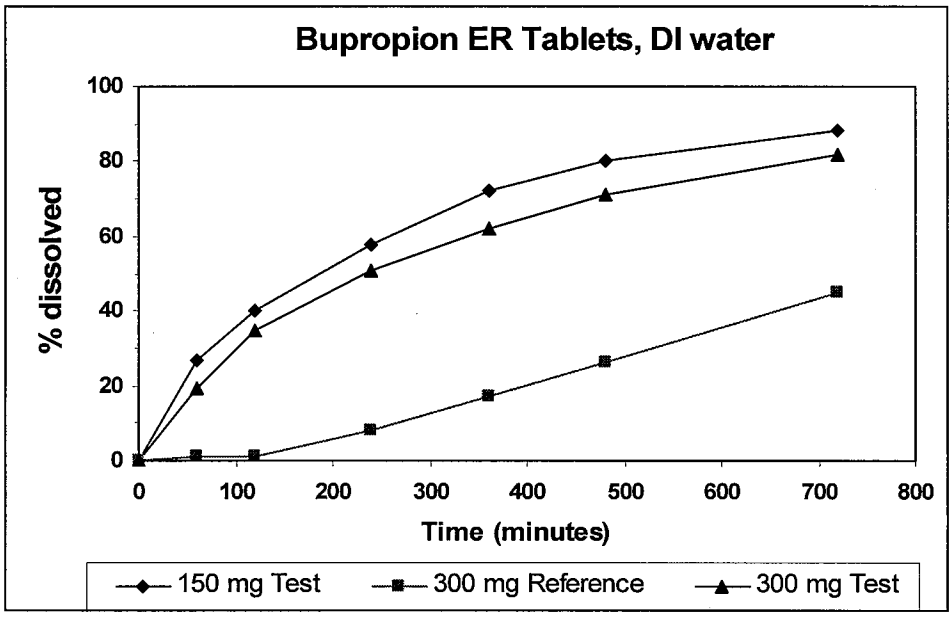
Sampling Time (min)	Impax's Bupropion Hydrochloride ER Tablets, Strength: 150 mg, Lot No. R04035-500 (Reference: C3.1, p 0096)			GlaxoSmithKline's WELLBUTRIN® XL Tablets, Strength: 300 mg, Lot No. 03K021P (Reference: C3.1, p 0100)			Impax's Bupropion Hydrochloride ER Tablets, Strength: 300 mg, Lot No. R04041-180 (Reference: C3.1, p 0096)		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
60	21	1.3	(b) (4)	20	0.5	(b) (4)	22	0.4	(b) (4)
120	35	2.8		38	0.8		31	0.7	
240	48	2.8		59	1.6		43	1.0	
360	59	3.1		74	2.3		52	1.2	
480	65	2.9		84	2.5		58	1.5	
720	67	2.4		92	1.9		64	1.7	

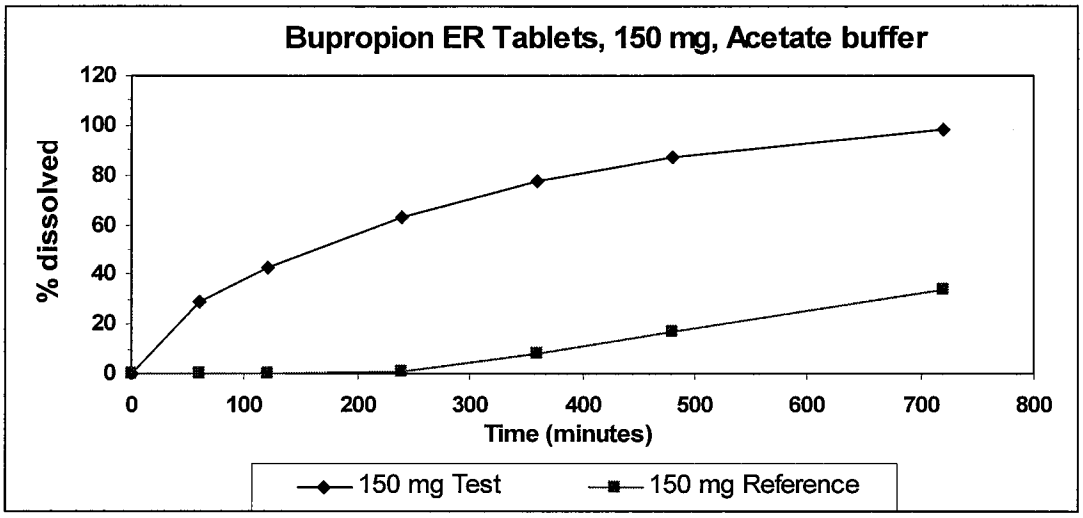
Figure 3 Dissolution Comparison

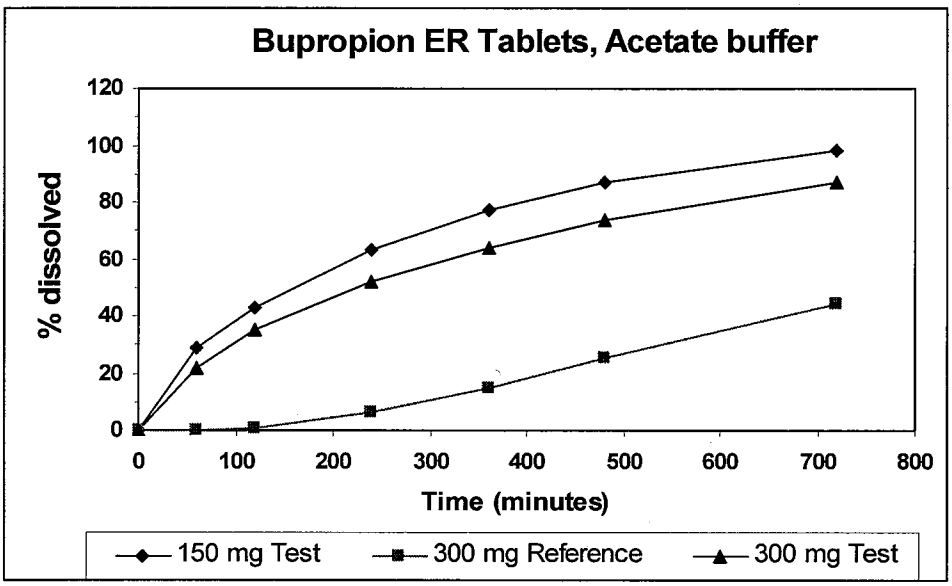


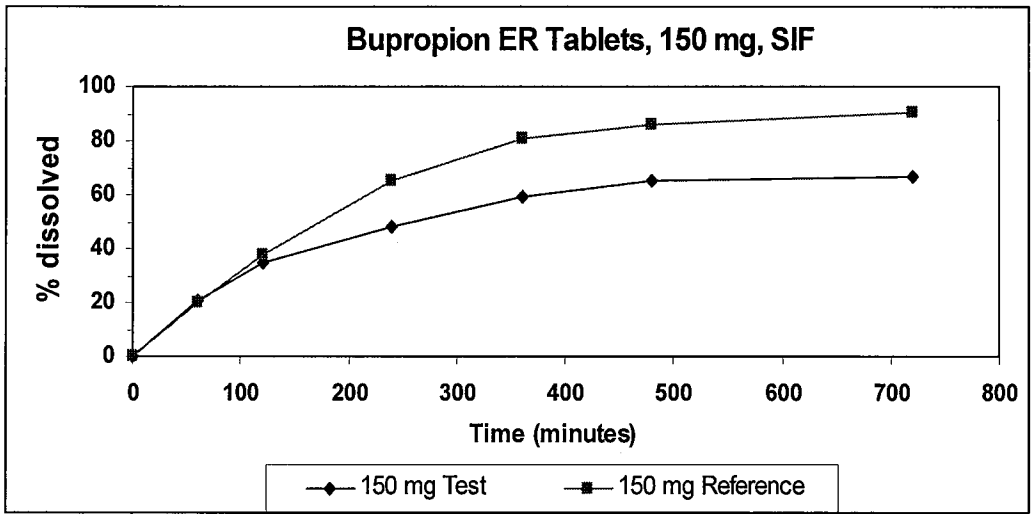



Bupropion ER Tablets, 150 mg, DI water
% dissolved
100
80
60
40
20
0
0
100
200
300
400
500
600
700
800
Time (minutes)
150 mg Test
150 mg Reference


Bupropion ER Tablets, DI water
% dissolved
100
80
60
40
20
0
0
100
200
300
400
500
600
700
800
Time (minutes)
150 mg Test
300 mg Reference
300 mg Test


Bupropion ER Tablets, 150 mg, Acetate buffer
% dissolved
120
100
80
60
40
20
0
0
100
200
300
400
500
600
700
800
Time (minutes)
150 mg Test
150 mg Reference


Bupropion ER Tablets, Acetate buffer
% dissolved
120
100
80
60
40
20
0
0
100
200
300
400
500
600
700
800
Time (minutes)
150 mg Test
300 mg Reference
300 mg Test


Bupropion ER Tablets, 150 mg, SIF
% dissolved
100
80
60
40
20
0
0
100
200
300
400
500
600
700
800
Time (minutes)
150 mg Test
150 mg Reference

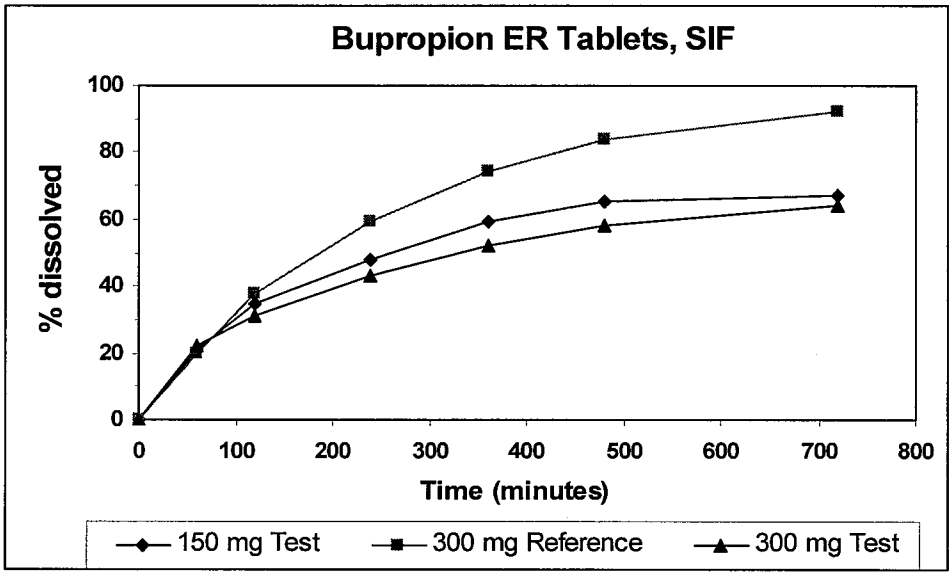

Bupropion ER Tablets, SIF
% dissolved
100
80
60
40
20
0
0
100
200
300
400
500
600
700
800
Time (minutes)
150 mg Test
300 mg Reference
300 mg Test

Table 32 f_2 calculation (calculated by the reviewer):

Test Product	Reference Product	Dissolution Medium	f_2
Impax's Bupropion Hydrochloride ER tablets, 150 mg, Lot No. R04035-500	GSK's WELLBUTRIN® XL, 150 mg, Lot No. 04C003P	0.1 N HCl	31.3
		DI water	16.7
		Acetate buffer (pH 4.5)	11.8
		SIF (pH~6.8)	38.3

Test Product	Product	Dissolution Medium	f_2 (Firm's)	f_2 (Reviewer calculated)
Impax's Bupropion Hydrochloride ER tablets, 300 mg Lot # R04041	Impax's Bupropion hydrochloride ER tablets, 150 mg Lot # 04035	0.1 N HCl	55	55
		DI water	56	56
		Acetate buffer (pH 4.5)	48	48
		SIF (pH~6.8)	65	65
	GSK's WELLBUTRIN® XL, 300 mg Lot # 03K021P	0.1 N HCl	NA	41
		DI water	NA	21
		Acetate buffer (pH 4.5)	NA	19
		SIF (pH~6.8)	NA	36

D. Consult Reviews

The Office of Generic Drugs (OGD) determined that the concentration of one of the inactive ingredients, [redacted] (b) (4), in the proposed formulation of Bupropion Hydrochloride Extended Release Tablets (by IMPAX Laboratories, Inc.; ANDA 77-451) exceeded the amount used in approved drug products. The OGD requested the Division of Neuropharmacological Drug Products (DNDP) to evaluate the potential toxicity of [redacted] (b) (4) in the proposed drug formulation.

The study done by DNDP (dated June 15, 2005) concluded as follows:

The available data suggests that [redacted] (b) (4) ***has a very low order of toxicity. Based on these considerations,*** [redacted] (b) (4) ***is anticipated to be safe in the proposed drug product.***

A copy of the report is provided here.

77415.Consult.PDF

E. SAS Output

	SAS DATA	SAS PROGRAM	SAS OUTPUT
Single-dose fasting BE study (Study # 04168)	 ANDA77415_ConcData_fasting.xls  ANDA77415_PkData_fasting.xls	 ANDA77415_SASprogram_fasting.txt	 ANDA77415_SASoutput_fasting.txt
Single-dose fed BE study (Study # 04169)	 ANDA77415_ConcData_fed.xls  ANDA77415_PkData_fed.xls	 ANDA77415_SASprogram_fed.txt	 ANDA77415_SASoutput_fed.txt

F. Additional Attachments

None

BIOEQUIVALENCE COMMENTS

ANDA: 77-415 APPLICANT: IMPAX Laboratories, Inc.

DRUG PRODUCT: Bupropion Hydrochloride Extended Release Tablets, 150 mg and 300 mg

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

We acknowledge that you have accepted the following dissolution method and specification:

The dissolution testing should be conducted in 900 mL of 0.1 N HCl at 37°C, using USP Apparatus I (basket) at 75 rpm. The test product should meet the following specifications:

1 hr: (b) (4)
2 hrs: %
4 hrs: %
8 hrs: %
12 hrs: (b) (4)% dissolved

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

Sincerely yours,

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

CC: ANDA 77-415
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ Reviewer Parthapratim Chandaroy
HFD-650/ Project manager B. Fritsch
HFD-650/ Team Leader M. Makary

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Printed in final on 08/24/05

Endorsements: (Final with Dates)
HFD-650/P. Chandaroy PC 8/24/05
HFD-650/M. Makary 8/24/05
HFD-650/D.P. Conner 8/24/05

BIOEQUIVALENCE – **Acceptable** Submission Date: November 30, 2004

1. **FASTING STUDY** (STF) Strength: 150 mg
Clinical: Gateway Medical Research, Inc. **Outcome: AC**
400 Fountain Lakes Blvd.
St. Charles, MO 63301

Analytical: (b) (4)

2. **FOOD STUDY** (STP) Strength: 150 mg
Clinical: Same as Fasting Study **Outcome: AC**

Analytical: Same as Fasting Study

3. **DISSOLUTION WAIVER** (DIW) Strength: 300 mg
Submission 28-Dec-2004 **Outcome: AC**

Outcome Decisions: AC - Acceptable
WinBio Comments: AC

AUG 24 2005

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 77-415	SPONSOR: IMPAX Laboratories, Inc.
DRUG AND DOSAGE FORM:	Bupropion Extended Release Tablets
STRENGTH(S):	150 mg and 300 mg
TYPES OF STUDIES:	Fasting and fed studies
CLINICAL STUDY SITE(S):	Gateway Medical Research, Inc.
ANALYTICAL SITE(S):	(b) (4)

STUDY SUMMARY: Fasting and fed studies are acceptable.

DISSOLUTION: The dissolution testing is acceptable. Waiver is granted for the 300 mg. tablet.

DSI INSPECTION STATUS

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

Proposed Dissolution Method and Spec from Original Submission Acceptable Yes _X_____
No_____
(If No, Project Manager (PM) should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Spec acknowledged by firm: Yes _____

PROJECT MANAGER: _____ DATE: _____

PRIMARY REVIEWER: Parthapratim Chandaroy, Ph.D. BRANCH: V

INITIAL: PC DATE: 8/24/05

TEAM LEADER: Moheb H. Makary, Ph.D. BRANCH: V

INITIAL: MHM DATE: 8/24/05

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

INITIAL: DPC DATE: 8/24/05

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-415
Drug Product Name	Bupropion Hydrochloride Extended Release Tablets
Strength	150 mg and 300 mg
Applicant Name	Impax Laboratories, Inc.
Address	30831 Huntwood Avenue, Hayward, CA 94544
Submission Date(s)	November 30, 2004
Amendment Date(s)	December 28, 2004 (new 300 mg strength), June 29, 2005 (Dissolution)
Reviewer	Parthapratim Chandaroy, Ph.D.
First Generic	No
File Location	v:\firmsam\impax\ltrs&rev\77415o0706.doc

Addendum to a Review

I. Executive Summary

Impax previously submitted in vitro and *in vivo* studies comparing its test product Bupropion Hydrochloride Extended Release Tablets, 150 mg and 300 mg, to the RLD WELLBUTRIN XL® (bupropion hydrochloride) Extended-Release Tablets, 150 mg and 300 mg. The firm also submitted dissolution testing data obtained from both test and RLD strengths of 150 mg and 300 mg tablets. The application has previously been found **acceptable**[1].

This is an addendum to the review of ANDA #77-415. Due to concern of dose dumping for the drug product, the Agency currently requests that the firm conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium. The testing conditions for the additional testing are described in the Deficiency Comments section.

II. Deficiency Comments

Due to concern of dose dumping for the drug product, the Agency currently requests that the firm conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL of 0.1 N HCl using apparatus I (basket) at 75 rpm, with and without alcohol:

Test 1: 12 units of the drug products analyzed according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units of the drug products analyzed by substituting 5% (v/v) of test medium with Alcohol USP, with data collected every 15 minutes for a total of 2 hours.

[1] DBE review , dated August 24, 2005 (v:\firmsam\impax\ltrs&rev\77415n1104.doc)

Test 3: 12 units of the drug products analyzed by substituting 20% (v/v) of test medium with Alcohol USP, with data collected every 15 minutes for a total of 2 hours.

Test 4: 12 units of the drug products analyzed by substituting 40% (v/v) of test medium with Alcohol USP, with data collected every 15 minutes for a total of 2 hours.

Both the test and the reference drug products must be tested accordingly and data must be provided on individual unit, means, range and %CV on both strengths.

III. Recommendations

The *in vitro* dissolution testing conducted by IMPAX Laboratories, Inc. on its Bupropion Hydrochloride Extended Release Tablets, 150 mg and 300 mg, is **incomplete** for the reasons cited in the Deficiency Comments above.

The firm is requested to conduct additional dissolution testing as described in the Deficiency Comments above.

Parthapratim Chandaroy 7/18/06

Parthapratim Chandaroy, Ph.D. Date
Reviewer, Branch V

Dhariwal 7/18/06

Kuldeep R. Dhariwal, Ph.D. Date
Team Leader, Branch V

Barbara McNeil 7/18/06

Dale P. Conner, Pharm.D. Date
Director, Division of Bioequivalence
Office of Generic Drug

CC: ANDA #77-415
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-658/ Reviewer P. Chandaroy
HFD-658/ Project Manager C. Thompson
HFD-658/ Team Leader K. Dhariwal

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Printed in final on 07/18/2006

Endorsements: (Final with Dates)
HFD-658/ P. Chandaroy PC 7/18/06
HFD-658/ K. Dhariwal 7/18/06
HFD-650/ D. Conner 7/18/06

BIOEQUIVALENCE – INCOMPLETE

Submission Date: November 30, 2004

1. **US Document** (Review Addendum)
   WC

Strengths: 150 mg and 300 mg
Outcome: IC

Outcome Decisions: IC - Incomplete

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-415
Drug Product Name	Bupropion Hydrochloride Extended Release Tablets
Strength	150 mg and 300 mg
Applicant Name	Impax Laboratories, Inc.
Address	30831 Huntwood Avenue, Hayward, CA 94544
Contact Information	Mark C. Shaw, Vice President, Regulatory Affairs and Compliance
Phone Number	(510) 476-2018
Fax Number	(510) 476-2091
Submission Date(s)	**August 04, 2006**
Amendment Date(s)	**August 08, 2006**
Reviewer	Parthapratim Chandaroy, Ph.D.
First Generic	No

Review of an Amendment

I. Executive Summary

Due to concern of dose dumping for the drug product, the Agency recently requested that the firm conduct additional dissolution testing using various concentrations of ethanol in the recommended dissolution medium of 0.1 N HCl. The testing conditions were described for the additional testing.

In the current amendment, the firm submitted the additional dissolution data as requested[1]. The data showed that there was no dose dumping in any additional media tested up to 120 minutes.

Following submission of this amendment, the Division of Bioequivalence (DBE) decided to re-evaluate the T_{max} data from the original submission. The median T_{max} values for bupropion as well as for hydroxybupropion were different for Impax's Bupropion HCl ER Tablet (test) compared to Wellbutrin XL® tablet (reference) in the fasting and fed studies conducted by Impax. As a result, the DBE requested a clinical consult[2], asking the opinion of the Director for Medical Affairs, the Office of Generic Drugs, on whether the firm's test products are expected to be bioequivalent to the Reference Listed Drug (GlaxoSmithKline's Wellbutrin XL® Extended-Release Tablets) based on the pharmacokinetic characteristics obtained from fasting and fed BE studies. The clinical consult review[3], dated October 6, 2006, concluded that "*At present, there are no available data demonstrating clinically meaningful differences among the immediate and modified release formulations of Wellbutrin or between the Wellbutrin products and the proposed Impax's product. Existing regulatory precedent in bupropion NDA reviews has not placed any significance on the rate of rise in serum concentrations of the drug.*"

[1] See Additional Attachments section (VII B) for the dissolution data in presence of alcohol in the dissolution medium

[2] See Additional Attachments section (VII D) for the clinical consult

[3] Clinical consult review for ANDA #77-415 located in DFS under file name **N 077415 N000 30-Nov-2004** (submission description: *clinical consult re Tmax*)

Thus, OGD's clinical team has concluded that any differences in T_{max} between Impax's Bupropion ER Tablets and Wellbutrin XL® will not impact the therapeutic equivalence of Impax's product. The application has previously been found **acceptable** with other bioequivalence requirement aspects[4]. Therefore, the Division of Bioequivalence concludes that this application is **acceptable** with no deficiencies.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Bupropion HCl ER Tablets, 150 mg and 300 mg
Reference Product	Wellbutrin XL® (bupropion HCl) Tablets, 150 mg and 300 mg
RLD Manufacturer	SmithKline Beecham[5]
NDA No.	21-515
RLD Approval Date	08/28/2003
Indication	indicated for the treatment of major depressive disorder

B. Contents of Submission

Study Types	Yes/No?	How many?
Amendments	Yes	2

IV.Review of submission

DBE Comment:

Due to concern of dose dumping for the drug product, the Agency currently requests that you conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows:

[4] Original ANDA review of ANDA #77-415 (\\cdsnas\ogds11\firmsam\impax\ltrs&rev\77415N1104.doc) submitted on March 17, 2006

[5] Electronic Orange Book (2006) entry for WELLBUTRIN XL®

Testing Conditions: *900 mL of 0.1 N HCl using apparatus I (basket) at 75 rpm, with and without alcohol:*

> ***Test 1:*** *12 units of the drug products analyzed according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.*
>
> ***Test 2:*** *12 units of the drug products analyzed by substituting 5% (v/v) of test medium with Alcohol USP, with data collected every 15 minutes for a total of 2 hours.*
>
> ***Test 3:*** *12 units of the drug products analyzed by substituting 20% (v/v) of test medium with Alcohol USP, with data collected every 15 minutes for a total of 2 hours.*
>
> ***Test 4:*** *12 units of the drug products analyzed by substituting 40% (v/v) of test medium with Alcohol USP, with data collected every 15 minutes for a total of 2 hours.*

Both the test and the reference drug products must be tested accordingly and data must be provided on individual unit, means, range and %CV on both strengths.

Firm's Response:

In the current amendment, the firm has submitted the additional dissolution data as requested. The additional dissolution data for the 150 mg and 300 mg strengths for both test and reference products are provided below:

150 mg Test:

Bupropion Hydrochloride Extended Release (XL) Tablets, 150 mg
Drug Release Summary (n=12)
Basket@75rpm, Bath temperature 37.0°C+/-0.5°C

LOT#: R04035-30, 0.1N HCl, (Ref: YC2011 p.1), 07/31/06

Time (mins)	% Dissolved V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range Min	Max	Mean	SD	%RSD
15												(b) (4)		(b) (4)	11	0.5	4.0%
30															17	0.8	4.8%
45															22	1.1	4.8%
60															28	1.3	4.8%
75															30	1.5	4.9%
90															33	1.5	4.8%
105															36	1.8	4.9%
120															39	1.9	4.8%

LOT#: R04035-30, 5% EtOH in 0.1N HCl, (Ref: YC2011 p.1), 07/31/06

Time (hours)	% Dissolved V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range Min	Max	Mean	SD	%RSD
15												(b) (4)		(b) (4)	10	0.6	5.8%
30															15	0.9	6.0%
45															20	1.2	5.9%
60															23	1.4	5.8%
75															27	1.6	5.8%
90															30	1.7	5.7%
105															33	1.9	5.8%
120															35	2.0	5.8%

LOT#: R04035-30, 20% EtOH in 0.1N HCl, (Ref: YC2011 p.1), 07/31/06

Time (hours)	% Dissolved V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range Min	Max	Mean	SD	%RSD
15												(b) (4)		(b) (4)	9	0.5	5.2%
30															15	0.8	5.7%
45															18	1.0	5.5%
60															23	1.2	5.5%
75															26	1.4	5.5%
90															29	1.6	5.5%
105															31	1.8	5.6%
120															34	1.8	5.4%

LOT#: R04035-30, 40% EtOH in 0.1N HCl, (Ref:YC2011 p.1), 08/03/06

Time (hours)	% Dissolved V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range Min	Max	Mean	SD	%RSD
15												(b) (4)		(b) (4)	9	0.6	6.8%
30															14	0.9	6.7%
45															18	1.2	6.5%
60															21	1.4	6.6%
75															24	1.4	5.9%
90															27	1.7	6.4%
105															29	1.9	6.4%
120															32	2.0	6.3%

150 mg Reference:

Bupropion Hydrochloride Extended Release (XL) Tablets, 150 mg
Drug Release Summary (n=12)
Basket@75rpm, Bath temperature 37.0°C+/-0.5°C

BRAND LOT#0610072F, 0.1N HCl, (Ref: YC2011 p.1), 05/04/06

Time (mins)	% Dissolved												Range		Mean	SD	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max			
15													(b) (4)	(b) (4)	0	0.0	#DIV/0!
30															0	0.0	#DIV/0!
45															0	0.0	#DIV/0!
60															0	0.0	#DIV/0!
75															0	0.0	#DIV/0!
90															0	0.3	401.4%
105															0	0.5	134.1%
120															1	0.9	80.6%

BRAND LOT#0610072F, 5% EtOH in 0.1N HCl, (Ref: YC2011 p.1), 05/04/06

Time (hours)	% Dissolved												Range		Mean	SD	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max			
15													(b) (4)	(b) (4)	0	0.0	#DIV/0!
30															0	0.0	#DIV/0!
45															0	0.0	#DIV/0!
60															0	0.0	#DIV/0!
75															0	0.2	233.8%
90															0	0.0	96.0%
105															1	0.0	55.0%
120															2	1.1	61.0%

BRAND LOT#0610072F, 20% EtOH in 0.1N HCl, (Ref: YC2011 p.1), 05/04/06

Time (hours)	% Dissolved												Range		Mean	SD	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max			
15													(b) (4)	(b) (4)	0	0.0	#DIV/0!
30															0	0.0	#DIV/0!
45															0	0.3	340.4%
60															1	0.8	69.4%
75															3	1.5	52.1%
90															5	2.3	43.0%
105															8	3.0	37.0%
120															11	3.8	31.5%

BRAND LOT#0610072F, 40% EtOH in 0.1N HCl, (Ref: YC2011 p.1), 05/04/06

Time (hours)	% Dissolved												Range		Mean	SD	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max			
15													(b) (4)	(b) (4)	0	0.0	#DIV/0!
30															1	0.3	23.1%
45															3	0.5	16.8%
60															6	0.7	12.5%
75															8	0.9	10.8%
90															11	1.0	9.3%
105															14	1.3	8.8%
120															16	1.4	8.2%

300 mg Test:

Bupropion Hydrochloride Extended Release (XL) Tablets, 300 mg
Drug Release Summary (n=12)
Basket@75rpm, Bath temperature 37.0°C+/-0.5°C

LOT#: 601302, 0.1N HCl, (Ref: YC2011 p.1), 08/01/06

Time (mins)	% Dissolved												Range		Mean	SD	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max			
15												(b) (4)		(b) (4)	10	0.2	2.1%
30															15	0.3	1.8%
45															19	0.3	1.9%
60															22	0.4	1.7%
75															25	0.4	1.7%
90															28	0.5	1.8%
105															30	0.5	1.7%
120															33	0.5	1.6%

LOT#: 601302, 5% EtOH in 0.1N HCl, (Ref: YC2011 p.1), 08/01/06

Time (hours)	% Dissolved												Range		Mean	SD	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max			
15												(b) (4)		(b) (4)	9	0.2	2.1%
30															13	0.2	1.6%
45															17	0.3	1.8%
60															20	0.4	1.8%
75															23	0.4	1.8%
90															26	0.4	1.7%
105															28	0.5	1.8%
120															30	0.5	1.7%

LOT#: 601302, 20% EtOH in 0.1N HCl, (Ref: YC2011 p.1), 08/01/06

Time (hours)	% Dissolved												Range		Mean	SD	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max			
15												(b) (4)		(b) (4)	8	0.3	3.5%
30															13	0.3	2.2%
45															17	0.3	2.0%
60															20	0.3	1.7%
75															23	0.3	1.3%
90															25	0.4	1.4%
105															27	0.4	1.4%
120															29	0.4	1.5%

LOT#: 601302, 40% EtOH in 0.1N HCl, (Ref: YC2011 p.1), 08/01/06

Time (hours)	% Dissolved												Range		Mean	SD	%RSD
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max			
15												(b) (4)		(b) (4)	8	0.2	2.0%
30															12	0.3	2.2%
45															15	0.3	2.0%
60															18	0.4	2.2%
75															20	0.4	2.0%
90															23	0.5	2.1%
105															25	0.5	2.1%
120															27	0.6	2.2%

300 mg Reference:

Bupropion Hydrochloride Extended Release (XL) Tablets, 300 mg
Drug Release Summary (n=12)
Basket@75rpm, Bath temperature 37.0°C+/-0.5°C

LOT#: 06E094p (Brand), 0.1N HCl, (Ref: YC2011 p.1), 08/03/06

Time (mins)	% Dissolved V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range Min	Max	Mean	SD	%RSD
15	(b) (4)												(b) (4)		0	0.0	#DIV/0!
30															0	0.0	#DIV/0!
45															0	0.0	#DIV/0!
60															0	0.0	#DIV/0!
75															0	0.2	198.3%
90															1	0.5	83.3%
105															2	1.2	78.4%
120															3	2.3	79.3%
															5	3.4	74.0%

LOT#: 06E094p (Brand), 5% EtOH in 0.1N HCl, (Ref: YC2011 p.1), 08/03/06

Time (hours)	% Dissolved V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range Min	Max	Mean	SD	%RSD
15	(b) (4)												(b) (4)		0	0.0	#DIV/0!
30															0	0.0	#DIV/0!
45															0	0.0	#DIV/0!
60															0	0.0	#DIV/0!
75															0	0.4	85.5%
90															1	0.7	51.0%
105															3	1.6	53.9%
120															5	2.6	53.3%
															7	3.5	47.5%

LOT#: 06E094p (Brand), 20% EtOH in 0.1N HCl, (Ref: YC2011 p.1), 08/03/06

Time (hours)	% Dissolved V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range Min	Max	Mean	SD	%RSD
15	(b) (4)												(b) (4)		0	0.0	#DIV/0!
30															0	0.2	182.3%
45															1	0.4	35.5%
60															3	0.7	25.8%
75															5	1.1	22.5%
90															7	1.6	21.3%
105															10	2.0	19.4%
120															14	2.4	17.8%

LOT#: 06E094p (Brand), 40% EtOH in 0.1N HCl, (Ref: YC2011 p.1), 08/04/06

Time (hours)	% Dissolved V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range Min	Max	Mean	SD	%RSD
15	(b) (4)												(b) (4)		0	0.1	30.7%
30															2	0.3	13.7%
45															4	0.4	9.1%
60															7	0.5	7.3%
75															10	0.7	6.7%
90															13	0.8	6.0%
105															16	1.0	6.1%
120															19	1.1	5.9%

In an amendment, submitted on August 8, 2006, the firm corrected some typographical errors: dissolution time should be in minutes, instead of hours, in some of the dissolution tables.

Reviewer's Comment:

According to the dissolution data submitted by the firm, the drug release rate for both the 150 mg and 300 mg strengths of the test product are similar in all the four media with different concentrations of alcohol. There is no difference in drug release with or without alcohol.

For both the 150 mg and 300 mg strengths of the reference product, there is a slight increase in drug release with increasing alcohol concentration in the medium. But the difference in % drug release, at any time point, between the media with the lowest and highest concentration of alcohol, 0% and 40% (v/v), respectively, is less than 20%.

It is important to note that drug release rate of both strengths of the test product is higher than those of the respective strengths of the reference product in all additional dissolution media, with or without alcohol. This difference in drug release rate between the test and reference products was also observed in water and pH 4.5 acetate buffer (see dissolution review and original review of ANDA)[6]. The mean % drug release, for both the strengths of the test and reference products, at the end of 2 hours show no significant dose dumping:

	Mean % Drug Release (at 2 hours)			
	0.1N HCl	5% Alcohol in 0.1 N HCl	20% Alcohol in 0.1 N HCl	40% Alcohol in 0.1 N HCl
150 mg				
Test	39	35	35	32
Reference	1	2	11	18
300 mg				
Test	33	30	30	27
Reference	5	7	14	19

The firm's response to the comment is **acceptable**.

V. Deficiency Comments

None

VI. Recommendations

The additional dissolution testing conducted by Impax Laboratories, Inc., on its Bupropion Hydrochloride Extended Release Tablets, 150 mg and 300 mg, as requested by the Division of Bioequivalence, is **acceptable.**

The firm should be informed of the above recommendation.

[6] Original review of ANDA #77-415 (\\cdsnas\ogds11\firmsam\impax\ltrs&rev\77415N1104.doc) and dissolution review of ANDA #77-415 (\\cdsnas\ogds11\firmsam\impax\ltrs&rev\77415D1104.doc)

VII. Additional Attachments

A. Proposal regarding the issue of dose dumping in presence of alcohol

From: Haidar, Sam H
Sent: Thursday, September 14, 2006 5:56 PM
To: Buehler, Gary J
Cc: Yu, Lawrence; Conner, Dale P; Davit, Barbara M; Haidar, Sam H
Subject: RE: BUPROPION EXTENDED-RELEASE (ONCE-A-DAY)

Gary,

Just to clarify, Dale, Barbara and I met this morning to discuss OGD's proposal for in vitro evaluation of dose dumping in the presence of alcohol. We briefly discussed Impax's data for bupropion. Clearly, there are no concerns for this product with respect to dose dumping in the presence of alcohol. The proposal we are working on would only serve to confirm this conclusion. Therefore, it is not necessary to delay action on Impax's application, pending finalizing and presentation of our proposal.

We'll share our conclusions with Vilayat.

Thanks.

Sam

B. Results of in vitro alcohol dose-dumping study comparing Impax's Bupropion HCl ER Tablet with Wellbutrin XL

The memo containing a detailed analysis of the study report is stored in the following location: \\cdsnas\ogds11\firmsam\impax\memos\77415bio09-06.doc

C. Request to the firms to submit additional dissolution data in presence of alcohol

The memo containing the study report is stored in the following location:
\\cdsnas\ogds11\firmsam\impax\memos\77415bio09-11-06.doc

D. Clinical Consult for ANDA #77-415

The medical officer's clinical review, authored by Nancy Chang, M.D. and written in response to DBE's clinical consult request, is stored in the following location in DFS: N 077415 N 000 30-Nov-2004 – Review.

DBE's clinical consult request is attached below.

To: Dena Hixon, M.D., Director for Medical Affairs, Office of Generic Drugs

From: Parthapratim Chandaroy, Reviewer, Division of Bioequivalence, Office of Generic Drugs

Through: Barbara M. Davit Ph.D., Deputy Director, Division of Bioequivalence, Office of Generic Drugs

Re: Request opinion on whether Impax's Bupropion Hydrochloride (HCl) Extended-Release (ER) Tablets are expected to be therapeutically equivalent to GlaxoSmithKline's Wellbutrin XL® Extended-Release Tablets based on the pharmacokinetic (PK) characteristics obtained from fasting and fed bioequivalence (BE) studies

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Introduction: Impax submitted single-dose fasting and non-fasting bioequivalence studies, under ANDA #77-415, to the Division of Bioequivalence (DBE) in support of its application to market a generic version of GlaxoSmithKline's Wellbutrin XL® Extended-Release Tablets. In these studies, Impax measured the parent drug bupropion, as well as the major active metabolite hydroxybupropion (formed via first-pass metabolism of bupropion). DBE uses confidence interval acceptance criteria for the parent only but the metabolite data are used to provide supportive evidence of comparable therapeutic outcome. Bupropion is extensively metabolized into three active metabolites: hydroxybupropion (major metabolite), threohydrobupropion, and erythrohydrobupropion. 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 at least comparable to or may exceed bupropion plasma concentrations.

Issue: Impax conducted two-way crossover fasting (n=36) and non-fasting (n=38) bioequivalence (BE) studies of its Bupropion HCl ER Tablet. The parent drug bupropion met BE acceptance criteria[7] in the fasting as well as the non-fasting study. Thus, the DBE deemed the two products bioequivalent.

Table 1 Summary of Statistical Analysis [Point estimate (90% CI)]:

Test/Reference	Fasting Study		Non-fasting Study	
	Bupropion	Hydroxybupropion	Bupropion	Hydroxybupropion
$LAUC_t$	0.98 (91.9-104.4)	1.02 (95.3-109.6)	1.08 (101.4-115.4)	1.08 (99.3-116.4)
$LAUC_\infty$	0.98 (92.1-103.9)	1.03 (96.0-109.6)	1.07 (100.4-113.7)	1.07 (98.8-116.0)
LC_{max}	0.89 (80.3-98.2)	1.06 (98.3-113.7)	1.10 (103.2-118.0)	1.17 (108.9-124.7)

The median T_{max} values for bupropion and hydroxybupropion are different for both Impax's Bupropion HCl ER Tablet (test) and Wellbutrin XL® (reference) products in both the studies. Mean T½ values were similar for both the test and reference products.

---

[7] A test and reference product are deemed bioequivalent if the 90% confidence intervals of the geometric mean AUC and C_{max} test/reference ratios fall between 80-125%.

Table 2 Median (range) T_{max} values for the two bioequivalence studies (units = hours)

	Bupropion		Hydroxybupropion	
	Test	Reference	Test	Reference
Fasting study	3 (1.5-5)	5 (2-12)	10 (4-24)	12 (3-24)
Non-fasting study	3 (1-6)	6 (3-10)	10 (7-24)	12 (8-24)

Table 3 Mean (%CV) Elimination Half-life values for the two bioequivalence studies (units = hours)

	Bupropion		Hydroxybupropion	
	Test	Reference	Test	Reference
Fasting study	19.0 (48.0)	19.2 (50.2)	24.8 (25.6)	25.0 (22.6)
Non-fasting study	16.4 (49.9)	18.8 (74.1)	22.0 (24.5)	22.5 (25.0)

In concluding that Impax's Bupropion HCl ER Tablet was bioequivalent to Wellbutrin XL®, the DBE considered the above information in light of available information on bupropion clinical pharmacology following dosing with Wellbutrin® immediate-release, Wellbutrin SR®, and Wellbutrin XL® Tablets.

However, DBE subsequently decided to request a clinical consult to determine whether Impax's Bupropion HCl ER Tablets and Wellbutrin XL® ER Tablets are expected to be therapeutically equivalent, considering the following PK characteristics:

- Bupropion AUC and C_{max} met BE acceptance criteria in both fasted and fed studies
- Mean (%CV) bupropion T_{max} values differ between the two products
  1. 2.8 (35.4) hours (Impax) versus 5 (31.0) hours (Wellbutrin XL®) in the fasting study
  2. 3.3 (37.7) hours (Impax) versus 6.2 (24.0) hours (Wellbutrin XL®) in the fed study
- Mean bupropion T ½ values are similar for the two products

A copy of the bioequivalence review is attached below to provide additional background information.

77415N1104.doc

Background: Wellbutrin XL® is indicated for the treatment of major depressive disorder. It is an antidepressant of the aminoketone class, its structure closely resembling to that of diethylpropion and it is related to phenylethylamines. 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. Wellbutrin XL® tablets are marketed by GlaxoSmithKline (GSK) in the strengths of 150 and 300 mg (NDA #21-515; approved on August 28, 2003).

Wellbutrin XL® was approved in 2003 under NDA #21-515. The only clinical trials submitted in support of approval were PK studies. Thus, NDA #21-515 rested primarily on PK studies rather than clinical efficacy.[8] GSK submitted a relative bioavailability (BA) crossover study in which healthy subjects (n=30) received either Wellbutrin XL® 300mg qd x 10 days or Wellbutrin immediate-release (IR) tablets 100mg tid x 3 days. The study met acceptance criteria of 80-125% for geometric mean AUC and C_{max} test/reference (XL versus IR) ratios. Values for T_{max} differed. The median T_{max}

[8] Filing meeting minutes, NDA 21-515, 1/14/03.

was 5 hours (range 3-7 hours) for Wellbutrin XL® and 1.5 hours (range 1-3 hours) for Wellbutrin. Also, median T_{max} values for all major metabolites differed by 3.5 to 4.5 hours between Wellbutrin IR and Wellbutrin XL, although all metabolites met BE criteria for AUC and C_{max}.

In the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) review of NDA #21-515, the reviewer states "although comparable exposure [between Wellbutrin IR and Wellbutrin XL] was demonstrated, there are differences in the shapes of the curves for bupropion in the Wellbutrin XL® formulation compared with IR formulation. The clinical relevance of these differences cannot be predicted based on the pharmacokinetics. However, the comparable exposure and the role of the metabolites in the exposure and pharmacologic activity support the approval of the Wellbutrin XL® formulation. Of note, for Wellbutrin SR, although there were also differences in the shapes of the plasma concentration curves compared to Wellbutrin IR, a clinical trial demonstrated efficacy of Wellbutrin SR in maintaining antidepressant response."

Safety: The following warning is in the label of Wellbutrin XL®: Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Wellbutrin XL® or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Wellbutrin XL® is not approved for use in pediatric patients. Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs in children and adolescents with MDD, obsessive compulsive disorder, or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidality, during the first few months of treatment, in those receiving antidepressants (4%) to those receiving placebo (2%). No suicides occurred in these trials.

Generics: There is no approved generic drug for Wellbutrin XL® tablets listed in the Orange Book. However, so far three ANDAs have been reviewed by DBE and were deemed bioequivalent (#77-284 from Anchen, #77-285 from Abrika, and #77-415 from Impax – the current application). A fourth application is currently under review (#77-715 from Watson).

Regimens: The usual adult target dose for Wellbutrin XL® tablets is 300 mg/day, given once daily in the morning. Dosing with Wellbutrin XL® 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 once daily, may be made as early as day 4 of dosing. There should be an interval of at least 24 hours between successive doses. As with other antidepressants, the full antidepressant effect of Wellbutrin XL® tablets may not be evident until 4 weeks of treatment or longer. An increase in dosage to the maximum of 450 mg/day, given as a single dose, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. It is particularly important to administer Wellbutrin XL® tablets in a manner most likely to minimize the risk of seizure. 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. Wellbutrin XL® should be swallowed whole and not crushed, divided, or chewed.

PK: Following a single dose of Wellbutrin XL®, T_{max} is approximately 5 hours (bupropion) and 7 hours (all three metabolites). As mentioned earlier, bupropion is extensively metabolized into three active metabolites. In vitro findings suggest that cytochrome P450IIB6 (CYP2B6) is the principal enzyme involved in the formation of hydroxybupropion. 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. Following Wellbutrin XL® dosing, the half-life for bupropion and its metabolites are: 21 (±9) hours (bupropion); 20 (±5) hours (hydroxybupropion); 33 (±10) hours (erythrohydrobupropion); 37 (±13) hours (threohydrobupropion).

Food: In a study with healthy volunteers, food did not affect the C_{max} or AUC of bupropion. Wellbutrin XL® tablets may be taken without regard to meals.

Conclusion: In both pivotal BE studies comparing Impax's Bupropion HCl ER Tablet to Wellbutrin XL®, the parent drug bupropion meets bioequivalence acceptance criteria, and statistical analysis of hydroxybupropion, the major active metabolite, suggests bioequivalence. The mean and median T_{max} values for bupropion and hydroxybupropion are different for the test (Impax's Bupropion HCl ER Tablet) and reference (Wellbutrin XL®) products in both studies, although the mean bupropion and hydroxybupropion plasma elimination half-life values are similar for both products. Therefore, the DBE asks if these two products are likely to be therapeutically equivalent.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-415 APPLICANT: IMPAX Laboratories, Inc.

DRUG PRODUCT: Bupropion Hydrochloride Extended Release Tablets, 150 mg and 300 mg

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

We acknowledge that the dissolution testing for the test products is conducted using the following method:

The dissolution testing should be conducted in 900 mL of 0.1 N HCl at 37°C, using USP Apparatus I (basket) at 75 rpm. The test products should meet the following specifications:

1 hr: (b) (4)
2 hrs: %
4 hrs: %
8 hrs: %
12 hrs: (b) (4) % dissolved

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

Sincerely yours,

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

BIOEQUIVALENCE – **ACCEPTABLE** Submission Date: August 04, 2006

1. Study Amendment (STA) Strength: 150 mg and 300 mg
Outcome: AC

OUTCOME DECISIONS: **AC** - Acceptable

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Parthapratim Chandaroy
10/12/2006 10:23:35 AM
BIOPHARMACEUTICS

Kuldeep R. Dhariwal
10/12/2006 10:39:17 AM
BIOPHARMACEUTICS

Barbara Davit
10/12/2006 10:46:29 AM
BIOPHARMACEUTICS

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #:	77-415 **SPONSOR:** Impax Laboratories, Inc.
DRUG & DOSAGE FORM:	Bupropion Hydrochloride Extended Release Tablets
STRENGTH(S):	150 mg and 300 mg
TYPES OF STUDIES:	Fasting and fed studies
CLINICAL STUDY SITE(S):	Fasting and Fed: Gateway Medical Research, inc., 400 Fountain Lakes Blvd., St. Charles, MO 63301
ANALYTICAL SITE(S):	Fasting and fed: (b) (4)

STUDY SUMMARY:	Fasting and fed studies on 150 mg tablets are acceptable.
DISSOLUTION:	The dissolution testing is acceptable. Waiver is granted for the 300 mg tablets.

DSI INSPECTION STATUS

Inspection needed:	No	**Inspection status:**	**Inspection results:**
First Generic	No		
New facility			
For cause			
Other			

Proposed Dissolution Method and Specifications from Original Submission Acceptable?

Yes _____ No X (If no, project Manager should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Specifications acknowledged by firm? Yes X No ____

AMENDMENT DATE: 6/29/05

PROJECT MANAGER: _____ **DATE:** _____

PRIMARY REVIEWER: Parthapratim Chandaroy, Ph.D. **BRANCH:** V
INITIAL: _____ DATE: _____

TEAM LEADER: Kuldeep R. Dhariwal, Ph.D. **BRANCH:** V
INITIAL: _____ DATE: _____

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: _____ DATE: _____

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Barbara Davit
10/12/2006 10:51:17 AM

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-415
Drug Product Name	Bupropion Hydrochloride Extended Release Tablets
Strength	150 mg and 300 mg
Applicant Name	Impax Laboratories, Inc.
Address	30831 Huntwood Avenue, Hayward, CA 94544
Submission Date(s)	**November 30, 2004**
Amendment Date(s)	**December 28, 2004** (new 300 mg strength), June 29, 2005 (Dissolution)
Reviewer	Parthapratim Chandaroy, Ph.D.
First Generic	No

Addendum to a Review

I. Executive Summary

This addendum contains recommendation which supersedes recommendation #4 of the original bioequivalence review[1]. Based on CFR 320.24 b(6), the Division of Bioequivalence (DBE) deems the test product, Impax's Bupropion Hydrochloride Extended Release Tablet, 300 mg, to be bioequivalent to the reference listed drug, GlaxoSmithKline's WELLBUTRIN XL® (bupropion hydrochloride) Tablet, 300 mg. Because of safety issue[2], DBE recommends to conduct bioequivalence studies on the 150 mg strength of the test and reference products.

[1] Original DBE review of ANDA #77-415 (\\cdsnas\ogds11\firmsam\impax\ltrs&rev\77415n1104.d0c)
[2] Clinical consult review # CD02-712 (\\cdsnas\ogds11\(b) (4)\controls\02-712md.doc)

ANDA #: 77-415

BIOEQUIVALENCE – ACCEPTABLE

Submission Date: November 30, 2004

1. **US Document** (Review Addendum) WC

Strengths: 150 mg and 300 mg
Outcome: AC

Outcome Decisions: AC - Acceptable

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Parthapratim Chandaroy
12/13/2006 04:05:08 PM
BIOPHARMACEUTICS

Devvrat Patel
12/13/2006 04:09:57 PM
BIOPHARMACEUTICS
Signing for Kuldeep Dhariwal

Barbara Davit
12/13/2006 04:21:01 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077415

PHARMACOLGY TOXICOLOGY REVIEW

3.1

COMPLETED JUN 15 2005

Consultation for ANDA [redacted] 77-415

Drug	Bupropion HCl Extended-release Tablets
Sponsor	Impax Pharmaceuticals, Inc
Submission Date	December 28, 2004
Consult to	Christine Bina, HFD-615
Date Received	April 18, 2005
Review Date	June 1, 2005
Reviewer	Paul Roney, Ph.D., D.A.B.T., HFD-120

Template 6/16/05

Paul Roney

Background

The sponsor submitted an Abbreviated New Drug Application (ANDA) for Bupropion HCl Extended-release Tablets (150 and 300 mg tablets) on December 28, 2004 to the Office of Generic Drugs (HFD-615) for the treatment of depression. The Office of Generic Drugs determined that the concentrations of [redacted] (b) (4) in the drug products exceeded the amount used in approved drug products. Each tablet contains [redacted] (b) (4) mg of [redacted] (b) (4) [redacted] (b) (4) Patients would take one tablet per day, so the daily exposure is [redacted] (b) (4) mg/day. Since patients have not been exposed to this dose of [redacted] (b) (4) in other drug products, the Office of Generic Drugs requested that the Division of Neuropharmacological Drug Products evaluate the potential toxicity of [redacted] (b) (4) in this drug formulation. [redacted] (b) (4) . No exposure limit is specified except that it should be used in accordance with good manufacturing practice. The World Health Organization does not specify an acceptable daily intake, although they note that [redacted] (b) (4) [redacted] (b) (4) [1] In addition, [redacted] (b) (4) are associated with [redacted] (b) (4) .

No studies in English were available for review in the open literature. The WHO summary of studies on [redacted] (b) (4) is attached below. It is noted that some of the studies were conducted at [redacted] (b) (4) and have not been validated. This laboratory has been associated with poor study conduct and results from this laboratory should be interpreted with caution.

[1] WHO. [redacted] (b) (4) WHO [redacted] (b) (4)

Following this page, 3 pages withheld in full (b)(4)-CCI/TS

(b) (4)

The available data suggest that (b) (4)

Conclusions

The available data suggest the (b) (4) has a very low order of toxicity. **Based on these considerations,** (b) (4) **is anticipated to be safe in the proposed drug product.**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077415

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

November 30, 2004

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA for Bupropion Hydrochloride Extended-release (XL) Tablets, 150 mg

Dear Mr. Buehler:

In accordance with Section 505 (j) of the Federal Food, Drug and Cosmetic Act, IMPAX Laboratories, Inc hereby submits an Abbreviated New Drug Application (ANDA) for Bupropion Hydrochloride Extended-release (XL) Tablets, 150 mg. The reference listed drug, Wellbutrin XL™ (bupropion hydrochloride) tablets, 150 mg, is the subject of SmithKline Beecham's approved NDA 21-515. The drug product, which is the subject of this ANDA, differs from the listed product in that the formulation contains different excipients.

This application meets the criteria for an ANDA in that 1) the conditions of use, active ingredient, route of administration, dosage form, and strength are identical to those of the listed drug, 2) bioequivalence has been demonstrated, and 3) patent certification is provided. The labeling complies with all labeling requirements. This application lists IMPAX Laboratories, Inc. as the manufacturing site for the drug product. The submission contains 13 volumes, organized and jacketed in accordance with FDA-OGD guidelines.

Also included with this ANDA is an electronic submission of the package insert word processor file, prepared in both Microsoft Word and PDF format. One (1) write-protected diskette is included in the archival copy of the submission, in a plastic insert. The labeling data contained in the electronic submission is identical to that contained in this hardcopy submission. Four (4) copies of the draft labels and labeling are included in both the archival and review copies of the application.

One (1) write-protected diskette containing the pharmacokinetic data resulting from the bioequivalence study is also included in the archival copy of this submission, in a plastic insert.

Should you have any additional questions regarding this ANDA, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200
www.impaxlabs.com

Paragraph IV Patent Certification

IMPAX Laboratories, Inc. has caused all of the following actions to be taken with respect to the following patent certification concerning its bupropion HCl extended-release tablets, 150 mg:

1. The publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book), 24th Edition, 2004, and Cumulative Supplement 8, August, 2004 have been examined for patent entries related to the listed drug (Wellbutrin XL™).

2. The U.S. Patent and Trademark Office's ("PTO's") August 19, 2004 list of Patent Terms Extended Under 35 U.S.C. § 156 (Waxman-Hatch extensions) has been examined for entries related to the listed drug.

Based upon the above identified actions, IMPAX Laboratories, Inc. certifies that, in its opinion and to the best of its knowledge; the following patents are invalid, unenforceable, or will not be infringed by the manufacture, use or sale of the bupropion HCl extended-release tablets, 150 mg, for which this application is submitted:

Patent Number	Inventor	Issue Date	Expiration Date
6,096,341	Pawan Seth	08/01/2000	October 30, 2018
6,143,327	Pawan Seth	11/07/2000	October 30, 2018

IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200
www.impaxlabs.com

Paragraph IV Statement

IMPAX Laboratories, Inc. hereby states, in accordance with § 505(j)(2)(B)(i) of the Federal Food, Drug, and Cosmetic Act ("the Act"), that, within 20 days of the postmark of FDA's letter acknowledging that this abbreviated new drug application is sufficiently complete to permit a substantive review, it will give notices containing the information required by § 505(j)(2)(B)(iv) of the Act and 21 C.F.R. § 314.95(c), to the following persons by U.S. Certified Mail, return receipt requested:

1. The owner of each of the following patent numbers:

   6,096,341
   6,143,327

   or the representative of each such owner designated to receive such notice; and

2. The holder of approved NDA number 21-515, or the representative of such holder designated to receive such notice.

IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200
www.impaxlabs.com

MARKET EXCLUSIVITY STATEMENT

The applicant has reviewed the entries concerning the reference listed drug contained in FDA's publication, entitled "APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS," 24th Edition (2004) (the "Orange Book"). Based upon that review, applicant states that exclusivity under Section 505 of the Federal Food, Drug, and Cosmetic Act has expired for the reference listed drug, as shown below:

EXCLUSIVITY TYPE	EXCLUSIVITY TERMINATION DATE
M-10 (Information regarding maintenance of an antidepressant effect up to 1 year of dosing)	June 11, 2004

IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

IMPAX LABORATORIES, INC.

MMS - S. Middleton 1/7/05

21

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

N/MC

December 15, 2004

General Correspondence
Via fax 301-594-1174

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attn: Martin Shimer

Re: ANDA 77-415: Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg

Dear Mr. Buehler:

Reference is made to IMPAX' original ANDA for the above listed product, submitted to the FDA on November 30, 2004. The application states that the quantitative composition of the colorant ((b) (4)) will be provided directly to the agency by the vendor (b) (4). Included with this correspondence please find a Drug Master File letter of authorization for this ingredient.

Should you have any questions regarding this information, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
DEC 17 2004
OGD / CDER

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

MJ - received via fax - S. Middleton 1/24/05

January 12, 2005

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

General Correspondence
Via fax 301-594-1174

N/mc

Attn: Saundra Middleton

Re: ANDA 77-415: Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg

Dear Mr. Buehler:

This correspondence follows a January 12, 2005 telephone conversation with Saundra Middleton of your office regarding the November 30, 2004 original ANDA for the above-listed product. Ms. Middleton requested the following information:

- Quantitative composition of the colorant ((b) (4))
- Container labeling for the (b) (4) configuration

The quantitative composition of the colorant ((b) (4)) will be provided directly to the agency by the vendor (b) (4). Labeling for the (b) (4) configuration is provided with this correspondence. Please note that IMPAX has also included labeling for the 300 mg strength, submitted to the agency as an amendment to ANDA 77-415 on December 28, 2004.

(b) (4)

Should you have any questions regarding this information, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
JAN 18 2005
OGD / CDER

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 77-415 **FIRM NAME:** IMPAX LABORATORIES INC.

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: BUPROPION HYDROCHLORIDE
DOSAGE FORM: EXTENDED- RELEASE TABLETS
150 MG

Bio Assignments:		Micro Review
☒ BPH	☐ BCE	☐
☐ BST	☒ BDI	

Random Queue: 10
Chem Team Leader: Rosencrance, Susan PM: Tom Hinchliffe Labeling Reviewer: Michelle Dillahunt

Letter Date: NOVEMBER 30, 2004	**Received Date:** DECEMBER 01, 2004
Comments: EC- 1 YES	**On Cards:** YES
Therapeutic Code: 2020100 ANTIDEPRESSANTS	
Archival Format: PAPER	**Sections** I **(356H Sections per EDR Email)**
Review copy: YES	E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections	
Field Copy Certification (Original Signature) YES – PS. 3630	
Methods Validation Package (3 copies PAPER archive) (Required for Non-USP drugs)	**YES**
Cover Letter YES	**Table of Contents** YES
PART 3 Combination Product Category	N Not a Part3 Combo Product
(Must be completed for ALL Original Applications)	Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Kendra J. Middleton	**Recommendation:**
Date 1/13/05	☑ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date:	**Date:** 18 Jan 2005
ADDITIONAL COMMENTS REGARDING THE AND	
Called 1/12/05 for breakdown of [redacted] (b) (4)	
[redacted] (b) (4)	
Top 200 Drug Product:	

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES (Statement regarding Rx/OTC Status) RX YES	☑
Sec. II	**Basis for Submission** **NDA# : 21-515** ✓ Ref Listed Drug: WELLBUTRIN Firm: SMITH KLINE BEECHAM ANDA suitability petition required? NO If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☑
Sec. III	**Patent Certification** 1. Paragraph: IV — pg. 8 2. Expiration of Patent: 10-30-2018 A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement:** YES — pg. 10 expired 6/11/04	☑
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use ✓ 2. Active ingredients ✓ 3. Route of administration ✓ 4. Dosage Form ✓ 5. Strength ✓	☑
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) 30 Ct [redacted] (b) (4) 1. 4 copies of draft (each strength and container) or 12 copies of FPL ✓ 2. 1 RLD label and 1 RLD container label ✓ 3. 1 side by side labeling comparison with all differences annotated and explained ✓ 4. Was a proprietary name request submitted? NO (If yes, send email to Labeling Rvwr indicating such.)	☑
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) YES — pg. 3032 **2. Request for Waiver of In-Vivo Study(ies): NO** **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) **4. Lot Numbers of Products used in BE Study(ies):** 0411684 01469 (Lot R04035) 5. Study Type: **IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☑
Study Type	IN-VIVO PK STUDY(IES) (i.e., fasting/fed/sprinkle) FASTING AND FED ON 150 MG a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) pg. 120 ✓ b. EDR Email: Data Files Submitted: YES SENT TO EDR c. In-Vitro Dissolution: YES — pg. 2970	☑

Study Type	IN-VIVO BE STUDY with CLINICAL ENDPOINTS NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	TRANSDERMAL DELIVERY SYSTEMS NO a. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. Adhesion Study c. Skin Irritation/Sensitization Study	☐
Study Type	NASALLY ADMINISTERED DRUG PRODUCTS NO a. Solutions (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. Suspensions (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES) NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation ✓ See sheets attached 2. Inactive ingredients as appropriate ✓	☑

Lot #. RO40135 MASTER [redacted] (b) (4) EXHIBIT [redacted] (b) (4) MADE [redacted] (b) (4) PACKAGED [redacted] (b) (4)

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers ✓ b. Type II DMF authorization letters or synthesis ✓ # (b) (4) c. COA(s) specifications and test results from drug substance mfgr(s) ✓ d. Applicant certificate of analysis ✓ e. Testing specifications and data from drug product manufacturer(s) ✓ f. Spectra and chromatograms for reference standards and test samples ✓ g. CFN numbers — 2. **Inactive Ingredients** a. Source of inactive ingredients identified — pg. 3043 b. Testing specifications (including identification and characterization) ✓ c. Suppliers' COA (specifications and test results) ✓ d. Applicant certificate of analysis	☐ ✓
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) ✓ 2. CGMP Certification: YES — 3093 3. CFN numbers ✓	☑
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address ✓ 2. Functions 3. CGMP Certification/GLP ✓ 4. CFN numbers ✓	☑
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) ✓ 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified ✓ 3.If sterile product: Aseptic fill / Terminal sterilization 4.Filter validation (if aseptic fill) 5. Reprocessing Statement — pg. 3161	☑
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation 2. In-process Controls - Specifications and data See pg. 3	☑
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) ✓ 2. Components Specification and Test Data (Type III DMF References) ✓ 3. Packaging Configuration and Sizes ✓ 4. Container/Closure Testing ✓ 5. Source of supply and suppliers address ✓	☐ ✓

Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data ✓ 2. Certificate of Analysis for Finished Dosage Form ✓ pg. 3407	☑
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted ✓ 2. Post Approval Commitments ✓ 3. Expiration Dating Period ✓ 24 months 4. Stability Data Submitted ✓ a. 3 month accelerated stability data ✓ b. Batch numbers on stability records the same as the test batch ✓	☑
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance ✓ 2. Finished Dosage Form ✓ 3. Same lot numbers ✓	☑
Sec. XVII	**Environmental Impact Analysis Statement** ✓	☑
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other:** 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) 2. Debarment Certification (original signature): YES — pg. 3619 3. List of Convictions statement (original signature)	☑

OGD Template Revised 04/01/2004 /T.Hinchliffe

ANDA 77-415

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

JAN 19 2005

Dear Sir:

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

Reference is made to the correspondence dated December 15, 2004.

Reference is also made to the telephone conversation dated January 12, 2005 and your correspondence dated January 12, 2005 and to the correspondence dated January 13, 2005 from (b) (4).

NAME OF DRUG: Bupropion Hydrochloride Extended-release Tablets USP, 150 mg

DATE OF APPLICATION: November 30, 2004

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 1, 2004

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (301) 827-5862.

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

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

Should you have questions concerning this application, contact:

Thomas Hinchliffe
Project Manager
(301) 827-5849

Sincerely yours,

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

ANDA 77-415
cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-92

Endorsement:
HFD-615/M. Shimer, Chief, RSB _____ date 18 Jan 05
HFD-615/S. Middleton, CSO _____ date 1/13/05
Word File
V:/FIRMSAM\IMPAX\LTRS&REV\77415.ACK
FT by StM 1/13/05

ANDA Acknowledgment Letter!

NAI labeling 7/28/05

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

February 25, 2005

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

General Correspondence
Via fax 301-594-1174

MC

Attn: Christine Bina

Re: ANDA 77-415: Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg and 300 mg

Dear Mr. Buehler:

This correspondence follows a February 25, 2005 telephone message from Christine Bina of your office regarding the December 28, 2004 New Strength amendment for the above-listed product. Ms. Bina requested the following information:

- Container labeling for the (b) (4) count configuration

(b) (4)

Should you have any questions regarding this information, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw for

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

AC

ANDA 77-415 Final Check List for Branch Chief

N/A 1) Check letter date and stamp date of ANDA vs. drafted letter.

✓ 2) Check for any NC arriving post stamp date but prior to Reg. Review.

N/A 3) Check for gross errors in letter.

N/A 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)

N/A 5) Check address and contact person on letter vs. 356h.

✓ 6) Check for any t-cons and verify date and correspondence date.

✓ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 8) Check for any comments or problems raised by reviewer on Check List.

N/A 9) If first generic, copy BE review and file.

✓ 10) Sign Check List.

✓ 11) Check electronic Orange Book to verify current patent information and correct RLD. Wellbutrin XL 300mg

N/A 12) Check for MOU patents

✓ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer. Wellbutrin XL 150 = RLD

✓ 14) Review Basis for Submission. 21-515

✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

✓ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

✓ 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.

✓ 18) Pull USP information. (USP ___yes ✓ no)

✓ 19) Final Grammar review on letter.

✓ 20) Verify information in OGD Patent Tracking System.

✓ 21) EES slip.

✓ 22) Document in record book.

Signature Martin H. Gruia date 28 Feb 2005

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 77-415 **FIRM NAME**: IMPAX LABORATORIES INC.

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: BUPROPION HYDROCHLORIDE
DOSAGE FORM: EXTENDED- RELEASE TABLETS,
150 MG AND 300 MG (NEW STRENGTH 300 MG)

Bio Assignments:		Micro Review
☒ BPH	☐ BCE	☐
☐ BST	☒ BDI	

Random Queue: 10
Chem Team Leader: Rosencrance, Susan PM: Tom Hinchliffe Labeling Reviewer: Michelle Dillahunt

Letter Date: DECEMBER 28, 2004 **Received Date**: DECEMBER 30, 2004

Comments: EC- 1+1=2 YES **On Cards:** YES
Therapeutic Code: 2020100 ANTIDEPRESSANTS

Archival Format: PAPER **Sections** I **(356H Sections per EDR Email)**
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections
Field Copy Certification (Original Signature) YES

Methods Validation Package (3 copies PAPER archive) **NO**
(Required for Non-USP drugs)

Cover Letter YES | **Table of Contents** YES

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Christine Bina

Date 2/25/2005

Recommendation:

☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: Mark Shaw **Date:** 28 Feb 2005

ADDITIONAL COMMENTS REGARDING THE ANDA:
Contact: Mark Shaw (510) 476-2018

Send Tox data on consult to ODEI for review of the proposed level of Hydroxypropyl Cellulose

(b) (4)

Note: Only 30 count bottle in How Supplied section, but firm did supply container closure information and stability data for the (b) (4) count and (b) (4) count container sizes as well as the 30 count container.

MMJ-
PK
Suit filed within 45 days 3/7/05. for 1341 on S. middleton 9/20/05

IMPAX LABORATORIES, INC.
30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

March 16, 2005

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

N/XP

Re: ANDA 77-415: Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg and 300 mg
Documentation of Paragraph IV Patent Notification and Receipt of Notice and Documentation of Litigation/Settlement Outcome

Dear Mr. Buehler:

In accordance with 21 CFR 314.95(b), IMPAX Laboratories, Inc. (IMPAX) hereby certifies that it has provided a Notice of Legal and Factual Basis of Non-Infringement for the above-referenced ANDA to the following parties and that the Notice met the content requirements specified in 21 CFR 314.95(c):

SmithKline Beecham Corporation
President
One Franklin Plaza
Philadelphia, Pennsylvania 19101-7599
150 mg: FedEx #8457-3319-6556
300 mg: FedEx #8482-5347-3881
150 mg: FedEx Proof of Delivery Date: 01/21/05
300 mg: FedEx Proof of Delivery Date: 01/26/05

Biovail Laboratories, Inc.
President
Building No. 2, Chelston Park
Collymore Rock
St. Michael, Barbados
150 mg: FedEx #8309-0643-5698
300 mg: FedEx #8309-0643-5713
150 mg: FedEx Proof of Delivery Date: 01/24/05
300 mg: FedEx Proof of Delivery Date: 01/25/05

Biovail Laboratories, Inc.
#34 B Street Iturregui Avenue
Carolina, Puerto Rico 00646
150 mg: FedEx #8309-0643-5702
300 mg: FedEx #8309-0643-5724
150 mg: FedEx Proof of Delivery Date: 01/24/05
300 mg: FedEx Proof of Delivery Date: 01/27/05

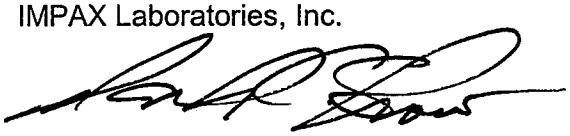
As required by 21 CFR 314.95(e), IMPAX is amending this application to provide documentation of receipt of the Notice of Legal and Factual Basis of Non-Infringement by the above-listed parties. A copy of the original Federal Express signature proof of delivery accompanies this letter. Permission to use FedEx was granted to IMPAX by Martin Shimer of OGD on January 24, 2005.

In addition, reference is made to the Office of Generic Drug's January 19, 2005 letter documenting the acceptance for filing of the above-referenced ANDA. The letter requested that IMPAX notify your office in the event that litigation occurred within the 45-day period following notification of the NDA Holder and Patent Owner.

IMPAX hereby confirms that Biovail Laboratories, Inc. initiated a lawsuit for the 150 mg strength only, within the 45-day period as provided for in section 505(j) (4)(B)(iii) of the Act. Accordingly, IMPAX is enclosing with this correspondence a copy of the complaint filed March 7, 2005 in the United States District Court for the Eastern District of Pennsylvania. Please note that IMPAX has only been sued for infringement of U.S. Patent No. 6,096,341.

Should you have any questions regarding this information, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.



Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

IMPAX
LABORATORIES, INC.

Amended Complaint Filed for '341 to include 300mg. S-Middleton 6/14/05

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

April 21, 2005

PATENT AMENDMENT

N/xP

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 77-415: Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg and 300 mg
Documentation of Litigation/Settlement Outcome

Dear Mr. Buehler:

Reference is made to the Office of Generic Drug's January 19, 2005 letter documenting the acceptance for filing of the above-referenced ANDA. IMPAX also references its Patent Amendment dated March 16, 2005, in which we provided evidence of documentation of delivery of notice as well as documentation of litigation for the 150 mg product.

IMPAX hereby confirms that Biovail Laboratories, Inc. has amended its complaint against IMPAX to include the 300 mg strength. Please note that the amended complaint was filed on April 7, 2005, following the expiration of the 45-day period as provided for in section 505(j) (4)(B)(iii) of the Act. IMPAX is enclosing with this correspondence a copy of the amended complaint filed April 7, 2005 in the United States District Court for the Eastern District of Pennsylvania. As with the original complaint, IMPAX has only been sued for infringement of U.S. Patent No. 6,096,341.

Should you have any questions regarding this information, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

BIOEQUIVALENCY AMENDMENT

ANDA 77-415

JUN 0 2 2005

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Impax Laboratories, Inc. TEL: 510.476.2018

ATTN: Mark Shaw FAX: 510.476.2091

FROM: Aaron Sigler PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on November 30, 2004, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Buproprion HCl Extended-Release Tablets, 150 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 9 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES JUN 0 2 2005

ANDA: 77-415 APPLICANT: Impax Laboratories, Inc.

DRUG PRODUCT: Bupropion Hydrochloride Extended-Release Tablets, 150 mg

The Division of Bioequivalence has completed its review of the dissolution testing portion and has the following deficiencies:

1. The dissolution testing comparing your test product, Bupropion Hydrochloride Extended-Release Tablets, 150 mg, with the reference product, GlaxoSmithKline's Wellbutrin® XL, 150 mg, is **incomplete.** Your proposed specification is not acceptable. The DBE requests you to accept FDA-recommended dissolution method and specification as follows:

Medium	0.1 N HCl
Volume	900 mL
Temperature	37°C ± 5°C
Apparatus	USP Apparatus 1 (Basket)
Rotational Speed	75 rpm
Specification	1hr: (b) (4)
	2hrs: %
	4hrs: %
	8hrs: %
	12hrs: (b) (4) % dissolved

2. In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could provide this information for any other applications pending in the Division and in applications to be submitted in the future.

3. In addition, there is a discrepancy in two applications in the notebook referenced for the 150 mg (lot R04035-500) dissolution data. In the original application the referenced notebook for 150 mg bupropion hydrochloride extended-release tablets dissolution data is "LO 1207, pp 45-49" (orange jacket v 1.11, p 2972), whereas the same data in the amendment application cited "JC1217, pp. 71-76" as the referenced notebook. (Orange jacket v 3.1, p 0093). You need to clarify which one is the correct referenced notebook for 150 mg bupropion hydrochloride extended-release tablets dissolution study.

Sincerely yours,

Barbara M. Davit for

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

Table 1. Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (units/mL)	T_{max} (hr)	AUC_{0-t} (units)	AUC_{∞} (units)	T½ (hr)	K_{el} (hr^{-1})	
Study #	Fasting study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #] Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M ± S.D. M ± S.D.	Mn or Md No SD	M ± S.D. M ± S.D.	M ± S.D. M ± S.D.	Mean No SD	Mean No SD	Vol. # p. #
Study #	Fed study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #] Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean y (range)	M ± S.D. M ± S.D.	Mn or Md No SD	M ± S.D. M ± S.D.	M ± S.D. M ± S.D.	Mean No SD	Mean No SD	Vol. # p. #

Table 2. Statistical Summary of the Comparative Bioavailability Data

Drug Dose (# x mg) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t}				
AUC^{∞}				
C_{max}				
Fed Bioequivalence Study				
Parameter	**Test**	**Reference**	**100*Ratio**	**90% C.I.**
AUC_{0-t}				
AUC^{∞}				
C_{max}				

Table 3. Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Provide the volume(s) and page(s)
Analyte	Provide the name(s) of the analyte(s)
Internal standard (IS)	Identify the internal standard used
Method description	Brief description of extraction method; analytical method
Limit of quantitation	LOQ, units
Average recovery of drug (%)	%
Average recovery of IS (%)	%
Standard curve concentrations (units/mL)	Standard curve range and appropriate concentration units
QC concentrations (units/mL)	List all the concentrations used
QC Intraday precision range (%)	Range or per QC
QC Intraday accuracy range (%)	Range or per QC
QC Interday precision range (%)	Range or per QC
QC Interday accuracy range (%)	Range or per QC
Bench-top stability (hrs)	hours @ room temperature
Stock stability (days)	days @ 4°C
Processed stability (hrs)	hours @ room temperature; hours @ 4°C
Freeze-thaw stability (cycles)	# cycles
Long-term storage stability (days)	17 days @ -20°C (or other)
Dilution integrity	Concentration diluted X-fold
Selectivity	No interfering peaks noted in blank plasma samples

Table 4. Summary of In Vitro Dissolution Studies

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range)				Study Report Location
					min	min	min	min	
Diss. study report #	Test prod name/ #	mg Tab./Cap./Susp.	Dissolution: Apparatus Speed of Rotation: rpm Medium: Volume: mL Temperature: °C	12					
Diss. study report #	Ref prod name/ #	mg Tab./Cap/Susp.		12					

Table 5. Formulation Data

Ingredient	Amount (mg) / Tablet		Amount (%) Tablet	
	Lower strength	Higher strength	Lower strength	Higher strength
Cores				
Coating				
Total			100.00	100.0

Table 6. Demographic Profile of Subjects Completing the Bioequivalence Study

Study No.		
	Treatment Groups	
	Test Product N =	Reference Product N =
Age (years)		
Mean ± SD	50 ± 15	
Range	20-85	
Groups		
< 18	N(%)	N(%)
18 – 40	N(%)	N(%)
40 – 64	N(%)	N(%)
65 – 75	N(%)	N(%)
> 75	N(%)	N(%)
Sex		
Female	N(%)	N(%)
Male	N(%)	N(%)
Race		
Asian	N(%)	N(%)
Black	N(%)	N(%)
Caucasian	N(%)	N(%)
Hispanic	N(%)	N(%)
Other	N(%)	N(%)
Other Factors		

Table 7. Incidence of Adverse Events in Individual Studies

Body System/Adverse Event	Reported Incidence by Treatment Groups					
	Fasted Bioequivalence Study Study No.		Fed Bioequivalence Study Study No.		Other Bioequivalence Study Study No.	
	Test	Reference	Test	Reference	Test	Reference
Body as a whole						
Dizziness	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Etc.	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cardiovascular						
Hypotension						
Etc.						
Gastrointestinal						
Constipation						
Etc.						
Other organ sys.						
Total	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Table 8. Reanalysis of Study Samples

Study No. Additional information in Volume(s), Page(s)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]								
Reason A (e.g. below LOQ)								
Reason B								
Reason C								
Etc.								
Total								

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

ORIG AMENDMENT

June 21, 2005

MINOR AMENDMENT

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 77-415: Bupropion Hydrochloride Extended-release Tablets, 150 mg and 300 mg

Dear Mr. Buehler:

This letter responds to your May 19, 2005, facsimile, listing deficiencies in the above-referenced ANDA. A copy of your correspondence accompanies this letter.

Each deficiency is listed in boldface type followed by IMPAX's response. As required to complete each response, additional data are provided as attachments in this submission. In addition to responding to the Chemistry deficiencies, IMPAX also acknowledges the following comments:

1. IMPAX acknowledges that the FDA is currently reviewing the bioequivalence information of the above-referenced ANDA and that any deficiencies will be communicated to IMPAX under a separate cover. In addition, any labeling deficiencies will be resolved prior to the approval of the ANDA.

2. IMPAX acknowledges that a satisfactory compliance evaluation for the firms referenced in the ANDA is required for approval.

3. IMPAX acknowledges that in the event of any dispute, the USP methods will be deemed the official methods.

4. This submission also includes in **Attachment 14** completed long term stability data for lots R04035 (150 mg) and R04041 (300 mg).

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 15.**

RECEIVED
JUN 23 2005
OGD/CDER

Should you have any additional questions regarding this response, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

for

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

cc: Rochelle Young, SFDO

RECORD OF TELEPHONE CONVERSATION

Background Information:
Instead of issuing a NA (MINOR) letter or making a conference call to Impax in requesting a telephone amendment, Lisa called the firm to inform them that a written copy of telephone amendment request would be faxed to them. This should save reviewer's, team leader's, project manager's time as well as the firm's time.

Telephone Conversation:
Lisa: We are going to fax to you a page of CMC deficiencies as the result of our review of your MINOR AMENDMENT dated June 21, 2005. Please treat the fax as our request for a Telephone amendment. Please respond by fax, followed by a hard copy. The response should be clearly marked as TELEPHONE AMENDEMENT. Please call me if you need clarification on the deficiencies.

Mark Shaw: We will do.

DATE: July 27, 2005
ANDA NUMBER 77-415
TELECON INITIATED BY AGENT OR SPONSOR **FDA**
PRODUCT NAME: Bupropion Hydrochloride Extended Release Tablets 150 mg and 300 mg
FIRM NAME: Impax (California)
FIRM REPRESENTATIVES: Mark C Shaw Vice president, Regulatory Affairs and Compliance
TELEPHONE NUMBER: Tel: (510) 476-2018 Direct Line Fax: (510) 476-2091
FDA REPRESENTATIVES LISA KWOK
SIGNATURES: Lisa Kwok 7/27/05

Orig: ANDA 77-415 cc: Team 11 T-con Log
V:\firmsam\impax\telecon\77415.tcon.072705.doc

ANDA 77-415

OFFICE OF GENERIC DRUGS

Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: 301-594-0180

FAX TRANSMISSION COVER SHEET

DATE: 7/27/05

TO: APPLICANT: Impax Laboratories, Inc. TEL: 510-476-2018

ATTN: Mark Shaw FAX: 510-476-2091

FROM: Lisa Kwok PROJECT MANAGER: 301-827-5746

TOTAL NUMBER OF PAGES : 1
(EXCLUDING COVER SHEET)

Special Instructions:

Please respond as a telephone amendment.

ANDA: 77-415 APPLICANT: Impax Laboratories, Inc.

DRUG PRODUCT: Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg

Please submit a Telephone Amendment to address the following deficiencies, which resulted from our review of your MINOR amendment dated June 21, 2005. Please provide a fax copy of your response followed by a hard copy to the Agency. The fax number is (301) 827-9274 [Attention: Lisa Kwok]

Deficiencies:

1. (b) (4)

2.

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 5, 2005

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

ORIG AMENDMENT

Re: ANDA 77-415: Bupropion Hydrochloride Extended-release Tablets, 150 mg and 300 mg

Dear Mr. Buehler:

This letter responds to your July 27, 2005, facsimile, listing deficiencies in the above-referenced ANDA. A copy of your correspondence accompanies this letter.

Each deficiency is listed in boldface type followed by IMPAX's response. As required to complete each response, additional data are provided as attachments in this submission.

Please note that a Field Copy of this submission has been submitted to the San Francisco District Office. A Field Copy certification is provided in **Attachment 2.**

Should you have any additional questions regarding this response, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

RECEIVED
AUG 10 2005
OGD/CDER

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

cc: Rochelle Young, SFDO

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

ORIG AMENDMENT
N/AF

September 28, 2005

LABELING AND CHEMISTRY AMENDMENT

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ATTN: RUBY WU

Re: ANDA 77-415: Bupropion Hydrochloride Extended-Release Tablets, USP, (XL) 150 mg and 300 mg

Dear Mr. Buehler:

This letter follows an August 27, 2005 facsimile from a Ms. Ruby Wu of your office regarding Labeling Deficiencies for the above-referenced ANDA.

Ms. Wu has requested that IMPAX submit revisions to the Container Labeling and Product Insert and add the Medication Guide as instructed in the attached copy of the facsimile. Enclosed in this Amendment are IMPAX's revisions to the container labeling for both the 150 mg and 300 mg strength, a revised product insert, and a medication guide.

Impax has also added a 90 count to each of the 150 mg and 300 mg strengths. Enclosed are IMPAX's proposed packaging records for 90 count tablets of 150 mg and 300mg as well as the USP test results for the bottle to be utilized in the 90 count **(Attachment 4).** Also included is the proposed container labeling for the 90 count.

A side-by-side comparison of the labeling changes is provided. Also included with the archival copy of this amendment are 12 copies of the final printed insert labeling. A complete copy of this labeling amendment, including specimens of the final printed labeling, is provided for the labeling reviewer in a separately labled binder.

Also included with this amendment is an electronic submission of the package insert, prepared in PDF format. One (1) write-protected diskette is included in the archival copy of the submission, in a plastic insert. The labeling data contained in the electronic submission is identical to that contained in this hardcopy submission.

Please note that a field copy of this submission has been submitted to the San Francisco District Office. A field copy certification is provided in **(Attachment 5).**

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

November 9, 2005

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

ORIG AMENDMENT
N/AF

ATTN: Melaine Shin

Re: ANDA 77-415, Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg and 300 mg

This letter responds to the November 4, 2005 facsimile, listing revisions to the IMPAX Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg and and 300 mg container labels and insert. A copy of your correspondence accompanies this letter.

A side-by-side comparison of the labeling changes is provided. Also included with the archival copy of this amendment are 12 copies of the final printed labeling. A complete copy of this labeling amendment, including specimens of the final printed labeling, is provided for the labeling reviewer in a separately labeled binder.

Also included with this amendment is an electronic submission of the package insert, prepared in PDF format. One (1) write-protected diskette is included in the archival copy of the submission, in a plastic insert. The labeling data contained in the electronic submission is identical to that contained in this hardcopy submission.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
NOV 14 2005
OGD / CDER

A10.1

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

June 5, 2006

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT –
FINAL APPROVAL REQUESTED

ORIG AMENDMENT
N-000-AM

Attn: Robert West, Deputy Director, OGD
Lisa Kwok, Project Manager, OGD

Re: ANDA 77-415
Bupropion HCl Extended Release Tablets (XL)

Dear Mr. Buehler:

With this letter IMPAX Laboratories, Inc. (IMPAX) hereby requests Final Approval and Tentative Approval, respectively, of the 300 mg and 150 mg strengths of Bupropion HCl Extended Release (XL) Tablets ('BPX-300' and 'BPX-150'), which are the subject of the above-referenced ANDA.

The information presented below summarizes the current status of *Final Printed Labeling*, *CMC Changes*, and *Patent and Legal*. The *Patent and Legal* section summarizes the basis for IMPAX's request for the Office of Generic Drugs to grant Final and Tentative Approval to BPX-300 and BPX-150, respectively.

Final Printed Labeling

Final printed labeling was submitted in correspondence dated November 9, 2005.

CMC Changes

IMPAX hereby confirms that no CMC changes have been made to this application since our August 5, 2005 Telephone Amendment, which responded to a July 27, 2005 facsimile from OGD.

Patent and Legal

Reference is made to IMPAX's November 30, 2004 original ANDA for BPX-150 and to our December 28, 2004 Major Amendment for BPX-300. The original ANDA was deemed acceptable for filing on December 1, 2004, as documented in OGD's Acceptance for Filing letter, dated January 19, 2005.

Following receipt of the Acceptance for Filing letter, IMPAX provided a Notice of Legal and Factual Basis of Non-Infringement to the NDA Holder of NDA 21-515 and to the Patent Owner of each patent listed in Approved Drug Products with Therapeutic Equivalence Evaluations ('Orange Book'), listed thereto as relevant to NDA 21-515.

Please refer to IMPAX's March 16, 2005 Patent Amendment providing proof of such notification. This Patent Amendment also confirmed that Biovail Laboratories, Inc. initiated a lawsuit for the 150 mg strength only. The suit was filed on March 7, 2005 in the U.S. District Court for the Eastern District of Pennsylvania (Civil Action No. 05-CV-1085).

Reference is also made to IMPAX's April 21, 2005 Patent Amendment in which we confirmed that Biovail Laboratories, Inc. had amended its complaint against IMPAX to include the 300 mg strength. However, the amended complaint was filed April 7, 2005, following expiration of the 45-day period provided for in section 505(j)(4)(B)(iii) of the FDCA, and thus no 30-month stay of approval applies to the 300 mg strength. IMPAX discussed this with Mr. Robert West of your office on November 22, 2005, and again on March 29, 2006, during a teleconference with Mr. West, IMPAX, TEVA Pharmaceuticals, Inc., and Anchen Pharmaceuticals, Inc. IMPAX's understanding is that FDA concurs that no 30-month stay applies to the 300 mg strength[1].

Citizen Petition, Docket No. 2005P-0498

As you know, Biovail Corporation filed a Citizen Petition on December 20, 2005, requesting that FDA refuse to approve any ANDA for a generic version of Wellbutrin XL® unless the ANDA includes additional bioequivalence data beyond that which is authorized and necessary for approval. IMPAX submitted comments to this Citizen Petition in a February 23, 2006 letter from Heller Ehrman, counsel to IMPAX, and concluded that the petition was wholly without merit and merely designed to delay the onset of generic competition for this important drug product. As such, IMPAX requested the prompt denial of this Citizen Petition.

IMPAX's understanding is that all substantive technical reviews of ANDA 77-415 are now complete. As such, BPX-300 and BPX-150 are eligible for final and tentative approvals, respectively. Were it not for Anchen Pharma's ("Anchen") 180-day statutory exclusivity, IMPAX's ANDA would be eligible for final approval. IMPAX reiterates its request that OGD take prompt action to issue the respective approval actions, irrespective of any final decision with respect to the Citizen Petition.

Relinquishment of First-to-File Exclusivity

Reference is made to ANDA 77-284, a tentatively approved application for Bupropion HCl Extended Release Tablets (XL), 150 mg and 300 mg, held by Anchen, which was granted Tentative Approval by OGD on November 14, 2005.

IMPAX's understanding is that Anchen was the first applicant to submit a substantially complete ANDA seeking approval of a generic version of Wellbutrin XL® and containing at least one Paragraph IV patent certification. As such, Anchen Pharma is entitled to 180-day exclusivity for its 150- and 300-mg strengths following final approval of its ANDA.

---

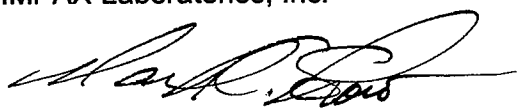
[1] Biovail Laboratories, Inc. is not the proper legal entity to have brought the lawsuit either on IMPAX's BPX-150 or BPX-300; however, IMPAX is not seeking any relief from the Agency as to this issue at this time.

IMPAX and its marketing partner, TEVA Pharmaceuticals, have entered into an agreement with Anchen regarding its relinquishment or selective waiver of exclusivity for the 300 mg strength[2,3], permitting FDA to grant final approval to IMPAX's BPX-300. As such, were it not for the frivolous Citizen Petition, final approval could be granted to IMPAX's BPX-300 and tentative approval to IMPAX's BPX-150.

Commensurate with receiving final approval, IMPAX plans to launch its BPX-300, through its marketing partner TEVA Pharmaceuticals, as early as August 2006.

Should you have any questions regarding this correspondence, please contact me by telephone (*510-476-2018*) or by telefax (*510-476-2091*).

Sincerely,
IMPAX Laboratories, Inc.



Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

cc: Margaret Choy (Anchen Pharma)
Debbie Jaskot (TEVA Pharmaceuticals)

---

[2] MASTER 300 mg AGREEMENT, dated as of January 24, 2006, among IMPAX LABORATORIES, INC., TEVA PHARMACEUTICALS CURACAO N.V., and ANCHEN PHRMAMACEUTICALS, INC.
[3] The decision as to relinquishment or selective waiver depends on the timing and outcome of Anchen's litigation.

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

Excl. update will not affect Mkt. until exclus. expire 6/12/09 for SND I-497 S. Middleton 8/10/06

July 10, 2006

PATENT AMENDMENT

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

XP

Attn: Martin Shimer, Regulatory Support Branch

Re: ANDA 77-415, Bupropion HCl Extended-Release Tablets (XL) 150 mg and 300 mg

Dear Mr. Buehler:

This correspondence provides an updated Market Exclusivity Statement, following the addition of I-497 Exclusivity (use of Wellbutrin XL in the prevention of seasonal major depressive episodes in patients with seasonal affective disorder). As stated in the revised Market Exclusivity Statement, the I-497 exclusivity expires on June 12, 2009.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

ORIG AMENDMENT
N/AF

July 12, 2006

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT
EXPEDITED REVIEW REQUESTED

ATTN: Michelle Dillahunt

Re: ANDA 77-415, Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg and 300 mg

Following the June 12, 2006 approval of revisions to Wellbutrin XL® labeling, IMPAX hereby submits revised labeling. The IMPAX labeling has been revised to include new text related to the change from Pregnancy Category B to Pregnancy Category C. IMPAX has not included text regarding the new indication for the prevention of seasonal major depressive episodes in patients with seasonal affective disorder, as we believe this indication is the subject of marketing exclusivity. A revised market exclusivity statement has been submitted under separate cover.

A side-by-side comparison of the labeling changes is provided. Also included with the archival copy of this amendment is 1 copy of the final printed labeling. Also included with this amendment is an electronic submission of the package insert, prepared in PDF format. One (1) compact disc is included in the archival copy of the submission, in a plastic insert. The labeling data contained in the electronic submission is identical to that contained in this hardcopy submission.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
JUL 13 2006
OGD / CDER

IMPAX
LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

July 26, 2006

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT
EXPEDITED REVIEW REQUESTED

ORIG AMENDMENT
N-AF

ATTN: Ann Vu and Michelle Dillahunt

Re: ANDA 77-415, Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg and 300 mg

Following the July 26, 2006 telephone conversation with Ann Vu of your office, IMPAX hereby withdraws its July 12, 2006 Labeling Amendment.

Following the June 12, 2006 approval of revisions to Wellbutrin XL® labeling, IMPAX hereby submits revised labeling. The IMPAX labeling has been revised to include new text related to the change from Pregnancy Category B to Pregnancy Category C. IMPAX has not included text regarding the new indication for the prevention of seasonal major depressive episodes in patients with seasonal affective disorder, as we believe this indication is the subject of marketing exclusivity. A revised market exclusivity statement has been submitted under separate cover.

A side-by-side comparison of the labeling changes is provided. Also included with the archival copy of this amendment is 1 copy of the final printed labeling. Also included with this amendment is an electronic submission of the package insert, prepared in PDF format. One (1) compact disc is included in the archival copy of the submission, in a plastic insert. The labeling data contained in the electronic submission is identical to that contained in this hardcopy submission.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
JUL 27 2006
OGD / CDER

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 4, 2006

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCY AMENDMENT

ORIG AMENDMENT
N-AB

Attn: Christina Thompson

Re: ANDA 77-415: Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg

Dear Mr. Buehler:

This letter responds to your July 26, 2006 facsimile listing deficiencies in the above-referenced ANDA. A copy of your correspondence accompanies this letter.

As requested in the July 26 correspondence, IMPAX has generated comparative dissolution data in varying concentrations of alcohol. The data show that dissolution of the IMPAX product remains essentially unchanged in the presence of alcohol. The data is provided as attachments as follows:

Attachment 1: IMPAX Lot R04035-30 (150 mg), 900 mL of 0.1 N HCl, using Apparatus 1 (basket) at 75 rpm and substitution of test medium with 0%, 5%, 20%, and 40% (v/v) Alcohol USP

Attachment 2: Wellbutrin XL® Lot 06E072P (150 mg), 900 mL of 0.1 N HCl, using Apparatus 1 (basket) at 75 rpm and substitution of test medium with 0%, 5%, 20%, and 40% (v/v) Alcohol USP

Attachment 3: IMPAX Lot 601302 (300 mg), 900 mL of 0.1 N HCl using Apparatus 1 (basket) at 75 rpm and substitution of test medium with 0%, 5%, 20%, and 40% (v/v) Alcohol USP

Attachment 4: Wellbutrin XL® Lot 06E094P (300 mg), 900 mL of 0.1 N HCl using Apparatus 1 (basket) at 75 rpm and substitution of test medium with 0%, 5%, 20% and 40% (v/v) Alcohol USP

Attachment 5: Comparison data graph of IMPAX Lot R04035-30 (150 mg) vs. Wellbutrin XL® Lot 06E072P (150 mg), 900 mL of 0.1 N HCl using Apparatus 1 (basket) at 75 rpm and substitution of test medium with 0%, 5%, 20%, and 40% (v/v) Alcohol USP

Attachment 6: Comparison data graph of IMPAX Lot 601302 (300 mg) vs. Wellbutrin XL® Lot 06E094P (300 mg), 900 mL of 0.1 N HCl using Apparatus 1 (basket) at 75 rpm and substitution of test medium with 0%, 5%, 20%, and 40% (v/v) Alcohol USP

Should you have any additional questions regarding this response, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 8, 2006

BIOEQUIVALENCY AMENDMENT

ORIG AMENDMENT
N-000-AB

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attn: Christina Thompson

Re: ANDA 77-415: Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg

Dear Mr. Buehler:

This letter follows IMPAX's Bioequivalency Amendment submission of August 4, 2006 that provided drug release data in varying concentrations of alcohol (EtOH). A correction needs to be made to the data tables submitted.

Due to a typographical error, the drug release time point units were mistakenly entered as hours instead of minutes. This error occurred in several tables: the tables for lot R04035-30 of 5%, 20%, and 40% EtOH on page 8, the tables for lot 06E072P of 5%, 20%, and 40% EtOH on page 10, the tables for lot 601302 of 5%, 20%, and 40% EtOH on page 12, and the tables for lot 06E094P of 5%, 20%, and 40% EtOH on page 14. The numerical data in the tables and the accompanying graphs are correct as submitted.

Should you have any additional questions regarding this information, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
AUG 0 9 2006
OGD / CDER

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 10, 2006

NEW CORRESP
NC

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT
EXPEDITED REVIEW REQUESTED

ATTN: Michelle Dillahunt

Re: ANDA 77-415, Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg and 300 mg

This letter responds to the August 7, 2006 facsimile, listing revisions to the IMPAX Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg and 300 mg container labels and insert. A copy of your correspondence accompanies this letter.

Please note that IMPAX provided a revised exclusivity statement in the Patent Amendment dated July 10, 2006.

A side-by-side comparison of the labeling changes is provided. Also included with the archival copy of this amendment is 1 copy of the final printed labeling. Also included with this amendment is an electronic submission of the package insert, prepared in PDF format. One (1) compact disc is included in the archival copy of the submission, in a plastic insert. The labeling data contained in the electronic submission is identical to that contained in this hardcopy submission.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
AUG 1 1 2006
OGD / CDER

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

August 16, 2006

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT
EXPEDITED REVIEW REQUESTED

ORIG AMENDMENT
N-AF

ATTN: Michelle Dillahunt

Re: ANDA 77-415, Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg and 300 mg

Dear Mr. Buehler:

IMPAX hereby withdraws the Labeling Amendment dated August 10, 2006. The labeling amendment contained herein replaces in its entirety the August 10, 2006 labeling submission.

This letter responds to the August 7, 2006 facsimile, listing revisions to the IMPAX Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg and 300 mg container labels and insert. A copy of your correspondence accompanies this letter.

Please note that IMPAX provided a revised exclusivity statement in the Patent Amendment dated July 10, 2006.

A side-by-side comparison of the labeling changes is provided. Also included with the archival copy of this amendment is 1 copy of the final printed labeling, and an electronic submission of the package insert, prepared in PDF format. One (1) compact disc is included in the archival copy of the submission, in a plastic insert. The labeling data contained in the electronic submission is identical to that contained in this hardcopy submission.

Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
AUG 17 2006
OGD / CDER

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

ORIG AMENDMENT
N-AF

August 18, 2006

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT
EXPEDITED REVIEW REQUESTED

ATTN: Michelle Dillahunt

Re: ANDA 77-415, Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg and 300 mg

Dear Mr. Buehler:

Reference is made to the August 16, 2006 Labeling Amendment and the August 17, 2006 request from Michelle Dillahunt that IMPAX provide labeling in the Microsoft Word format.

Included with the archival copy of this amendment is the electronic submission of the package insert, Patient Information, and Medication Guide, prepared in Microsoft Word. This text of the MS Word labeling is identical to that contained in the August 16, 2006 Labeling Amendment.

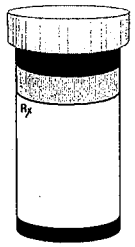
Should you have any additional questions regarding this amendment, please contact me by telephone (510-476-2018) or by telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance

RECEIVED
AUG 21 2006
OGD / CDER

Fax Cover Sheet



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

To:	Mark Shaw IMPAX Laboratories, Inc.	**Phone:** 510-476-2018 **Fax:** 510-476-2091
From:	Sarah Park Labeling Reviewer	**Phone:** 301-827-7344 **Fax:** 301-827-7884

Number of Pages (including cover sheet): 4 **Date:** September 15, 2006

COMMENTS:

ANDA 77-415

The following are requested labeling revisions from review of your amendments dated August 16, and August 18, 2006 for ANDA 77-415 (Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg and 300 mg (Once Daily). The revisions are "POST-APPROVAL" revisions and may be submitted as a "Supplement – Changes Being Effected," provided the changes are described in full.

1. CONTAINER: Please decrease the prominence of the net quantity statement relative to the expression of strength.

2. PACKAGE INSERT / MEDICATION GUIDE / PATIENT INFORMATION - GENERAL COMMENTS: Add "(XL)" to the established name wherever WELLBUTRIN XL is used, including the black box warning, medication guide, and patient information leaflet [e.g. bupropion hydrochloride extended release tablets (XL)].

3. INSERT

a. GENERAL COMMENT: Table Headings – Please replace "Bupropion ER Tablets (SR)" in all table headings to read "Bupropion Hydrochloride Sustained-Release Formulation".

b. CONTRAINDICATIONS, second paragraph - Revise as follows:

Bupropion hydrochloride extended release tablets (XL) are contraindicated in patients treated with ZYBAN® [(bupropion hydrochloride extended release tablets (SR)]; WELLBUTRIN® (bupropion hydrochloride tablets), the immediate-release formulation; WELLBUTRIN SR® [bupropion hydrochloride extended release tablets (SR)], the sustained release formulation; or any other medications that contain bupropion because the incidence of seizure is dose dependent.

c. WARNINGS

i. Screening Patients for Bipolar Disorder, second paragraph – Revise as follows:

Patients should be made aware that bupropion hydrochloride extended release tablets (XL) contain the same active ingredient found in ZYBAN®, used as an aid to smoking cessation treatment, and that bupropion hydrochloride extended release tablets (XL) should not be used in combination with ZYBAN®, or any other medications that contain bupropion, such as WELLBUTRIN SR® [bupropion hydrochloride extended release tablets (SR)], the sustained-release formulation or WELLBUTRIN® (bupropion hydrochloride tablets), the immediate-release formulation.

ii. Seizures, second paragraph, first bullet – Delete "[bupropion extended-release tablets (SR)]"

d. PRECAUTIONS

i. General: Agitation and Insomnia, first paragraph, second sentence – Delete "bupropion hydrochloride extended-release tablets (SR)"

ii. Table 1, title – Replace "Bupropion Extended-Release Tablets (SR)" with "the sustained-release formulation of bupropion"

iii. Altered Appetite and Weight, first paragraph – Delete "bupropion extended-release tablets (SR)"

iv. Table 2, title – Replace "Bupropion Extended-Release Tablets (SR)" with "the sustained-release formulation of bupropion"

v. Clinical Worsening and Suicide Risk, second paragraph – Revise as follows:

Patients should be made aware that bupropion hydrochloride extended release tablets (XL) contain the same active ingredient found in ZYBAN®, used as an aid to smoking cessation treatment, and that bupropion hydrochloride extended release tablets (XL) should not be used in combination with ZYBAN®, or any other medications that contain bupropion, such as WELLBUTRIN SR® [bupropion hydrochloride extended-release tablets (SR)], the sustained-release formulation, or WELLBUTRIN® (bupropion hydrochloride tablets), the immediate-release formulation.

e. ADVERSE REACTIONS

i. First paragraph, second sentence – Delete "bupropion extended-release tablets (SR)"

ii. Second paragraph

(1) Revise the sub-section heading as follows:

Adverse Events Leading to Discontinuation of Treatment With the Immediate Release or Sustained Release Formulations of Bupropion

(2) Delete "bupropion extended-release tablets (SR)"

iii. Forth paragraph – Revise the sub-section heading as follows:

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated With the Immediate Release or Sustained Release Formulations of Bupropion

iv. Eighth paragraph – Replace "bupropion extended-release tablets (SR)" with "the sustained-release formulation of bupropion"

v. Ninth paragraph – Revise the sub-section heading as follows:

300 mg/day of the Sustained-Release Formulation

vi. Tenth paragraph – Revise the sub-section heading as follows:

400 mg/day of the Sustained-Release Formulation

f. OVERDOSE, Human Overdose Experience, second paragraph, first sentence – Delete "rarely". [This comment applies to the package insert for the 300 mg strength]

g. DOSAGE AND ADMINISTRATION

i. Seventh paragraph – Revise as follows:

Switching Patients from Wellbutrin® (bupropion hydrochloride tablets) or from Wellbutrin SR® [bupropion hydrochloride extended-release tablets (SR)] : When switching patients from Wellbutrin® (bupropion hydrochloride tablets) to bupropion hydrochloride extended-release tablets (XL) or from Wellbutrin SR® [bupropion hydrochloride extended-release tablets (SR)] to bupropion hydrochloride extended release tablets (XL), give the same total daily dose when possible. Patients who are currently being treated with Wellbutrin® (bupropion hydrochloride tablets) at 300 mg/day (for example, 100 mg 3 times a day) may be switched to bupropion hydrochloride extended-release tablets (XL) 300 mg once daily. Patients who are currently being treated with Wellbutrin SR® [bupropion hydrochloride extended-release tablets (SR)] at 300 mg/day (for example, 150 mg twice daily) may be switched to bupropion hydrochloride extended release tablets (XL) 300 mg once daily.

ii. Eight paragraph – Delete this paragraph which starts "Maintenance Treatment: It is generally agreed..." to be in accord with the labeling for the reference listed drug. This paragraph is identical to the sixth paragraph.

h. HOW SUPPLIED, last sentence – "ZYBAN, WELLBUTRIN® and WELLBUTRIN SR® are registered trademarks of GlaxoSmithKline."

4. PATIENT INFORMATION:

a. Who should not take bupropion hydrochloride extended-release tablets (XL)? Do not take bupropion hydrochloride extended-release tablets if you – Revise the second bullet as follows:

- **are taking ZYBAN® (used to help people stop smoking) or any other medicines that contain bupropion hydrochloride, such as WELLBUTRIN® (bupropion hydrochloride tablets) or WELLBUTRIN SR® [bupropion hydrochloride extended-release tablets (SR)].** Bupropion is the same active ingredient that is in bupropion hydrochloride extended-release tablets (XL).

b. Please add Zyban®, Wellbutrin® and Wellbutrin SR® to your list of registered trademarks and their manufacturers.

RECORD OF TELEPHONE CONVERSATION

Background Information:
Instead of issuing a deficiency letter, Lisa called the firm to inform that a written copy of telephone amendment request would be faxed to them.

Telephone Conversation:
Kwok: We are going to fax to you one page of CMC deficiencies and comments. Please treat the fax as our request for a telephone amendment. Please respond by fax, followed by a hard copy (to the CDR). The response should be clearly marked as TELEPHONE AMENDEMENT. Please call me if you need clarification on the deficiencies.

DATE: October 31, 2006
ANDA NUMBER 77-415
TELECON INITIATED BY: **LISA KWOK** **DR. ALOKA SRINIVASAN**
PRODUCT NAME: Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg
FIRM NAME: Impax
FIRM REPRESENTATIVES: Mark Shaw
TELEPHONE NUMBER: (510)-476-2018
FDA REPRESENTATIVES Lisa Kwok
SIGNATURES: Lisa Kwok 10/31/06

Orig: ANDA
Cc: Division File
Chem. III Telecon Binder

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36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-415 APPLICANT: Impax Laboratories, Inc.

DRUG PRODUCT: Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg

Please submit a Telephone Amendment to address the following deficiencies. Please provide a fax copy of your response followed by a hard copy to the Agency. The fax number is 301-827-9274 [Attn. Aloka Srinivasan, Ph.D., Reviewing Chemist and Lisa Kwok, Pharm.D., Project Manager].

A. Deficiencies:

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

FROM: Cecelia M. Parise
Regulatory Policy Advisor to the Director
Office of Generic Drugs
Center for Drug Evaluation and Research

THROUGH: Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

SUBJECT: Pharmaceutical Equivalents

TO: ANDA 77-415, Impax Pharmaceuticals, Bupropion Extended-release Tablets

Impax' Bupropion Hydrochloride ER Tablets differ in formulation from the reference listed drug (RLD) Wellbutrin XL -- and also from at least one other ANDA product (Anchen ANDA 77-284) -- in that the Impax product does not have an enteric, delayed-release, coating layer. Due to the lack of the delayed-release coating, a question was raised regarding whether the Impax product was considered to be pharmaceutically equivalent to the RLD Wellbutrin XL. However, the labeling of the RLD does not describe the drug product as delayed-release and extended-release. Wellbutrin XL is defined in its labeling as extended-release tablets. On further input from the Division of Chemistry III and the Division of Bioequivalence, Impax' product was determined to be pharmaceutically equivalent. In addition, there is a USP monograph for Bupropion Extended-release Tablets and the Impax product meets the USP monograph (except for the dissolution, which is typically different for each extended-release mechanism and is usually resolved by amending the monograph after approval; Currently there are three dissolution methods listed in the USP monograph for Bupropion Extended-release Tablets).

Pharmaceutical equivalents are defined in the regulations at 21 CFR 320.1(c)

> (c) *Pharmaceutical equivalents* means drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled

> syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

Although the mechanism of release is different for the Impax Bupropion Extended-release Tablets, they are still the same dosage form -- extended-release tablets. The definition of pharmaceutical equivalents permits inactive ingredients to differ and says nothing about requiring identical mechanisms. The issue of the agency permitting products with different release mechanisms to be considered pharmaceutically equivalent was previously addressed in the response to Docket No. 93P-0421, dated August 12, 1997.

Dosage Forms

The term "dosage form" is not defined in the Federal Food, Drug, and Cosmetic Act (Act). However, in FDA's regulations the term dosage form is used in the definition of a "drug product," which is defined as "a finished dosage form, for example, tablet, capsule, or solution that contains a drug substance...." (21 CFR 314.3(b).) The Agency, at its discretion, has listed dosage forms in Appendix C of the Orange Book. These dosage forms are based on and are generally consistent with the forms used by the United States Pharmacopeia (USP) in its drug monographs. A dosage form is a convenient way of identifying the drug by its physical form, which is linked both to the physical appearance of the drug product and to the way it is administered. For instance, although an orally administered drug product may come in the form of a tablet, gum, or oral solution, the three appear differently and may have different absorption characteristics.

The Orange Book and the USP describe two types of modified release dosage forms: extended-release and delayed release. Consistent with the Orange Book and USP classifications, the Center for Drug Evaluation and Research explains the terms "modified release" dosage form and "extended-release" dosage form in a guidance document titled *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations*, March 2003. In this guidance, an extended-release dosage form is defined as:

> dosage forms that allow a reduction in dosing frequency as compared to when the drug is present in an immediate-release dosage form. These drug products can be developed to reduce fluctuations in plasma concentrations. Extended-release products can be capsules, tablets, granules, pellets, and suspensions.

The Impax product meets this definition because it has been determined to be bioequivalent to the reference listed drug. The regulations at 21 CFR 320.1(e) define bioequivalence.

> (e) Bioequivalence means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain extended-release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

Dosage form does not mean release mechanism

There is nothing in the legislative history to the Drug Price Competition and Patent Term Restoration Act of 1984 (1984 Amendments) to suggest that Congress intended the FDA to construe the term "dosage form" with particular regard to release mechanism. In fact, in the 1984 Amendments, Congress specifically did not require generic drug products to be identical in all respects to innovator products. For example, Congress did not require generic drug products to contain the same formulation with regard to inactive ingredients. (See 21 U.S.C. 355(j)(3)(H); H. Rep. No. 857 (Part I), 98th Cong., 2d Sess. at 21 (1984).) Moreover, when passing the 1984 Amendments, Congress continued FDA's prior system, which included several dosage form distinctions, none of which were based on release mechanism. Congress' choice not to address the ongoing FDA system of dosage forms suggests congressional approval of the FDA system. A review of the dosage form classifications currently used demonstrates that the Agency has consistently chosen not to base its dosage form descriptions on release mechanism. For example, there are at least three types of release mechanisms used in the dosage form "extended-release films" (e.g., "patches" used in drugs such as nitroglycerin). These extended-release films may vary in several ways, including the way they "house" the drug, the "reservoir" of drug, and the size of the patches, which vary from two inches wide to very small. Despite these differences in release technologies, the drugs are all the same dosage form. Similarly, sprays may vary in the type of propellants, stoppers, or actuators used, and yet FDA considers all sprays to be the same dosage form in spite of differences in release technologies.

In implementing the Act's provisions through regulations, the Agency found no scientific basis for distinguishing dosage forms on the basis of release mechanism. Indeed, in the preamble to the final rule implementing the 1984 Amendments, the Agency distinguished the term "dosage

form" from the term "controlled release mechanism." (See 57 FR 17950, 17969 (April 28, 1992).) In the regulation detailing reasons to refuse to approve an application, the Agency implicitly acknowledges that "release mechanism" is a part of the composition or formulation of the drug rather than the "dosage form" of the drug.' (21 CFR 314.127(a)(8)(ii).)

The Agency could refuse to approve an ANDA if it found that a difference in release mechanism caused the composition of the proposed drug product to be unsafe. (21 CFR 314.127(a)(8)(i)(B).) The regulations state that the Agency will refuse to approve an ANDA if information shows that the inactive ingredients or composition of the drug product are unsafe. (21 CFR 314,127(a)(8)(i) and (ii).) The regulations list several examples of proposed changes that may raise serious questions of safety for which the Agency could refuse to approve a product. (21CFR 314.127(a)(8)(ii)(A).) Among these changes are "the use of a delivery or modified release mechanism never before approved for the drug." (21 CFR 314.127(a)(ii)(A)(5).)

Summary

An ANDA applicant must show that its proposed drug's rate and extent of absorption do not show a significant difference from the rate and extent of absorption of the listed drug. (21 U.S.C. 355(j)(7)(C)(i); 21 CFR 320.1(e); 21 CFR 314.127(a)(6).) The FDA believes that its bioequivalence standards assure the therapeutic equivalence of any pharmaceutically equivalent extended-release product. If applicants are unable to demonstrate bioequivalence between their product and the RLD, the product is not approved. (21 U.S.C. 355(j)(3)(F); 21 CFR 314.127(a)(6).) Pharmaceutically equivalent drug products shown by appropriate data to be bioequivalent and which meet other criteria are therapeutically equivalent, regardless of their formulation, including inactive ingredients or release mechanism used for the extended-release functions of the tablet. (Orange Book at viii.) FDA's bioequivalence standards ensure that an approved generic with the same dosage form as the innovator is therapeutically equivalent to the innovator, even if the generic has a different release mechanism.

Therefore, the Agency may consider products with different mechanisms of release to be the same dosage form and to be pharmaceutically equivalent. Impax' bupropion extended-release product is the same dosage form as the RLD, Wellbutrin XL, and is considered to be pharmaceutically equivalent, bioequivalent and therefore therapeutically equivalent to the RLD. [1]

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[1] ***Therapeutic Equivalents.*** Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not

present a known or potential bioequivalence problem, and they meet an acceptable *in vitro* standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations. *The concept of therapeutic equivalence, as used to develop the list, applies only to drug products containing the same active ingredient(s) and does not encompass a comparison of different therapeutic agents used for the same condition (e.g., ibuprofen vs. naproxen for the treatment of pain).* Any drug product in the list repackaged and/or distributed by other than the application holder is considered to be therapeutically equivalent to the application holder's drug product even if the application holder's drug product is single source or coded as non-equivalent (e.g., **BN**). Also, distributors or repackagers of an application holder's drug product are considered to have the same code as the application holder. Therapeutic equivalence determinations are not made for unapproved, off-label indications.

FDA considers drug products to be therapeutically equivalent if they meet the criteria outlined above, even though they may differ in certain other characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time and minor aspects of labeling (e.g., the presence of specific pharmacokinetic information) and storage conditions. When such differences are important in the care of a particular patient, it may be appropriate for the prescribing physician to require that a particular brand be dispensed as a medical necessity. With this limitation, however, FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.

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/s/

Patricia L. Downs
11/20/2006 09:06:37 AM
SECRETARY

Cecelia Parise
11/20/2006 09:18:50 AM
CSO

Gary Buehler
11/21/2006 08:14:57 AM
DIRECTOR

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20855

To: ANDA 77284
ANDA 77415
ANDA 77715

From: Barbara M. Davit, Ph.D., J.D., Deputy Director, Division of Bioequivalence, Office of Generic Drugs

Re: Recommendations for in vivo bioequivalence studies of chlorpromazine tablets

Date: December 13, 2006

This memorandum provides clarification on the issue of metabolites discussed in the Agency response to Biovail's December 20, 2005 citizen petition (Docket # 2005P-0498).

Based on its experience and expertise, the Agency developed the guidance titled *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (BA/BE guidance). The BA/BE guidance provides recommendations on bioavailability and bioequivalence (including the Agency's current thinking on when it may be appropriate to measure metabolites).

The sponsor for Wellbutrin XL measured the parent drug bupropion as well as the three metabolites hydroxybupropion, threohydrobupropion, and erythrohydrobupropion. Sponsors submitting new drug applications (NDA) generally conduct studies to demonstrate the safety and effectiveness of the drug and, in the process, often collect as much information as they can to characterize the drug product. This may include information on all detectable metabolites. In this setting, the purpose of an in vivo bioavailability or bioequivalence study is to determine whether certain conditions consistent with a controlled-release dosage form are met. (BA/BE guidance, at p. 15-16; see also 21 CFR 320.25(f)(2)).

Sponsors submitting abbreviated new drug applications (ANDA), on the other hand, generally conduct studies for a different purpose than do NDA applicants. That is, an ANDA applicant is expected to submit information on (among other things) bioequivalence to demonstrate that its product delivers the active ingredient or moiety at the same rate and extent as the NDA sponsor's reference listed drug.

The Agency applied the current recommendations in the BA/BE guidance to ANDA applicants for generic bupropion HCl extended-release tablets in considering which metabolites should be measured for the purposes of generic drug bioequivalence.[1]

---

[1] We note that before the Agency developed and posted the BA/BE guidance, the Agency expected ANDA applicants for bupropion HCl tablets to measure the parent drug bupropion as well as the three metabolites hydroxybupropion, threohydrobupropion, and erythrohydrobupropion. After re-evaluating the metabolite issue in

Accordingly, we currently expect ANDA applicants for generic bupropion HCl extended-release tablets to measure the parent drug bupropion and the metabolite hydroxybupropion. We do not expect ANDA applicants to measure the other two metabolites (i.e., threohydrobupropion and erythrohydrobupropion). As explained in the Agency's response to the above-referenced citizen petition, our expectation is based, in part, on the relative potencies and exposure of the parent drug and metabolites. In addition, there is currently insufficient scientific evidence upon which we can reasonably determine whether threohydrobupropion and erythrohydrobupropion are formed as a result of gut wall or other presystemic metabolism. We expect that measurement of bupropion, together with the metabolite hydroxybupropion, would be a scientifically reasonable and reliable indicator of the drug's activity for purposes of demonstrating that generic bupropion HCl extended-release tablets are bioequivalent to Wellbutrin XL.

The Office of Generic Drugs consulted with the Division of Neurology Products and the Division of Pharmacology I on the application of the BA/BE guidance with respect to the issue of metabolites. All three components of the Agency concurred that measurement of bupropion, together with the metabolite hydroxybupropion, would be a reliable and reasonable indicator of the drug's activity for the purposes of demonstrating generic drug bioequivalence.

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light of the current recommendations in the BA/BE guidance, the Agency concluded it was not necessary for ANDA applicants to measure all three metabolites as discussed above.

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/s/

Barbara Davit
12/13/2006 07:42:30 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20855

To: ANDA 77284
ANDA 77415
ANDA 77715

From: Barbara M. Davit, Ph.D., J.D., Deputy Director, Division of Bioequivalence, Office of Generic Drugs

Re: Metabolite measurement in bioequivalence studies of bupropion hydrochloride extended-release tablets submitted to ANDAs

Date: December 14, 2006

Please note that this memo was originally submitted to DFS on December 13, 2006. This memo corrects an error in the title of the December 13th memo, but is otherwise identical.

This memorandum provides clarification on the issue of metabolites discussed in the Agency response to Biovail's December 20, 2005 citizen petition (Docket # 2005P-0498).

Based on its experience and expertise, the Agency developed the guidance titled *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (BA/BE guidance). The BA/BE guidance provides recommendations on bioavailability and bioequivalence (including the Agency's current thinking on when it may be appropriate to measure metabolites).

The sponsor for Wellbutrin XL measured the parent drug bupropion as well as the three metabolites hydroxybupropion, threohydrobupropion, and erythrohydrobupropion. Sponsors submitting new drug applications (NDA) generally conduct studies to demonstrate the safety and effectiveness of the drug and, in the process, often collect as much information as they can to characterize the drug product. This may include information on all detectable metabolites. In this setting, the purpose of an in vivo bioavailability or bioequivalence study is to determine whether certain conditions consistent with a controlled-release dosage form are met. (BA/BE guidance, at p. 15-16; see also 21 CFR 320.25(f)(2)).

Sponsors submitting abbreviated new drug applications (ANDA), on the other hand, generally conduct studies for a different purpose than do NDA applicants. That is, an ANDA applicant is expected to submit information on (among other things) bioequivalence to demonstrate that its product delivers the active ingredient or moiety at the same rate and extent as the NDA sponsor's reference listed drug.

The Agency applied the current recommendations in the BA/BE guidance to ANDA applicants for generic bupropion HCl extended-release tablets in considering which metabolites should be measured for the purposes of generic drug bioequivalence.[1]
Accordingly, we currently expect ANDA applicants for generic bupropion HCl extended-release tablets to measure the parent drug bupropion and the metabolite hydroxybupropion. We do not expect ANDA applicants to measure the other two metabolites (i.e., threohydrobupropion and erythrohydrobupropion). As explained in the Agency's response to the above-referenced citizen petition, our expectation is based, in part, on the relative potencies and exposure of the parent drug and metabolites. In addition, there is currently insufficient scientific evidence upon which we can reasonably determine whether threohydrobupropion and erythrohydrobupropion are formed as a result of gut wall or other presystemic metabolism. We expect that measurement of bupropion, together with the metabolite hydroxybupropion, would be a scientifically reasonable and reliable indicator of the drug's activity for purposes of demonstrating that generic bupropion HCl extended-release tablets are bioequivalent to Wellbutrin XL.

The Office of Generic Drugs consulted with the Division of Neurology Products and the Division of Pharmacology I on the application of the BA/BE guidance with respect to the issue of metabolites. All three components of the Agency concurred that measurement of bupropion, together with the metabolite hydroxybupropion, would be a reliable and reasonable indicator of the drug's activity for the purposes of demonstrating generic drug bioequivalence.

[1] We note that before the Agency developed and posted the BA/BE guidance, the Agency expected ANDA applicants for bupropion HCl tablets to measure the parent drug bupropion as well as the three metabolites hydroxybupropion, threohydrobupropion, and erythrohydrobupropion. After re-evaluating the metabolite issue in light of the current recommendations in the BA/BE guidance, the Agency concluded it was not necessary for ANDA applicants to measure all three metabolites as discussed above.

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/s/

Barbara Davit
12/14/2006 11:54:51 AM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20855

To: ANDA 77284
ANDA 77415
ANDA 77715

From: Barbara M. Davit, Ph.D., J.D., Deputy Director, Division of Bioequivalence, Office of Generic Drugs

Re: Acceptability of in vitro dissolution testing on 300-mg strength of Bupropion Hydrochloride Extended-Release Tablets

Date: December 14, 2006

Upon a final look at the ANDA reviews for bupropion hydrochloride extended-release tablets, we determined that the ANDA applicants' approach to demonstrating bioequivalence for the 300 mg had not been characterized accurately. The reviews indicate that a waiver was granted for the 300 mg strength and 21 CFR 320.22(d) is cited as the regulatory basis for the waiver. The term waiver and 21 CFR 320.22(d) should not have been used to characterize the applicants' approach to demonstrating bioequivalence for the 300 mg strength.

Wellbutrin XL (150 mg) is the reference listed drug. As stated in the response to the Agency's citizen petition, ANDA applicants conducted both fed and fasted in vivo bioequivalence studies (Docket No. 2005P-0498). ANDA applicants used the 150 mg strength in these in vivo studies to demonstrate bioequivalence.

Bioequivalence studies are generally conducted using the highest strength of the drug product. Given the dose-related risk of seizures associated with bupropion, however, we had determined that it was appropriate to conduct the in vivo bioequivalence studies using the 150 mg strength. Bioequivalence studies for the 300 mg dose of the extended-release tablet were conducted in vitro. In other words, we concluded that in vivo bioequivalence studies, which are conducted using healthy volunteers rather than patients, should not be done using the 300 mg strength. Dena Hixon, M.D., OGD's Associate Director for Medical Affairs, previously concurred with this approach for the sustained-release formulation. Based on the labeling for the Wellbutrin products, 300 mg Wellbutrin gives the same daily systemic bupropion exposure regardless of whether the drug product is IR, SR, or XL. One can infer that the 300-mg dose will provide the same toxicity. Therefore, the reasoning regarding bioequivalence studies for the sustained-release product is applicable to the 300 mg dose of the XL tablet.

Therefore, the Agency deemed it appropriate for ANDA applicants to demonstrate bioequivalence for the 300 mg strength by submitting data showing that their 150 and 300 mg strength formulations were proportionally similar in their active and inactive ingredients and establishing acceptable in vitro dissolution profiles. This approach is consistent with 21 CFR 320.24(b)(6).

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/s/

Barbara Davit
12/14/2006 12:00:31 PM
BIOPHARMACEUTICS

IMPAX LABORATORIES, INC.

30831 Huntwood Avenue, Hayward, CA 94544
(510) 476-2000 Fax (510) 471-3200

December 14, 2006

MINOR AMENDMENT
REQUEST FOR IMMEDIATE FINAL APPROVAL

MC

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re ANDA 77-415
Bupropion HCl Extended Release Tablets, 300 mg (XL)

Attn: Robert West (Deputy Director, OGD)
Lisa Kwok (Project Manager, OGD)

Dear Mr. Buehler:

We submit herewith a request for immediate final approval of ANDA 77-415.

This request is made in conjunction with a selective waiver of 180-day exclusivity from the holder of ANDA 77-284, Anchen Pharmaceuticals, Inc., to IMPAX Laboratories Inc. A copy of this selective waiver request is provided herein for your review.

Please note that it is our belief that all of the Agency's questions and comments regarding ANDA 77-415 have been adequately addressed during the course of its review. Therefore, immediate final approval may be granted in light of Anchen's selective waiver request.

Should you have any questions or comments, please contact me by telephone (510-476-2018) or telefax (510-476-2091).

Sincerely,
IMPAX Laboratories, Inc.

Mark C. Shaw
Vice President, Regulatory Affairs and Compliance