CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 077284

Name: Bupropion HCl Extended-release (XL) Tablets, USP 150 mg and 300 mg

Sponsor: Anchen Pharmaceuticals, Inc.

Approval Date: December 14, 2006

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077284

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077284

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-284

Anchen Pharmaceuticals, Inc
Attention: Margaret L. Choy
Vice President, Regulatory Affairs
5 Goodyear
Irvine, CA 92618

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated September 21, 2004, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (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 May 16, 2005; June 23, July 7, August 9, 17, 18, 21 and 28, September 18, and October 2, 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. Accordingly the ANDA is approved. The Division of Bioequivalence has determined your Bupropion Hydrochloride Extended-release Tablets USP, (XL) 150 mg and 300 mg (Once Daily Dosing) to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Wellbutrin XL Extended-release of SmithKline Beecham Corp.

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

Dissolution Testing should be conducted in

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:

2 hours: ≤ (b) (4) %
4 hours: (b) (4) %
8 hours: %
16 hours: NLT (b) (4) %

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement - Changes Being Effected when there are no revisions to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The 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 entitled 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 Anchen Pharmaceuticals, Inc. (Anchen) for infringement of one or more of the patents that were the subjects of paragraph IV certifications. You notified the agency that Anchen complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation for infringement of the '341 and '327 patents was brought against Anchen in the United States District Court for the Central District of California, Western Division [Biovail Laboratories, Inc., and SmithKline Beecham Corp. v. Anchen Pharmaceuticals, Inc., Civil Action No. CV-SACV04-1468]. You also notified the agency that the court dismissed the case with respect to the '327 patent, and decided that the '341 patent was not infringed. Therefore, under section 505(j)(5)(B)(iii) of the Act, your ANDA is eligible for approval.

With respect to 180-day generic drug exclusivity, we note that Anchen was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification to the '341 and '327 patents. Therefore, with this approval, Anchen is eligible for 180-days of generic drug exclusivity for Bupropion Hydrochloride Extended-release Tablets USP, (XL). This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, will begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA informing the agency of the date the exclusivity begins to run.

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

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.

Sincerely yours,

{See appended electronic signature page}

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

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

/s/

Robert L. West
12/14/2006 02:08:08 PM
for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077284

TENTATIVE APPROVAL LETTER

ANDA 77-284

NOV 14 2005

Anchen Pharmaceuticals, Inc.
Attention: Margaret L. Choy
Vice President, Regulatory Affairs
5 Goodyear
Irvine, CA 92618

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated September 21, 2004, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (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 April 7, August 18, September 8, October 11, November 7, and November 9, 2005.

We have completed the review of this ANDA, and based upon the information you have presented to date we 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 ANDA at this time because of the patent issue discussed below. Therefore, the ANDA is **tentatively approved.** This determination is based upon information available to the agency at this time (i.e., information in your application and the status of current good manufacturing practices 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. In addition, this letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The reference listed drug (RLD) upon which you have based your ANDA, Wellbutrin XL® Extended-release Tablets, 150 mg and 300 mg, of SmithKline Beecham Corp., is subject to periods of patent protection. As noted in the agency's publication entitled 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 Anchen Pharmaceuticals, Inc. (Anchen) for infringement of one or more of the patents that were the subjects of paragraph IV certifications. This action must be brought against Anchen 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 Anchen complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation for infringement of the '341 and '327 patents was brought against Anchen in the United States District Court for the Central District of California, Western Division [Biovail Laboratories, Inc., and SmithKline Beecham Corp. v. Anchen Pharmaceuticals, Inc., Civil Action No. CV-SACV04-1468].

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) or such shorter or longer period as the court may have ordered, or,

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

   c. the '341 and '327 patents have expired, and

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

[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.

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 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 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 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 and 21 U.S.C. 331(d). Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under 21 U.S.C. 355, and will not be listed in the "Orange Book".

For further information on the status of this ANDA, or prior to submitting additional amendments, please contact Thomas Hinchliffe, Project Manager, at 301-827-5849.

Sincerely yours,

Gary Buehler 11/14/01
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 77-284
Division File
Field Copy
HFD-610/R. West
HFD-205
HFD-610/Orange Book Staff
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Endorsements:
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HFD-640/S.Rosencrance/ 10/28/05
HFD-617/T.Hinchliffe/ 10/28/05
HFD-613/M.Shin/ 10/27/05 per attached email
HFD-613/L.Golson/ 11/9/05

11/14/2005

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F/T by

TENTATIVE APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077284

LABELING

150868-9 FRONT 12.25" x 30" FOLD: 1.25" x 2.5" PRINTS BLACK 08/17/06

Bupropion Hydrochloride Extended-Release Tablets USP (XL)

Bupropion Hydrochloride Extended-Release Tablets USP (XL)

001-01

001-01

PRESCRIBING INFORMATION

Bupropion hydrochloride extended-release tablets USP (XL)

"Medication Guide" 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 (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. Bupropion hydrochloride extended-release tablets (XL) are not approved for the use in pediatric patients. (See WARNINGS and PRECAUTIONS: Pediatric Use).

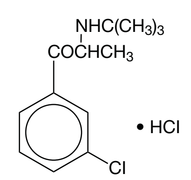
Pooled analyses of short term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) 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 (XL), an antidepressant of the aminoketone class, are chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines.

It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is $C_{13}H_{18}ClNO \cdot HCl$. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa.

The structural formula is:



Bupropion hydrochloride extended-release tablets (XL) are supplied for oral administration as 150-mg and 300-mg, round white to off-white extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: ethyl alcohol, ethylcellulose, hydrochloric acid, hydroxypropylcellulose, methacrylic acid copolymer, povidone, silicon dioxide and hydrogenated vegetable oil. The tablets are printed with edible black ink. The insoluble shell of the extended-release tablet may remain intact during gastrointestinal transit and is eliminated in the feces. USP drug release testing 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 (XL) 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 (XL) 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 (XL) 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 (XL). Following administration of bupropion hydrochloride extended-release tablets (XL), 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 1½-fold for hydroxybupropion and about 2½-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 end-stage 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 end-stage 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-blinded 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 (XL), studies have demonstrated similar bioavailability of bupropion hydrochloride extended-release tablets (XL) to both the immediate-release formulation and to the sustained-release formulations of bupropion under steady-state conditions, i.e., bupropion hydrochloride extended-release tablets (XL) 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 both peak plasma concentration and extent of absorption, for parent drug and metabolites.

INDICATIONS AND USAGE

Major Depressive Disorder: Bupropion hydrochloride extended-release tablets (XL) 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 PHARMACOLOGY).

A major depressive episode (DSM-IV) implies the presence of 1) depressed mood or 2) loss of interest or pleasure; in addition, at least 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 (XL) for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

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

Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients treated with ZYBAN® or bupropion hydrochloride sustained-release tablets, WELLBUTRIN® or bupropion hydrochloride immediate-release formulation, WELLBUTRIN SR® or bupropion hydrochloride sustained-release formulation, or any other medications that contain bupropion because the incidence of seizure is dose dependent.

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

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

The concurrent administration of bupropion hydrochloride extended-release tablets (XL) 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 (XL).

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

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 (XL) 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 (XL) are not approved for use in treating bipolar depression.

Patients should be made aware that bupropion hydrochloride extended-release tablets (XL) contain the same active ingredient found in ZYBAN or bupropion hydrochloride sustained-release tablets 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 bupropion hydrochloride sustained-release tablets, or any other medications that contain bupropion, such as WELLBUTRIN SR or bupropion hydrochloride sustained-release formulation; and WELLBUTRIN or bupropion hydrochloride 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 (XL). Bupropion hydrochloride extended-release tablets (XL) should be discontinued and not restarted in patients who experience a seizure while on treatment.

As bupropion hydrochloride extended-release tablets (XL) 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 (XL), 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, 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 (XL). 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., antipsychotics, antidepressants, theophylline, systemic steroids) are known to lower seizure threshold.**

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

- **the total daily dose of bupropion hydrochloride extended-release tablets (XL) does *not* exceed 450 mg,**
- **the rate of incrementation of dose is gradual.**

Bupropion hydrochloride extended-release tablets (XL) 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 (XL) 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 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

Adverse Event Team	Sustained-release formulation of bupropion 300 mg/day (n=376)	Sustained-release formulation of bupropion 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 tablet (XL) is expected to pose similar risks.

Altered Appetite and Weight: In placebo-controlled studies of major depressive disorder using 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

Weight Change	Sustained-release formulation of bupropion 300 mg/day (n=339)	Sustained-release formulation of bupropion 400 mg/day (n=112)	Placebo (n=347)
Gained >5lbs	3%	2%	4%
Lost >5lbs	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 (XL) 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 post-marketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. A patient should stop taking bupropion hydrochloride extended-release tablets (XL) and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

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

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

Data from a comparative study of the sustained-release formulation of bupropion, 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 a 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 a sustained-release formulation of bupropion 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 (XL) 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 (XL) 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 (XL) 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 end-stage 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 end-stage 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 (XL) 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 (XL) and should counsel them in its appropriate use. A Medication Guide About Using Antidepressants in Children and Teenagers is available for bupropion hydrochloride extended-release tablets (XL). The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guides is reprinted at the end of this document.

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

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 (XL) contains the same active ingredient found in ZYBAN or a sustained-release formulation of bupropion, 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 a sustained-release formulation of bupropion, or any other medications that contain bupropion hydrochloride (such as other sustained-release formulation of bupropion, and immediate-release formulation of bupropion).

Patients should be told that bupropion hydrochloride extended-release tablets (XL) 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 (XL) 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 (XL) 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 (XL). 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 (XL) 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 (XL) whole so that the release rate is not altered. Do not chew, divide, or crush tablets.

Patients should be advised that they may notice in their stool something that looks like a tablet. This is normal. The medication in bupropion hydrochloride extended-release tablets (XL) is contained in a non-absorbable shell that has been specially designed to slowly release drug in the body. When this process is completed, the empty shell is eliminated from the body.

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 (XL) 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 (XL) 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 (XL) 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 (XL) 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 congenial 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 (XL) 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 (XL) 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 (XL), 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 (XL) 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 (XL) 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 the sustained-release formulation of bupropion.

Adverse Events Leading to Discontinuation of Treatment With the Immediate-Release or Sustained-Release Formulations of Bupropion: 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 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

Adverse Event Team	Sustained-release formulation of bupropion 300 mg/day (n=376)	Sustained-release formulation of bupropion 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 the Immediate-Release or Sustained-Release Formulations of Bupropion: 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.

PHARMACIST—DETACH HERE
AND GIVE MEDICATION GUIDE TO PATIENT.

Medication Guide

Bupropion hydrochloride extended-release tablets USP (XL)

Read this Medication Guide carefully before you start using bupropion hydrochloride extended-release tablets (XL) and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about bupropion hydrochloride extended-release tablets (XL), ask your doctor or pharmacist.

IMPORTANT: Be sure to read the section of this Medication Guide beginning with "What is the most important information I should know about bupropion hydrochloride extended-release tablets (XL)?" It contains important information about this medication. It immediately follows the next section called "About Using Antidepressants in Children and Teenagers."

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.

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 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 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 of 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.

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

There is a chance of having a seizure (convulsion, fit) with bupropion hydrochloride extended-release tablets (XL), 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 (XL). For more information, see the sections "Who should not take bupropion hydrochloride extended-release tablets (XL)?" and "What should I tell my doctor before using bupropion hydrochloride extended-release tablets (XL)?" 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 (XL) unless your doctor has said it is okay to take them**.

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

For additional information see section above entitled "About Using Antidepressants in Children and Teenagers." bupropion hydrochloride extended-release tablet (XL) has not been studied in children under the age of 18 and is not approved for use in children and teenagers.

What are bupropion hydrochloride extended-release tablets (XL)?

Bupropion hydrochloride extended-release tablets (XL) are 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 (XL)?

Do not take bupropion hydrochloride extended-release tablets (XL) 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 or bupropion hydrochloride sustained-release tablets.** Bupropion is the same active ingredient that is in bupropion hydrochloride extended-release tablets (XL).
- 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 (XL), 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 (XL).

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

- **Tell your doctor about your medical conditions.** Tell your doctor if you
  - **are pregnant or plan to become pregnant.** It is not known if bupropion hydrochloride extended-release tablets (XL) can harm your unborn baby.
  - **are breastfeeding.** Bupropion hydrochloride extended-release tablets (XL) passes through your milk. It is not known if bupropion hydrochloride extended-release tablets (XL) 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 (XL).

Bupropion hydrochloride extended-release tablets (XL) have not been studied in children under the age of 18 years.

How should I take bupropion hydrochloride extended-release tablets (XL)?

- Take bupropion hydrochloride extended-release tablets (XL) exactly as prescribed by your doctor.
- **Do not chew, cut, or crush bupropion hydrochloride extended-release tablets (XL).** You must swallow the tablets whole. **Tell your doctor if you cannot swallow medicine tablets.**
- Take bupropion hydrochloride extended-release tablets (XL) at the same time each day.
- Take your doses of bupropion hydrochloride extended-release tablets (XL) at least 24 hours apart.
- You may take bupropion hydrochloride extended-release tablets (XL) 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 (XL) can increase your chance of having a seizure.
- If you take too much bupropion hydrochloride extended-release tablets (XL), or overdose, call your local emergency room or poison control center right away.
- The bupropion hydrochloride extended-release tablet (XL) is covered by a shell that slowly releases the medicine inside your body. You may notice something in your stool that looks like a tablet. This is normal. This is the empty shell passing from your body.
- **Do not take any other medicines while using bupropion hydrochloride extended-release tablets (XL) unless your doctor has told you it is okay.**
- If you are taking bupropion hydrochloride extended-release tablets (XL) for the treatment of major depressive disorder, it may take several weeks for you to feel that bupropion hydrochloride extended-release tablets (XL) is working. Once you feel better, it is important to keep taking bupropion hydrochloride extended-release tablets (XL) exactly as directed by your doctor. Call your doctor if you do not feel bupropion hydrochloride extended-release tablets (XL) is working for you.
- Do not change your dose or stop taking bupropion hydrochloride extended-release tablets (XL) without talking with your doctor first.

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

- Do not drink a lot of alcohol while taking bupropion hydrochloride extended-release tablets (XL).

  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 (XL) affects you. Bupropion hydrochloride extended-release tablets (XL) can impair your ability to perform these tasks.

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

- **Seizures.** Some patients get seizures while taking bupropion hydrochloride extended-release tablets (XL). **If you have a seizure while taking bupropion hydrochloride extended-release tablets (XL), stop taking the tablets and call your doctor right away.** Do not take bupropion hydrochloride extended-release tablets (XL) 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 (XL). 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 (XL) 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 (XL), 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 (XL). For a complete list, ask your doctor or pharmacist.

How should I store bupropion hydrochloride extended-release tablets (XL)?

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

General Information about bupropion hydrochloride extended-release tablets (XL).

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use bupropion hydrochloride extended-release tablets (XL) for a condition for which it was not prescribed. Do not give bupropion hydrochloride extended-release tablets (XL) to other people, even if they have the same symptoms you have. It may harm them. Keep bupropion hydrochloride extended-release tablets (XL) out of the reach of children.

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

What are the ingredients in bupropion hydrochloride extended-release tablets (XL)?

Active ingredient: bupropion hydrochloride.

Inactive ingredients: dehydrated alcohol, ethylcellulose, hydrochloric acid, hydroxypropylcellulose, methacrylic acid copolymer, povidone, silicon dioxide, hydrogenated vegetable oil and ethyl alcohol. The tablets are printed with edible black ink.

*The following are registered trademarks of their respective manufacturers: PROZAC®/Eli Lilly and Company; ZOLOFT®/Pfizer Pharmaceuticals; LUVOX®/Solvay Pharmaceuticals, Inc/ANAFRANIL®/Mallinckrodt Inc.; NARDIL®/Warner Lambert Company; MARPLAN®/Oxford Pharmaceutical Services, Inc.; PARNATE/ GlaxoSmithKline.

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

Rx only

Manufactured by:
Anchen Pharmaceuticals, Inc.
Irvine, CA 92618

08/06

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

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

* Adverse events that occurred in at least 1% of patients treated with either 300 or 400 mg/day of 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 the sustained-release formulation of bupropion 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 the Sustained-Release Formulation: Anorexia, dry mouth, rash, sweating, tinnitus, and tremor.

400 mg/day of the Sustained-Release Formulation: 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 non-depressed 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 (XL) 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 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, hemoperfusion, or exchange transfusion in the management of bupropion overdoses. No specific antidotes for bupropion are known.

Due to the dose-related risk of seizures with bupropion hydrochloride extended-release tablets (XL), 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 (XL) 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 (XL) should be swallowed whole and not crushed, divided, or chewed. Bupropion hydrochloride extended-release tablets (XL) may be taken without regard to meals.

Major Depressive Disorder: Initial Treatment: The usual adult target dose for bupropion hydrochloride extended-release tablets (XL) is 300 mg/day, given once daily in the morning. Dosing with bupropion hydrochloride extended-release tablets (XL) 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 (XL) 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 (XL) 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 Hydrochloride Sustained-Release Tablets: When switching patients from bupropion hydrochloride tablets to bupropion hydrochloride extended-release tablets (XL) or from bupropion hydrochloride sustained-release tablets to bupropion hydrochloride extended-release tablets (XL), 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 (XL) 300 mg once daily. Patients who are currently being treated with bupropion hydrochloride sustained-release tablets at 300 mg/day (for example, 150 mg twice daily) may be switched to bupropion hydrochloride extended-release tablets (XL) 300 mg once daily.

Dosage Adjustment for Patients With Impaired Hepatic Function: Bupropion hydrochloride extended-release tablets (XL) 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 (XL) 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 (XL) 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 USP (XL) 150 mg, are white to off-white, round, tablets printed with "A101". They are supplied as follow:

Bottles of 30 NDC # 10370-101-03
Bottles of 60 NDC # 10370-101-06
Bottles of 90 NDC # 10370-101-09

Bupropion hydrochloride extended-release tablets USP (XL) 300 mg, are white to off-white, round, tablets printed with "A102". They are supplied as follow:

Bottles of 30 NDC # 10370-102-03
Bottles of 60 NDC # 10370-102-06
Bottles of 90 NDC # 10370-102-09

Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature]

*The following are registered trademarks of their respective manufacturers: ZYBAN®, WELLBUTRIN®, and WELLBUTRIN SR®/GlaxoSmithKline.

Medication Guide

Bupropion hydrochloride extended-release tablets USP (XL)

Read this Medication Guide carefully before you start using bupropion hydrochloride extended-release tablets (XL) and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about bupropion hydrochloride extended-release tablets (XL), ask your doctor or pharmacist.

IMPORTANT: Be sure to read the section of this Medication Guide beginning with "What is the most important information I should know about bupropion hydrochloride extended-release tablets (XL)?" It contains important information about this medication. It immediately follows the next section called "About Using Antidepressants in Children and Teenagers."

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.

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 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 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 of 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.

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

There is a chance of having a seizure (convulsion, fit) with bupropion hydrochloride extended-release tablets (XL), 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 (XL). For more information, see the sections "Who should not take bupropion hydrochloride extended-release tablets (XL)?" and "What should I tell my doctor before using bupropion hydrochloride extended-release tablets (XL)?" 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 (XL) unless your doctor has said it is okay to take them**.

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

For additional information see section above entitled "About Using Antidepressants in Children and Teenagers." bupropion hydrochloride extended-release tablet (XL) has not been studied in children under the age of 18 and is not approved for use in children and teenagers.

What are bupropion hydrochloride extended-release tablets (XL)?

Bupropion hydrochloride extended-release tablets (XL) are 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 (XL)?

Do not take bupropion hydrochloride extended-release tablets (XL) 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 or bupropion hydrochloride sustained-release tablets.** Bupropion is the same active ingredient that is in bupropion hydrochloride extended-release tablets (XL).
- 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 (XL), 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 (XL).

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

- **Tell your doctor about your medical conditions.** Tell your doctor if you
  - **are pregnant or plan to become pregnant.** It is not known if bupropion hydrochloride extended-release tablets (XL) can harm your unborn baby.
  - **are breastfeeding.** Bupropion hydrochloride extended-release tablets (XL) passes through your milk. It is not known if bupropion hydrochloride extended-release tablets (XL) 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 (XL).

Bupropion hydrochloride extended-release tablets (XL) have not been studied in children under the age of 18 years.

How should I take bupropion hydrochloride extended-release tablets (XL)?

- Take bupropion hydrochloride extended-release tablets (XL) exactly as prescribed by your doctor.
- **Do not chew, cut, or crush bupropion hydrochloride extended-release tablets (XL).** You must swallow the tablets whole. **Tell your doctor if you cannot swallow medicine tablets.**
- Take bupropion hydrochloride extended-release tablets (XL) at the same time each day.
- Take your doses of bupropion hydrochloride extended-release tablets (XL) at least 24 hours apart.
- You may take bupropion hydrochloride extended-release tablets (XL) 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 (XL) can increase your chance of having a seizure.
- If you take too much bupropion hydrochloride extended-release tablets (XL), or overdose, call your local emergency room or poison control center right away.
- The bupropion hydrochloride extended-release tablet (XL) is covered by a shell that slowly releases the medicine inside your body. You may notice something in your stool that looks like a tablet. This is normal. This is the empty shell passing from your body.
- **Do not take any other medicines while using bupropion hydrochloride extended-release tablets (XL) unless your doctor has told you it is okay.**
- If you are taking bupropion hydrochloride extended-release tablets (XL) for the treatment of major depressive disorder, it may take several weeks for you to feel that bupropion hydrochloride extended-release tablets (XL) is working. Once you feel better, it is important to keep taking bupropion hydrochloride extended-release tablets (XL) exactly as directed by your doctor. Call your doctor if you do not feel bupropion hydrochloride extended-release tablets (XL) is working for you.
- Do not change your dose or stop taking bupropion hydrochloride extended-release tablets (XL) without talking with your doctor first.

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

- Do not drink a lot of alcohol while taking bupropion hydrochloride extended-release tablets (XL).

  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 (XL) affects you. Bupropion hydrochloride extended-release tablets (XL) can impair your ability to perform these tasks.

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

- **Seizures.** Some patients get seizures while taking bupropion hydrochloride extended-release tablets (XL). **If you have a seizure while taking bupropion hydrochloride extended-release tablets (XL), stop taking the tablets and call your doctor right away.** Do not take bupropion hydrochloride extended-release tablets (XL) 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 (XL). 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 (XL) 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 (XL), 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 (XL). For a complete list, ask your doctor or pharmacist.

How should I store bupropion hydrochloride extended-release tablets (XL)?

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

General Information about bupropion hydrochloride extended-release tablets (XL).

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use bupropion hydrochloride extended-release tablets (XL) for a condition for which it was not prescribed. Do not give bupropion hydrochloride extended-release tablets (XL) to other people, even if they have the same symptoms you have. It may harm them. Keep bupropion hydrochloride extended-release tablets (XL) out of the reach of children.

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

What are the ingredients in bupropion hydrochloride extended-release tablets (XL)?

Active ingredient: bupropion hydrochloride.

Inactive ingredients: dehydrated alcohol, ethylcellulose, hydrochloric acid, hydroxypropylcellulose, methacrylic acid copolymer, povidone, silicon dioxide, hydrogenated vegetable oil and ethyl alcohol. The tablets are printed with edible black ink.

*The following are registered trademarks of their respective manufacturers: PROZAC®/Eli Lilly and Company; ZOLOFT®/Pfizer Pharmaceuticals; LUVOX®/Solvay Pharmaceuticals, Inc/ANAFRANIL®/Mallinckrodt Inc.; NARDIL®/Warner Lambert Company; MARPLAN®/Oxford Pharmaceutical Services, Inc.; PARNATE/ GlaxoSmithKline.

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

Rx only

Manufactured by:
Anchen Pharmaceuticals, Inc.
Irvine, CA 92618

08/06

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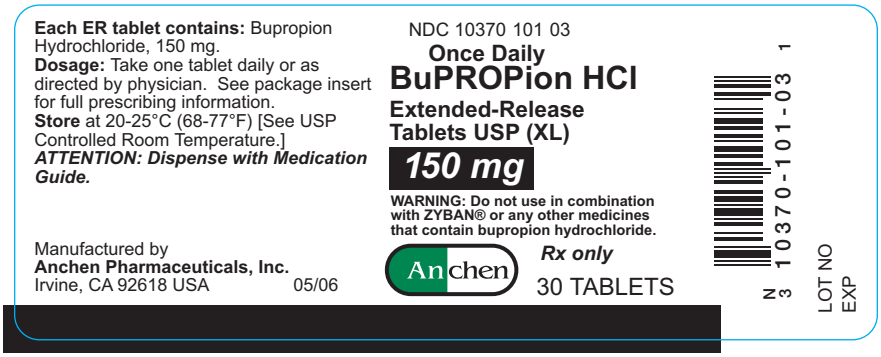
proof approval form

proof date: 5/26/06

(b) (4)



Each ER tablet contains: Bupropion Hydrochloride, 150 mg.
Dosage: Take one tablet daily or as directed by physician. See package insert for full prescribing information.
Store at 20-25°C (68-77°F) [See USP Controlled Room Temperature.]
ATTENTION: Dispense with Medication Guide.

Manufactured by
Anchen Pharmaceuticals, Inc.
Irvine, CA 92618 USA 05/06

NDC 10370 101 03
Once Daily
BuPROPion HCl
Extended-Release Tablets USP (XL)
150 mg
WARNING: Do not use in combination with ZYBAN® or any other medicines that contain bupropion hydrochloride.
Anchen
Rx only
30 TABLETS

N 10370-101-03 1
LOT NO
EXP

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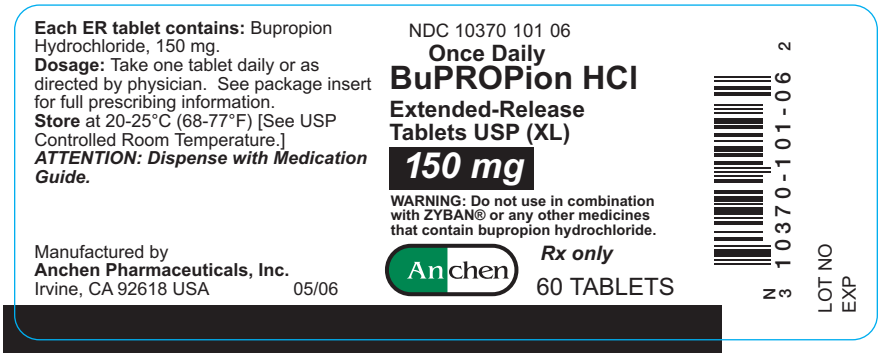

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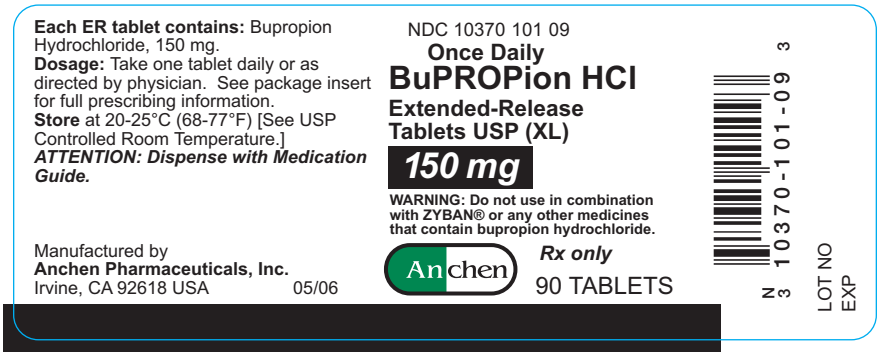

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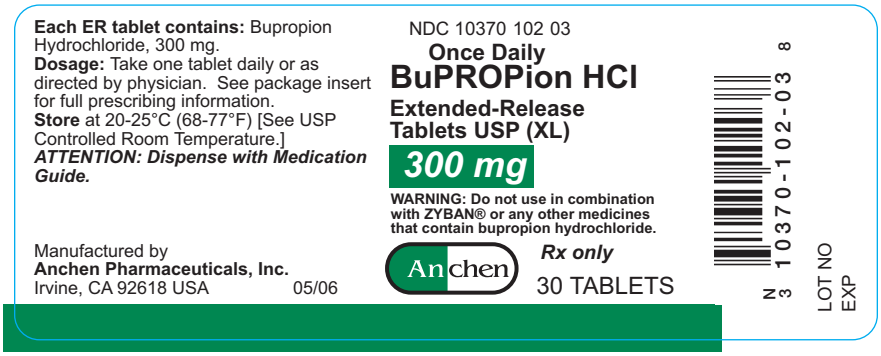

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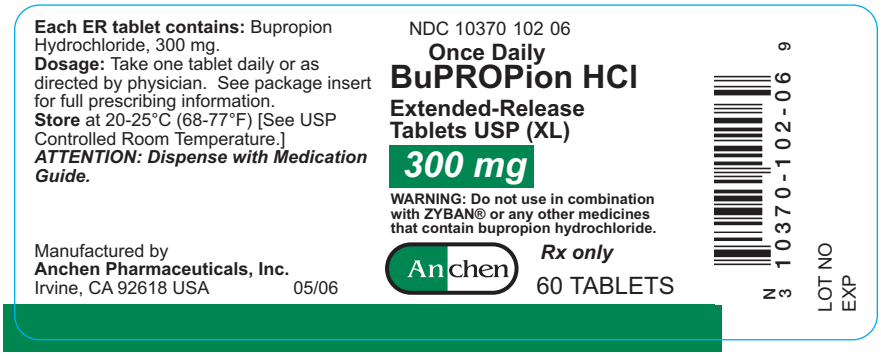

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proof date: 05/26/06

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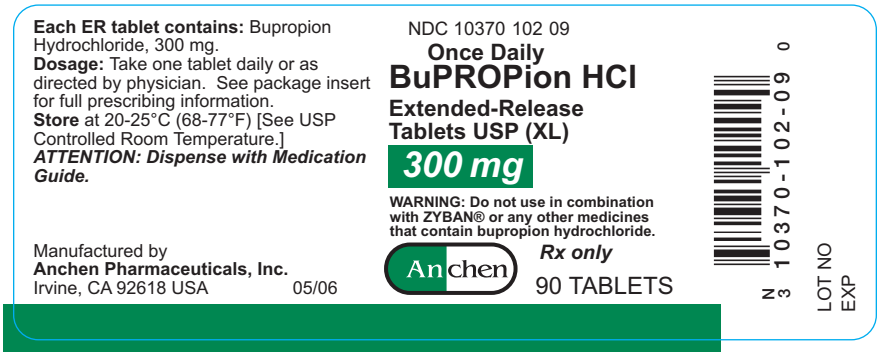

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077284

LABELING REVIEWS

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

ANDA Number: **77-284**

Date of Submission: **September 21, 2004 (Original Submission)**

Applicant's Name: Anchen Pharmaceuticals, Inc.

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

Labeling Deficiencies:

GENERAL

- The Division of Neuropharmacological Drug Products and the Office of New Drug Evaluation I have determined that, in order to ensure that safety information is provided with all antidepressant products, the products are ONLY to be distributed in unit-of-use packages with each package having a MedGuide affixed to the container. The unit-of-use packages should be designed for direct dispensing to the patient, with child-resistant closures, and with package sizes based on monthly usage (30's, 60's, 90's, etc.) up to a three months supply. Please note that you should transition to the unit of use packaging by January 2006.
- This drug product appears to be a subject of USP 28 monograph. Please include the term "USP" in association with the established name.
- Submit your proposal for dissemination of the medication guide for review.
- Reformat your principal display panel to include all the information shown below as an example.

Once Daily BUPROPION HCL EXTENDED-RELEASE TABLETS (XL) XXX mg **Warning: Do not use in combination with ZYBAN® or any other medicines that contain bupropion hydrochloride.** XXX Tablets Rx only **ATTENTION: Dispense with Medication Guide**

CONTAINER: 30s and (b) (4) (150 mg & 300 mg)

- See comments under **GENERAL**

PHYSICIAN INSERT/MEDICATION GUIDE

- Update your labeling based on the attached approved labeling for the reference listed drug, Wellbutrin XL, approved January 12, 2005.

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. 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, please provide a side-by-side comparison of your proposed labeling with the attached reference listed drug 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 (Wellbutrin XL) labeling

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Wellbutrin XL (Glaxo Wellcome; Approved 1-12-05) NDA 21-515/S-009.

2. PATENT/EXCLUSIVITY STATEMENT

Patent Data

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:

There is no unexpired exclusivity for the RLD.

3. DESCRIPTION

The inactive ingredients are listed accurately in the DESCRIPTION section.

(Vol. 1.1 Page 85)

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Anchen Pharmaceuticals, Inc.
5 Goodyear
Irvine, CA 92618

(Vol. 1.1. Page 257).

5. TABLET IMPRINT

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

(Vol. 1.2 page 798 & 808)

6. Summary of Container/Closure system:

Packaging Size		150 mg	300 mg
Bottle of 30s	Container	100 cc wide mouth, round, white bottle	100 cc wide mouth, round, white bottle
	Closure	38 mm CRC, ribbed white with (b) (4) printed liner.	38 mm CRC, ribbed white with (b) (4) printed liner.
(b) (4)			

[Vol. 1.2 page 636]

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

8. Storage/dispensing recommendations:

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

   ANDA - Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]"

9. The RLD is available in 150 mg and 300 mg strengths – both in 30s.
   The ANDA will be available (150 mg and 300 mg) in container of 30s and (b) (4).

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

Date of Review: June 13, 2005 Date of Submission: September 21, 2004

Primary Reviewer: 6-17-05
Melaine Shin Date:

Team Leader: 6-17-05
Lillie Golson Date

cc:

ANDA: 77-284
DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)
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V:\FIRMSAM\ANCHEN\LTRS\77284 NA1.labeling.doc

DRAFT: June13, 2005
FINAL: June 17, 2005

Following this page, 21 pages withheld in full- Reference Listed Drug labeling

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

ANDA Number:	77-284
Date of Submission:	August 18, 2005
Applicant's Name:	Anchen Pharmaceuticals, Inc.
Established Name:	Bupropion Hydrochloride Extended-release Tablets USP, (XL) 150 mg and 300 mg

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Labeling Deficiencies:

GENERAL

- This drug product appears to be a subject of USP 28 monograph. Please include the term "USP" in association with the established name as follows:

  "Bupropion Hydrochloride Extended Release Tablets USP (XL)"

- Your proposal for dissemination of the medication guide is acceptable.

CONTAINER: 30s and (b) (4) (150 mg & 300 mg)

- See comments under **GENERAL**

- As requested previously, reformat your principal display panel to include all the information shown below as an example. The "Attention:" statement could be located on the side panel if there is not enough space on the principal display panel.

Once Daily

BUPROPION HCL
EXTENDED-RELEASE TABLETS USP (XL)
XXX mg

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

XX Tablets Rx only

ATTENTION: Dispense with Medication Guide

PHYSICIAN INSERT/MEDICATION GUIDE

- Under PRECAUTIONS: Cardiovascular Effect; 2nd paragraph, 4th sentence.

  Replace "sustained-release formulation of bupropion" with "Zyban" as appears on the RLD.

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

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

** The firm did not make the recommended changes in the previous NA letter.

1. MODEL LABELING

This review was based on the labeling for Wellbutrin XL (Glaxo Wellcome; Approved 1-12-05) NDA 21-515/S-009.

2. PATENT/EXCLUSIVITY STATEMENT

Patent Data

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:

There is no unexpired exclusivity for the RLD.

3. DESCRIPTION

The inactive ingredients are listed accurately in the DESCRIPTION section.

(Vol. 1.1 Page 85)

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Anchen Pharmaceuticals, Inc.
5 Goodyear
Irvine, CA 92618

(Vol. 1.1. Page 257).

5. TABLET IMPRINT

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

(Vol. 1.2 page 798 & 808)

6. Summary of Container/Closure system:

Packaging Size		150 mg	300 mg
Bottle of 30s	Container	100 cc wide mouth, round, white bottle	100 cc wide mouth, round, white bottle
	Closure	38 mm CRC, ribbed white with (b) (4) printed liner.	38 mm CRC, ribbed white with (b) (4) printed liner.
(b) (4)			

[Vol. 1.2 page 636]

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

8. Storage/dispensing recommendations:

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

   ANDA - Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]"

9. The RLD is available in 150 mg and 300 mg strengths – both in 30s.
   The ANDA will be available (150 mg and 300 mg) in container of 30s and (b) (4).

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

Date of Review: September 19, 2005, Date of Submission: August 18, 2005

Primary Reviewer: Melaine Shin Date: 9-23-05

Team Leader: Lillie Golson Date 9/23/05

cc:

ANDA: 77-284
DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)

File Path: V:\FIRMSAM\ANCHEN\LTRS&REV\77284 NA2.labeling.doc

Review

FINAL: September 23, 2005

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

ANDA Number: 77-284

Date of Submission: October 11, 2005

Applicant's Name: Anchen Pharmaceuticals, Inc.

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

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 – 30s, 60s, and 90s for 150 mg & 300 mg

Satisfactory in final print as of October 11, 2005 submission

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\\Cdsesub1\n77284\N_000\2005-10-11\labeling\proposed.pdf\bottle_300-30.pdf
\\Cdsesub1\n77284\N_000\2005-10-11\labeling\proposed.pdf\bottle_300-60.pdf
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PROFESSIONAL PACKAGE INSERT

Satisfactory in final print as of October 11, 2005 submission

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REVISIONS NEEDED POST-APPROVAL:

1. **The firm will revise the established name with the use of "Tall Man" letters to read as "BuPROPion"**

2. **The firm will add the "USP drug release test is pending" statement to the DESCRIPTION section of the package insert.**

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: Glaxo Wellcome

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

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:

1. The firm will revise the established name with the use of "Tall Man" letters to read as "BuPROPion" This was recommended in the "Name Differentiation Project" in order to minimize medication errors resulting from look-alike confusion.

2. Per Nhan Tran's email, 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.

3. MODEL LABELING

   This review was based on the labeling for Wellbutrin XL (Glaxo Wellcome; Approved 1-12-05) NDA 21-515/S-009.

4. PATENT/EXCLUSIVITY STATEMENT

   Patent Data

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

   There is no unexpired exclusivity for the RLD.

5. DESCRIPTION

   The inactive ingredients are listed accurately in the DESCRIPTION section.

   (Vol. 1.1 Page 85)

6. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

   Anchen Pharmaceuticals, Inc.
   5 Goodyear
   Irvine, CA 92618

   (Vol. 1.1. Page 257).

7. TABLET IMPRINT

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

   (Vol. 1.2 page 798 & 808)

8. Summary of Container/Closure system:

Packaging Size		150 mg	300 mg
Bottle of 30s	Container	100 cc wide mouth, round, white bottle	100 cc wide mouth, round, white bottle

	Closure	38 mm CRC, ribbed white with (b) (4) printed liner.	38 mm CRC, ribbed white with (b) (4) printed liner.
(b) (4)			

[Vol. 1.2 page 636]

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

8. Storage/dispensing recommendations:

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

   ANDA - Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]"

9. The RLD is available in 150 mg and 300 mg strengths – both in 30s.
   The ANDA will be available (150 mg and 300 mg) in container of 30s, 60s, and 90s for both strengths.

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

Date of Review: October 19, 2005 Date of Submission: October 11, 2005

Primary Reviewer: Melaine Shin 10-24-05 Date:

Team Leader: Michelle Lillehaugh Golson Lillie Golson 10-26-05 Date

cc:

ANDA: 77-284
DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)
Review

File Path: V:\FIRMSAM\ANCHEN\LTRS&REV\77284 AP .LABELING.doc

FINAL: October 24, 2005

THIS REVIEW SUPERSEDES THE APPROVAL SUMMARY FOR THE 10/11/05 SUBMISSION

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

ANDA Number:	77-284
Date of Submission:	June 23, 2006
Applicant's Name:	Anchen Pharmaceuticals, Inc.
Established Name:	Bupropion Hydrochloride Extended-release Tablets USP, (XL) 150 mg and 300 mg
Proprietary Name:	None

Labeling Deficiencies:

A. GENERAL

1. 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.

2. Please provide chemistry data for your package sizes of 60s and 90s, if you have not already done so.

B. CONTAINER (30s, 60s, 90s)

Satisfactory in draft as of the June 23, 2006 amendment.

C. INSERT

Due to changes in the insert labeling for the reference listed drug, Wellbutrin XL® Tablets (NDA 21-515/S-018), approved June 12, 2006, please revise your labeling to be in accordance. This labeling can be found on the following website;
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
You should address all exclusivities and patents listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") and revise your insert labeling accordingly.

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.

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

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

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

CONTAINER LABELS – 30s, 60s, and 90s for 150 mg & 300 mg

Satisfactory in final print as of submission

PROFESSIONAL PACKAGE INSERT

Satisfactory in final print as of submission

REVISIONS NEEDED POST-APPROVAL:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 21-515

NDA Drug Name: Bupropion Hydrochloride Extended-Release Tablets (XL)

NDA Firm: Glaxo Wellcome

Date of Approval of NDA Insert and supplement #: S-018 Approved 6-12-06 (See FTR)

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:

1. The firm has revised the established name with the use of "Tall Man" letters to read as "BuPROPion" This was recommended in the "Name Differentiation Project" in order to minimize medication errors resulting from look-alike confusion.

2. Per Nhan Tran's email, 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.

3. 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.

4. PATENT/EXCLUSIVITY STATEMENT

   Patent Data 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

5. DESCRIPTION

   The inactive ingredients are listed accurately in the DESCRIPTION section.

   (Vol. 1.1 Page 85)

6. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

   Anchen Pharmaceuticals, Inc.
   5 Goodyear
   Irvine, CA 92618

   (Vol. 1.1. Page 257).

7. TABLET IMPRINT

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

(Vol. 1.2 page 798 & 808)

8. bSummary of Container/Closure system:

Packaging Size		150 mg	300 mg
Bottle of 30s	Container	100 cc wide mouth, round, white bottle	100 cc wide mouth, round, white bottle
	Closure	38 mm CRC, ribbed white with (b) (4) printed liner.	38 mm CRC, ribbed white with (b) (4) printed liner.
(b) (4)			

[Vol. 1.2 page 636]

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

8. Storage/dispensing recommendations:

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

   ANDA - Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]"

9. The RLD is available in 150 mg and 300 mg strengths – both in 30s.
   The ANDA will be available (150 mg and 300 mg) in container of 30s, 60s, and 90s for both strengths.

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

Date of Review: August 2, 2006

Date of Submission: June 23, 2006

Primary Reviewer: Michelle Dillahunt — Date: 8/7/06

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

cc:

ANDA: 77-284
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
Review
File Path: V:\FIRMSAM\ANCHEN\LTRS&REV\77284 NA3 .LABELING.doc

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

ANDA Number: 77-284

Date of Submission: August 17, 2006

Applicant's Name: Anchen Pharmaceuticals, Inc.

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

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 – 30s, 60s, and 90s for 150 mg & 300 mg

Satisfactory in final print as of August 17, 2006 submission

150 mg	30	file:///\\Cdsesub1\n77284\N_000\2006-08-17\labeling\final.pdf\bottle_150_30.pdf
	60	file:///\\Cdsesub1\n77284\N_000\2006-08-17\labeling\final.pdf\bottle_150_60.pdf
	90	file:///\\Cdsesub1\n77284\N_000\2006-08-17\labeling\final.pdf\bottle_150_90.pdf
300 mg	30	file:///\\Cdsesub1\n77284\N_000\2006-08-17\labeling\final.pdf\bottle_300_30.pdf
	60	file:///\\Cdsesub1\n77284\N_000\2006-08-17\labeling\final.pdf\bottle_300_60.pdf
	90	file:///\\Cdsesub1\n77284\N_000\2006-08-17\labeling\final.pdf\bottle_300_90.pdf

PROFESSIONAL PACKAGE INSERT/MEDICATION GUIDE

Satisfactory in final print as of August 17, 2006 submission
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REVISIONS NEEDED POST-APPROVAL:

CONTAINER

1. Side panel, change "ER" to "extended-release".

INSERT

1. GENERAL

   Delete "USP" in association with your established name since the USP drug release test is pending.

2. DESCRIPTION

   Move "USP drug release test pending" to a separate line.

In an effort to reduce confusion between the various bupropion dosage forms, we ask that you further revise your labeling as follows:

3. CONTRAINDICATIONS, revise second paragraph as follows;
   "Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients treated with ZYBAN® (bupropion hydrochloride) Sustained-release Tablets, bupropion hydrochloride tablets (immediate-release formulation), bupropion hydrochloride extended-release tablets (SR) (sustained-release formulation), or any other medications that contain bupropion because the incidence of seizure is dose dependent."

4. WARNINGS

Screening Patients for Bipolar Disorder, second paragraph, revise to read;
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.

5. PRECAUTIONS

a. Information for Patients, first paragraph, last sentence, change "Guides" to "Guide".

b. 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.

6. DOSAGE AND ADMINISTRATION

Switching Patients from Wellbutrin® (bupropion hydrochloride tablets) or from Wellbutrin® SR (bupropion hydrochloride extended-release tablets (SR), revise subsection as follows:
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.

7. MEDICATION GUIDE

Who should not take bupropion hydrochloride extended-release tablets (XL)?, revise as follows:
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 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).
- 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.

BASIS OF APPROVAL:

Patent Data

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

Code/sup	Expiration	Use Code	Description		Labeling Impact
I-497	6-12-09		PREVENTION OF SEASONAL MAJOR DEPRESSIVE EPISODES IN PATIENTS WITH SEASONAL		Carved out

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

FOR THE RECORD:

1. The firm will revise the established name with the use of "Tall Man" letters to read as "BuPROPion" This was recommended in the "Name Differentiation Project" in order to minimize medication errors resulting from look-alike confusion.

2. Per Nhan Tran's email dated 8/31/06, regarding USP

   As a result of our work (Larry Ouderkirk and I) with the USP, at the present time, there are three (3) drug release tests in the USP for bupropion HCl ER tablets, with Test 1 corresponding to GlaxoSmithKline, Test 2 for Eon (ANDA 75-932) and Test 3 for Impax (ANDA 75-913).

   In the USP, there is no distinction between SR or XL, but just extended release and I think it is perfectly correct since both SR or XL is just a term for extended release dosage form. And one does not need to know which test is for what formulation provided it meets any of the USP test (Test 1, 2 or 3), since they are all for ER tablets. If a company meets the USP test along with USP specifications, the company can label for example, it meets the USP test #1 or 2 or 3.
   Only when the product cannot meet either tests, then the labeling should state: Drug release test is pending. In majority of cases, the test formulation will not be able to meet the USP test, but this is not unusual, because for an extended release (ER) formulation, the drug release characteristics of each formulation are different and consequently the drug release test will be different.

   Thanks much Tran. So, for the XL applications, we will include "USP" with the established name once we determine which test their formulation meets. For the ones for which a determination has not been made, we will have the firms include the "pending..." statement.

3. 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.
- 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.

4. For consistency in the generic labeling, the following revisions should be made to all bupropion hydrochloride extended-release tablets (XL);

CONTRAINDICATIONS, revised second paragraph as follows;
"Bupropion hydrochloride extended-release tablets (XL) are contraindicated in patients treated with ZYBAN® (bupropion hydrochloride) Sustained-release Tablets, bupropion hydrochloride tablets (immediate-release formulation), bupropion hydrochloride extended-release tablets (SR) (sustained-release formulation), or any other medications that contain bupropion because the incidence of seizure is dose dependent."

WARNINGS
Screening Patients for Bipolar Disorder, second paragraph, revised to read;
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.

PRECAUTIONS

Clinical Worsening and Suicide Risk, second paragraph, revised 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.

DOSAGE AND ADMINISTRATION

Switching Patients from Wellbutrin® (bupropion hydrochloride tablets) or from Wellbutrin® SR (bupropion hydrochloride extended-release tablets (SR), revise subsection as follows:
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.

MEDICATION GUIDE

Who should not take bupropion hydrochloride extended-release tablets (XL)?
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 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).
- 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.

5. DESCRIPTION

The inactive ingredients are listed accurately in the DESCRIPTION section.

(Vol. 1.1 Page 85)

6. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Anchen Pharmaceuticals, Inc.
5 Goodyear
Irvine, CA 92618
(Vol. 1.1. Page 257).

7. TABLET IMPRINT

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

(Vol. 1.2 page 798 & 808)

8. Summary of Container/Closure system:

Packaging Size		150 mg	300 mg
Bottle of 30s	Container	100 cc wide mouth, round, white bottle	100 cc wide mouth, round, white bottle

	Closure	38 mm CRC, ribbed white with (b) (4) printed liner.	38 mm CRC, ribbed white with (b) (4) printed liner.
(b) (4)			

[Vol. 1.2 page 636]

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

10. Storage/dispensing recommendations:

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

    ANDA - Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]"

11. The RLD is available in 150 mg and 300 mg strengths – both in 30s.
    The ANDA will be available (150 mg and 300 mg) in container of 30s, 60s, and 90s for both strengths.

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

Date of Review: September 11, 2006

Date of Submission: August 17, 2006

Primary Reviewer: Michelle Dillahunt — Date: 9/14/06

Team Leader: Lillie Golson — Date: 9/14/06

cc:

ANDA: 77-284
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
Review
File Path: V:\FIRMSAM\ANCHEN\LTRS&REV\77284 AP2 .LABELING.doc

Final 9/14/06

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077284

CHEMISTRY REVIEWS

#1

ANDA 77-284

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

Anchen Pharmaceuticals, Inc.

Bing Wu, Ph.D.

Division of Chemistry II
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-284

2. REVIEW #: 1

3. REVIEW DATE: 22-FEB-2005

4. REVIEWER: Bing Wu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	September 21, 2004
Patent Amendment	January 13, 2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Anchen Pharmaceuticals, Inc.
Address:	5 Goodyear Irvine, CA 92618
Representative:	Maggie Chang
Telephone:	(949) 837-6178 ext. 102
Fax:	(949) 837-6120

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	N/A
b) Non-Proprietary Name (USAN):	Bupropion Hydrochloride Extended-Release Tablets

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Wellbutrin XL™ Tablets, marketed by GlaxoSmithKline, NDA 21-515. Two listed patents, US Patent Nos. 6,096,341 and 6,143,327, which claim the reference drug and expire on October 30, 2018. The applicant certifies that the two patents are invalid, unenforceable, or will not be infringed by the manufacturer, use, or sale of the Anchen's drug product. The Paragraph IV patent certification is provided on p. 18.

An exclusivity statement is provided on p. 19. There is an M-10 exclusivity for the RLD, which 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

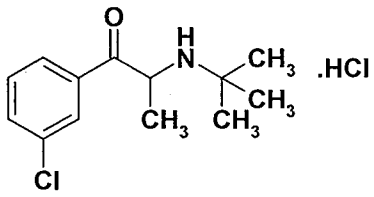
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Bupropion Hydrochloride



Chemical Name:	(±)-1-(3-Chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone 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	1/22/05	
	IV			3	Adequate	5/20/99	
	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:

Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	2/7/05	
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 77-284

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable – The firm needs to address the minor deficiencies identified in the review.

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 is structurally related to phenylethylamines. Its chemical name is (±)-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.

Bupropion hydrochloride extended-release tablets (Bupropion HCl ER Tablets) are supplied for oral administration as 150 mg and 300 mg, round white to off-white extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the following inactive ingredients: (b) (4) alcohol, ethylcellulose, hydroxypropylcellulose, methacrylic acid copolymer, povidone, silicon dioxide, and hydrogenated vegetable oil. The tablets are printed with edible black ink. The insoluble shell of the extended-release tablet may remain intact during gastrointestinal transit and is eliminated in the feces. Bupropion HCl ER Tablets, 150 mg and 300 mg, are supplied in HDPE bottles of 30's and (b) (4).

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

Bupropion HCl ER Tablet is indicated for the treatment of major depression disorder.

C. Basis for Approvability or Not-Approval Recommendation

Not-approval is recommended for the ANDA 77-284 for the following deficiencies:

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Endorsements (Draft and Final with Dates)

HFD-640/BWu/2/22/05,3/7/05 3/9/05
HFD-640/SRosencrance/DSkanchy 3/8/05 3/9/05
HFD-617/Thinchliffe/3/8/05 3/9/05

C. CC Block

ANDA 77-284
DIV FILE
Field Cop

Following this page, 25 pages withheld in full (b)(4)-CCI/TS

ANDA: 77-284

APPLICANT: Anchen Pharmaceuticals, Inc.

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

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

1.

2.

3.

4.

5.

6. (b) (4)

7.

8. (b) (4)

9.

10.

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

1. The test specification and test method for Drug Release will be evaluated by the Division of Bioequivalence, comments, if any, will be provided to you separately.

2. Please provide all available room temperature stability data in your next amendment.

Sincerely yours,

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

cc: ANDA 77-284
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/BWu/2/22/05,3/7/05 3/9/05

HFD-640/SRosecrance/DSkanchy 3/8/05 3/9/05

HFD-617/THinchliffe/3/8/05 3/9/05

F/T by: rad3/9/05

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TYPE OF LETTER: NOT APPROVABLE – MINOR AMENDMENT

A2

ANDA 77-284

Bupropion HCl Extended-Release Tablets (XL) USP, 150 mg and 300 mg

Anchen Pharmaceuticals, Inc.

Bing Wu, Ph.D.

Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-284

2. REVIEW #: 2b Chemistry review #2 not located

3. REVIEW DATE: 31-AUG-2005; 18-SEP-2005

4. REVIEWER: Bing Wu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	September 21, 2004
Telephone Amendment	October 15, 2004
Patent Amendment	January 13, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	April 7, 2005
Telephone Amendment	**Sept. 8, 2005**

7. NAME & ADDRESS OF APPLICANT:

Name:	Anchen Pharmaceuticals, Inc.
Address:	5 Goodyear Irvine, CA 92618
Representative:	Margaret Choy
Telephone:	(949) 837-6178 ext. 127
Fax:	(949) 837-6120

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

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

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Wellbutrin XL™ Tablets, marketed by GlaxoSmithKline, NDA 21-515. Two listed patents, US Patent Nos. 6,096,341 and 6,143,327, which claim the reference drug and expire on October 30, 2018. The applicant certifies that the two patents are invalid, unenforceable, or will not be infringed by the manufacturer, use, or sale of the Anchen's drug product. The Paragraph IV patent certification is provided on p. 18.

An exclusivity statement is provided on p. 19. There is an M-10 exclusivity for the RLD, which 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

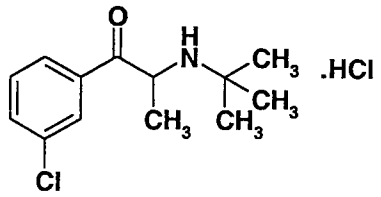
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

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

Bupropion Hydrochloride



Chemical Name:	(±)-1-(3-Chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone 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	8/2/05	Reviewed by H.A. Hahm.
	IV			3	Adequate	5/20/99	
	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	2/7/05	Per OC
Methods Validation	N/A		
Labeling	Acceptable	10/27/05	Melaine Shin
Bioequivalence	Acceptable (full review)	7/15/05	Hoainhon Nguyen
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 77-284

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval is recommended.

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 is structurally related to phenylethylamines. Its chemical name is (±)-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.

Bupropion hydrochloride extended-release tablets (Bupropion HCl ER Tablets) are supplied for oral administration as 150 mg and 300 mg, round white to off-white extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the following inactive ingredients: (b) (4) alcohol, ethylcellulose, hydroxypropylcellulose, methacrylic acid copolymer, povidone, silicon dioxide, and hydrogenated vegetable oil. The tablets are printed with edible black ink. The insoluble shell of the extended-release tablet may remain intact during gastrointestinal transit and is eliminated in the feces. Bupropion HCl ER Tablets, 150 mg and 300 mg, are supplied in HDPE bottles of 30's and (b) (4).

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

Bupropion HCl ER Tablet is indicated for the treatment of major depression disorder.

C. Basis for Approvability or Not-Approval Recommendation

Approval is recommended for the ANDA 77-284. All CMC deficiencies have been satisfactorily addressed.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Endorsements (Draft and Final with Dates)

HFD-640/BWu/8/31/05;9/18/05 10/28/05
HFD-640/DSkanchy/9/19/05 10/28/05
HFD-617/Thinchliffe/10/28/05 10/28/05

C. CC Block

ANDA 77-284
DIV FILE
Field Cop

Following this page, 29 pages withheld in full (b)(4)- CCI/TS

(b) (4)

[redacted]

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Anchen Pharmaceuticals, Inc. has requested a categorical exclusion from the requirement of an Environmental Assessment Statement in accordance with 21 CFR 25.31.

cc: ANDA 77-284
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/BWu/8/31/05;9/18/05 10/28/05

HFD-640//DSkanchy/9/19/05 10/28/05

HFD-617/THinchliffe/10/28/05 10/28/05

F/T by: TOH10/28/05

V:\FIRMSAM\ANCHEN\LTRS&REV\77284Rev2b.ap.doc

TYPE OF LETTER: APPROVAL

[redacted]

ANDA 77-284

Bupropion HCl Extended-Release Tablets (XL) USP, 150 mg and 300 mg

Anchen Pharmaceuticals, Inc.

Bing Wu, Ph.D.

Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-284

2. REVIEW #: 3b Chemistry review #3 not located

3. REVIEW DATE: 27-SEP-2006; 17-OCT-2006

4. REVIEWER: Bing Wu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	September 21, 2004
Telephone Amendment	October 15, 2004
Patent Amendment	January 13, 2005
Chemistry Review #1 (Not approvable)	February 22, 2005
Minor Amendment	April 7, 2005
Telephone Amendment	Sept. 8, 2005
Chemistry Review #2 (Approvable)	September 18, 2005
FDA Approval letter (Tentative approval)	November 14, 2005
Minor Amendment	June 23, 2006
Minor Amendment	August 18, 2006
Minor Amendment	August 21, 2006
Correspondence (Keller and Heckman LLP for Biovail Corporation)	August 27, 2006
Chemistry Review #3 (Not approval, T-con)	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Telephone amendment	September 18, 2006
Telephone amendment	**October 2, 2006**

7. NAME & ADDRESS OF APPLICANT:

Name:	Anchen Pharmaceuticals, Inc.
Address:	5 Goodyear Irvine, CA 92618
Representative:	Margaret Choy
Telephone:	(949) 837-6178 ext. 127

Fax: (949) 837-6120

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Bupropion Hydrochloride Extended-Release Tablets

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Wellbutrin XL™ Tablets, marketed by GlaxoSmithKline, NDA 21-515. Two listed patents, US Patent Nos. 6,096,341 and 6,143,327, which claim the reference drug and expire on October 30, 2018. The applicant certifies that the two patents are invalid, unenforceable, or will not be infringed by the manufacturer, use, or sale of the Anchen's drug product. The Paragraph IV patent certification is provided on p. 18.

An exclusivity statement is provided on p. 19. There is an M-10 exclusivity for the RLD, which has expired on June 11, 2004.

Anchen Pharmaceuticals has requested in the 8/21/06 amendment a final approval of the drug product application based on a court decision on the non-infringement or invalidity of the patents, US Patent Nos. 6,096,341 and 6,143,327, included in the Paragraph IV certification. On August 1, 2006, the United States District Court granted Anchen' Motion for Summary Judgment of Non-Infringement of all asserted claims of the US Patent No. 6,096,341 (Exhibit 1). Biovail Laboratories, Inc. previously dismissed with prejudice all claims for infringement of the US Patent No. 6,143,327 (Exhibit 2).

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

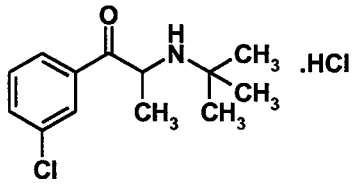
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__x__Not a SPOTS product

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

Bupropion Hydrochloride



Chemical Name:	(±)-1-(3-Chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone 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	10/10/06	
	IV			3	Adequate	5/20/99	
	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	Overall EES is acceptable	10/12/06	Per OC
Methods Validation	N/A		
Labeling	Acceptable	9/11/06	Michelle Dillahunt
Bioequivalence	Acceptable (full review)	8/24/06	Hoainhon Nguyen
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. ____Yes __X__No If no, explain reason(s) below: Minor Amendments

Chemistry Assessment Section

The Chemistry Review for ANDA 77-284

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval is recommended, pending for an acceptable EER for the new manufacturing facility at (b) (4) for the drug substance.

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 is structurally related to phenylethylamines. Its chemical name is (±)-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.

Bupropion hydrochloride extended-release tablets (Bupropion HCl ER Tablets) are supplied for oral administration as 150 mg and 300 mg, round white to off-white extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the following inactive ingredients: (b) (4) alcohol, ethylcellulose, hydroxypropylcellulose, methacrylic acid copolymer, povidone, silicon dioxide, and hydrogenated vegetable oil. The tablets are printed with edible black ink. The insoluble shell of the extended-release tablet may remain intact during gastrointestinal transit and is eliminated in the feces. Bupropion HCl ER Tablets, 150 mg and 300 mg, are supplied in HDPE bottles of 30's, 60's, 90's and (b) (4).

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

Bupropion HCl ER Tablet is indicated for the treatment of major depression disorder.

C. Basis for Approvability or Not-Approval Recommendation

Approval is recommended. All review issues regarding CMC information and data submitted in the ANDA have been satisfactorily addressed.

Following this page, 11 pages withheld in full (b)(4)-CCI/TS

Chemistry Assessment Section

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-284

APPLICANT: Anchen Pharmaceuticals, Inc.

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

A. Deficiencies:

None. All review issues regarding CMC information and data submitted in the ANDA have been satisfactorily addressed.

cc: ANDA 77-284
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/BWu/9/27/06;10/17/06

HFD-640//NYa/10/19/06

HFD-617/THinchliffe/10/19/06

F/T by:

O:\Draft Reviews\77284Rev03b.doc

TYPE OF LETTER: APPROVAL IS RECOMMENDED

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

/s/

Bing Wu
10/20/2006 10:26:29 AM
CHEMIST

Naiqi Ya
10/20/2006 10:30:33 AM
CHEMIST

Thomas Hinchliffe
10/31/2006 10:43:29 AM
PHARMACIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077284

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	77-284
Drug Product Name	Bupropion HCl ER Tablets
Strength	150 mg and 300 mg
Applicant Name	Anchen
Submission Date(s)	09-23-04
First Generic	Yes
Reviewer	Ethan M. Stier, Ph. D.
File Location	**V:\firmsam\anchen\ltrs&rev\77284D0904 .doc**
Clinical Site	Gateway Medical Research, Inc. 400 Fountain Lakes Blvd. St. Charles, MO 63301
Analytical Site	(b) (4)

EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is a USP method for this product. However, the firm did not conduct dissolution testing using the USP method (electronic version of USP 28).

The firm conducted comparative dissolution testing in three dissolution media (0.1 N HCl, pH 4.5 buffer, and pH 6.8 buffer) using USP apparatus *I (Basket),* on both 300 mg and 150 mg ER tablets. It is requesting a bioequivalence study waiver for the 150 mg tablet.

The firm will be asked to conduct additional dissolution testing using the USP method and in the three media using the USP apparatus *II (Paddle)* at 50 rpm.

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

RLD METHOD

Medium	Water (* USP Method)
Volume	900 mL
Temperature	37°C
Apparatus	II
Rotational Speed	50 RPM
Specification	1 hour: between 25% and 45% 4 hours: between 60% and 85% 8 hours: not less than 80%

***Source of Method:** USP

Table 1. Summary of In Vitro Dissolution Data in 0.1 N HCl

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range)						Study Report Location
					60 min	120 min	240 min	360 min	480 min	960 min	
Not Provided (N.P.)	04B044P / GlaxoSmithKline K-32370	150 mg E.R. Tab	Dissolution: Apparatus 1 (USP) Speed of Rotation: 75 rpm Medium: 0.1 N HCl at 37°C	12	0	2	23	49	73	95 (b) (4)	V 1.1 p. 40
N.P.	P000104 / Anchen	150 mg E.R. Tab		12	0	2	27	52	70	98 (b) (4)	
N.P.	03K056P/ GlaxoSmithKline K-32369	300 mg E.R. Tab		12	0	3	29	51	70	95 (b) (4)	V 1.1 p. 43
N.P.	P000204/ Anchen	300 mg E.R. Tab		12	0	2	22	42	57	90 (b) (4)	

Table 2a. Summary of In Vitro Dissolution Data in Acetate Buffer, pH 4.5

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range)							Study Report Location
					120 min	180 min	240 min	300 min	360 min	480 min	600 min	
Not Provided (N.P.)	04B044P / GlaxoSmithKline K-32370	150 mg E.R. Tab	Dissolution: Apparatus I (USP) Speed of Rotation: 75 rpm Medium: pH 4.5 acetate buffer at 37°C	12	0	0	2	3	6	13	22 (b) (4)	V 1.1 p. 46
N.P.	P000104 / Anchen	150 mg E.R. Tab			4	21	39	54	66	85	95 (b) (4)	
					720 min	840 min	960 min	1080 min	1200 min	1440 min		
N.P.	03K056P/ GlaxoSmithKline K-32369	300 mg E.R. Tab			30	40	49	57	65	76 (b) (4)		
N.P.	P000204/ Anchen	300 mg E.R. Tab			98	98	99	98	99	99 (b) (4)		

Table 2b. Summary of In Vitro Dissolution Data in Acetate Buffer, pH 4.5

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range)							Study Report Location
					120 min	180 min	240 min	300 min	360 min	480 min	600 min	
Not Provided (N.P.)	04B044P / GlaxoSmithKline K-32370	150 mg E.R. Tab	Dissolution: Apparatus I (USP) Speed of Rotation: 75 rpm Medium: pH 4.5 acetate buffer at 37°C	12	0	1	1	2	4	10	18 (b) (4)	V 1.1 p. 49
N.P.	P000104 / Anchen	150 mg E.R. Tab			4	16	30	43	54	72	84 (b) (4)	
					720 min	840 min	960 min	1080 min	1200 min	1440 min		
N.P.	03K056P/ GlaxoSmithKline K-32369	300 mg E.R. Tab			27	43	51	58	58	70 (b) (4)		
N.P.	P000204/ Anchen	300 mg E.R. Tab			92	96	98	98	98	98 (b) (4)		

Table 3. Summary of In Vitro Dissolution Data in pH 6.8 Buffer

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range)							Study Report Location
					60 min	120 min	180 min	240 min	360 min	480 min	600 min	
Not Provided (N.P.)	04B044P / GlaxoSmithKline K-32370	150 mg E.R. Tab	Dissolution: Apparatus 1 (USP) Speed of Rotation: 75 rpm Medium: pH 6.8 buffer at 37°C	12	19	39	54	67	82	88	90 (b) (4)	V 1.1 p. 52
N.P.	P000104 / Anchen	150 mg E.R. Tab		12	20	42	59	70	85	91	94 (b) (4)	
N.P.	03K056P/ GlaxoSmithKline K-32369	300 mg E.R. Tab		12	18	37	51	61	76(71	86	91 (b) (4)	V 1.1 p. 55
N.P.	P000204/ Anchen	300 mg E.R. Tab		12	14	32	45	56	71	82	89 (b) (4)	

DEFICIENCY COMMENTS:

1. The firm did not conduct dissolution testing using the USP method which uses water and apparatus II at 50 rpm.

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.

RECOMMENDATIONS:

1. The in vitro dissolution testing conducted by Anchen on its test products, Bupropion HCl Extended-Release Tablets, USP comparing it to GlaxoSmithKline's Wellbutrin XL® is incomplete.

2. The firm should conduct dissolution testing as per the USP recommended method and specification for Bupropion HCl ER Tablets. The firm should also conduct dissolution testing in the three dissolution media (e.g. pH 1.2, 4.5, and 6.8 buffers) using USP apparatus II (paddle) at 50 rpm.

   The firm should be informed of the above recommendations #1-2.

Ethan M. Stier 4-12-05

Ethan M. Stier, Ph.D.
Team II
Division of Bioequivalence
Office of Generic Drugs

Gur-Jai Pal Singh 4-13-05

Gur-Jai Pal Singh, Ph.D.
Team II
Division of Bioequivalence
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Dale P. Conner 4/13/05

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

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-284 APPLICANT: Anchen

DRUG PRODUCT: Bupropion HCl ER Tablets

The Division of Bioequivalence has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiencies have been identified:

1. Please conduct comparative dissolution testing using 12 dosage units of the test and reference products using the following USP method:

Medium:	water
Volume:	900 mL
Temperature:	37°C
Apparatus:	Apparatus II (paddles)
Rotation:	50 rpm
Specification:	(b) (4) % in 1 hour % in 4 hours n 8 hours

2. In addition, please conduct dissolution testing in at least three other dissolution media (e.g. pH 1.2, 4.5, and 6.8) using the USP apparatus II (paddle) at 50 rpm.

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.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the *in vivo* studies.

Sincerely yours,

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

ANDA: 77-284

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)	$T_{1/2}$ (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

CC: ANDA 77-284
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ E. Stier

V:\FIRMSAM\Anchen\LTRS&REV\77284A0904.doc
Printed in final on 04/12/2005

Endorsements: (Final with Dates)
HFD-655/ E. Stier 4/13/05
HFD-655/ GJP Singh 4-13-05
HFD-617/ K. Suh
HFD-650/ D. Conner 4/13/05

BIOEQUIVALENCE - INCOMPLETE Submission date: 09-23-04

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

1. DISSOLUTION (Dissolution Data) Strengths: 150 mg and 300 mg
Outcome: IC

Outcome Decisions: AC or IC – Acceptable or Incomplete
WinBio Comments: AC or IC

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-284
Drug Product Name	Bupropion HCl ER Tablets
Strength	150 mg & 300 mg
Applicant Name	Anchen Pharmaceutical
Address	Irvine, CA
Submission Date(s)	September 21, 2004
Amendment Date(s)	May 16, 2005
Reviewer	Hoainhon Nguyen
First Generic	Yes
File Location	**V:\firmsam\anchen\ltrs&rev\77284n0904.doc**

I. Executive Summary

The firm has submitted a single-dose, 2-way crossover fasting bioequivalence study and a single-dose, 2-way crossover nonfasting bioequivalence study comparing the test product, Bupropion HCl Extended Release Tablets, 150 mg, with the RLD product, SmithKline Beecham's Wellbutrin XL® (bupropion HCl) Tablets, 150 mg. The fasting study was performed in 17 normal males and 15 normal females at a dose of 1x150 mg and resulted in acceptable data (point-estimate, 90% CI) that demonstrate BE in the fasted state (Bupropion: AUCt 1.02, 93.5-111.3; AUCinf 1.05, 98.3-112.8; Cmax 1.10, 99.1-122.6. Hydroxybupropion: AUCt 0.97, 88.9-106.5; AUCinf 0.97, 89.1-106.4; Cmax 1.01, 91.6-110.5). The nonfasting study was performed in 17 normal males and 14 normal females at a dose of 1x150 mg and resulted in acceptable data (point-estimate, 90% CI) that demonstrate BE in the fed state (Bupropion: AUCt 0.99, 95.0-104.0; AUCinf 1.01, 95.8-105.8; Cmax 0.99, 93.2-104.7. Hydroxybupropion: AUCt 0.97, 91.6-102.6; AUCinf 0.97, 91.9-102.7; Cmax 0.99, 94.1-104.1).

The comparative dissolution data comparing both strengths of the test product with the reference product were acceptable. The firm's proposed dissolution method was acceptable. However, the specifications recommended by the DBE for the test product based on the data submitted are different from the firm's proposed specifications. The firm is requested to acknowledge the DBE's recommended specifications.

The formulations of the 150 mg and 300 mg strengths of the test product are proportionally similar. The waiver request for the 300 mg strength is granted.

The application is **incomplete** pending the firm's response concerning the dissolution specifications.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Bupropion HCl ER Tablets, 150 mg & 300 mg
Reference Product	Wellbutrin XL® (bupropion HCl) Tablets, 150 mg & 300 mg
RLD Manufacturer	SmithKline Beecham
NDA No.	21-515
RLD Approval Date	08/28/2003
Indication	indicated for the treatment of major depressive disorder

B. PK/PD Information (Reference: PDR 2005)

Bioavailability	Not yet determined
Food Effect	Food did not affect the C_{max} or AUC of bupropion.
Tmax	5 hours for bupropion; approximately 6 hours for the three active metabolites.
Metabolism	Bupropion is extensively metabolized in humans. There are three active metabolites: hydroxybupropion and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via hydroxylation of the *tert* -butyl group of bupropion and/or reduction of the carbonyl group. 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.
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. The fraction of the oral dose of bupropion excreted unchanged was only 0.5%.
Half-life	21 hours for bupropion; 20 hours for hydroxybupropion, 37 hours for threohydrobupropion, and 33 hours for erythrohydrobupropion

Relevant OGD or DBE History

1. Prior to the issuance of the general BA/BE guidance in October 2000, the DBE had recommended the following for the drug product: a single-dose fasting bioequivalence study, a single-dose nonfasting bioequivalence study and a multiple-dose bioequivalence study. Bupropion, hydroxybupropion and a combination of threohydrobupropion and erythrobupropion were measured for the studies. The sampling schedule was generally up to 168 hours or 192 hours for single-dose studies. The practice was reflected in the reviews of the following documents: Protocol #98-021 ((b) (4); 07/20/98), Control Documents #98-200 ((b) (4); 05/21/98) and 99-009 ((b) (4); 01/06/99), ANDA (b) (4) ((b) (4); 06/17/99), ANDA (b) (4) ((b) (4); 09/10/99), ANDA #75-932 (Eon; 07/26/2000) and ANDA (; 06/30/2000).

2. Control Document #97-285 ((b) (4) 10/02/97) and 98-018 ((b) (4); 01/21/98): The DBE recommended the following: *" Wellbutrin SR® and Zyban® are considered separate reference listed drug products and cannot be considered to be therapeutically equivalent to each other because the products have different labeled indications. However, an in vivo bioequivalence study conducted on Wellbutrin SR® (Bupropion Hydrochloride Extended-release Tablets, 150 mg) may be referenced to support a request for a waiver of evidence of in vivo bioequivalence for Zyban® (Bupropion Hydrochloride Extended-release Tablets, 150 mg) or vice versa."* In addition, *"A separate abbreviated new drug application is required for each of these reference listed drug products."*

The above recommendation was applied to the waiver request of the following ANDAs: # (b) (4) ((b) (4); 08/10/99), ANDA # (b) (4) ((b) (4); 06/30/2000) and ANDA #75-913 (Impax; 06/22/2000).

3. Control Document #01-068 ((b) (4); 02/06/2001): The DBE had revised the recommendations concerning the bioequivalence requirements for the drug product based on the general BA/BE guidance (issued 10/2000). A single dose, replicate, fasting bioequivalence study on the highest strength, and a single dose, two way crossover, nonfasting bioequivalence study on the same strength were recommended. Measurement of bupropion and hydroxybupropion were requested but only bupropion data should be subject to the confidence interval criteria.

4. Control Document #01-149 ((b) (4), 03/08/2001): As the general BA/BE guidance was revised, the DBE revised its recommendations accordingly: A single dose, **nonreplicate**, fasting bioequivalence study on the highest strength, 150 mg, and a single dose, two way crossover, nonfasting bioequivalence study on the same strength were recommended. Measurement of bupropion and hydroxybupropion which is formed presystemically were requested. A biowaiver may be granted for the lower strength, 100 mg, based on formulation proportionality, comparable dissolution profiles between strengths and acceptable bioequivalence studies on the 150 mg.

5. The RLD product, Wellbutrin XL® Tablet, 150 mg and 300 mg, (NDA 21-515) were approved on 08/28/03 to provide improved once-daily formulations for patients who have been treated with Wellbutrin SR® Tablet, which was approved (06/14/02). The two formulations and their release-controlling technologies are different. NDA 21-515 was approved based on a confirmatory bioequivalence study comparing this formulation with Wellbutrin® Tablets (immediate-release formulation). Since the 150 mg and 300 mg strengths are not formulation proportional, a steady-state bioequivalence study comparing the two strengths using 300 mg dosage was also submitted for NDA 21-515. It should be noted that Wellbutrin SR® Tablet product was approved based on a bioequivalence study comparing this formulation with Wellbutrin® Tablets (immediate-release formulation) also. The interchangeability of Wellbutrin® products is addressed in the labeling of Wellbutrin XL®. According to this labeling, *"When switching patients from WELLBUTRIN Tablets to WELLBUTRIN XL or from WELLBUTRIN SR Sustained-Release Tablets to WELLBUTRIN XL, give the same total daily dose when possible. Patients who are currently being treated with WELLBUTRIN Tablets at 300 mg/day (for example, 100 mg 3 times a day) may be switched to WELLBUTRIN XL 300 mg once daily. Patients who are currently being treated with WELLBUTRIN SR Sustained-Release Tablets at 300 mg/day (for example, 150 mg twice daily) may be switched to WELLBUTRIN XL 300 mg once daily."*

The labeling of Wellbutrin XL® Tablets also recommends that *"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."* The 150 mg strength, therefore, is designated in the Orange Book as the RLD strength. Due to the safety concern, the 300 mg strength of the generic version can be waived of *in vivo* bioequivalence testing provided that the formulation of the higher strength is proportionally similar to that of the 150 mg strength, and the dissolution profiles of the two strengths are comparable.

6. Three different dissolution methods have been recommended for different

ANDAs of bupropion HCl ER products.
Method 1: USP Apparatus II (paddle) at 50 rpm, with 900 mL of water (recommended for ANDAs #75-913, 75-914, (b) (4))
Method 2: USP Apparatus II (paddle) at 50 rpm, with 900 mL of pH 1.5 SGF (without enzyme) (recommended for ANDA # (b) (4))
Method 3: USP Apparatus I(basket) at 50 rpm, with 900 mL of 0.1 N HCl, pH 1.5 (recommended for ANDA #75-932)

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	1
Waiver requests	Yes	1
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments		

D. Pre-Study Bioanalytical Method Validation

	Parent	Metabolite
Analyte name	Bupropion	Hydroxybupropion
Internal Standard	(b) (4)	Same
Method description	LC/MS/MS	Same
QC range	1.00-160 ng/mL	5.00-800 ng/mL
Standard curve range	1.00-200 ng/mL	5.00-1000 ng/mL
Limit of quantitation	1.00 ng/L	5.00 ng/ml
Average recovery of Drug (%)	91.3%	95.0%
Average Recovery of Int. Std (%)	92.2%	Same
Intraday precision range (%CV)	1.71-7.48%	1.68-2.60%
Intraday accuracy range (%)	98.5-110%	101-113%
Interday precision range (%CV)	2.28-5.37%	2.56-4.96%
Interday accuracy range (%)	101-110%	104-110%
Bench-top stability (hrs)	6 hours	6 hours
Stock stability (days)	16 hours (RT); 94 days* (4°C)	16 hours (RT); 94 days* (4°C)
Processed stability (hrs)	48 hours	48 hours
Freeze-thaw stability (cycles)	3	3
Long-term storage stability (days)	56 days	56 days
Dilution integrity	10-fold, 98.8%	10-fold, 101%
Specificity	Yes	Yes
SOPs submitted	Yes	Yes
Bioanalytical method is acceptable	Yes	Yes
20% Chromatograms included (Y/N)	Yes	Yes
Random Selection of Serial Chrom	Yes	Yes

*Data were submitted in the amendment dated 05/16/05

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	04083
Study Design	Two-way randomized crossover
No. of subjects enrolled	32
No. of subjects completing	32
No. of subjects analyzed	32
Subjects (Normal/Patients?)	Normal healthy subjects
Sex(es) included (how many?)	Male: 17 Female: 15
Test product	Anchen's Bupropion HCl ER Tablets, 150 mg
Reference product	Wellbutrin XL® Tablets, 150 mg
Strength tested	150 mg
Dose	1x150 mg

Summary of Statistical Analysis : Bupropion (N=32) Additional Information in Appendix, Table 6 and Table 7		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.02	93.5-111.3
AUC_{∞}	1.05	98.3-112.8
C_{max}	1.10	99.1-122.6

Summary of Statistical Analysis : Hydroxybupropion (N=32) Additional Information in Appendix, Table 6 and Table 7		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	0.97	88.9-106.5
AUC_{∞}	0.97	89.1-106.4
C_{max}	1.01	91.6-110.5

Reanalysis of Study Samples Additional information in Appendix, Table 5								
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**
All samples were reassayed for analytical reasons only.								
Total								

Did use of recalculated plasma concentration data change study outcome? N/A

Comments on Fasting Study:

2. Single-dose Fed Bioequivalence Study

Study No.	04100
Study Design	Two-way, randomized, crossover
No. of subjects enrolled	32
No. of subjects completing	31
No. of subjects analyzed	31
Subjects (Normal/Patients?)	Normal healthy subjects
Sex(es) included (how many?)	Male: 17 Female: 14
Test product	Anchen's Bupropion HCl ER Tablets, 150 mg
Reference product	Wellbutrin XL® Tablets, 150 mg
Strength tested	150 mg
Dose	1x150 mg

Summary of Statistical Analysis: Bupropion (N=31) Additional Information in Appendix, Table 15 and Table 17		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	0.99	95.0-104.0
AUC∞	1.01	95.8-105.8
Cmax	0.99	93.2-104.7

Summary of Statistical Analysis: Hydroxybupropion (N=31) Additional Information in Appendix, Table 15 and Table 17		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	0.97	91.6-102.6
AUC∞	0.97	91.9-102.7
Cmax	0.99	94.1-104.1

Reanalysis of Study Samples Additional information in Appendix, Table 14								
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**
All samples were reassayed for analytical reasons only.								
Total								

Did use of recalculated plasma concentration data change study outcome? N/A

Comments on fed study: The study is acceptable.

F. Formulation

Location in appendix	Section B, Page 29
Inactive ingredients within IIG Limits (yes or no)	**Yes**
If no, list ingredients outside of limits	
If a tablet, is the product scored? (yes or no)	**No**
If yes, which strengths are scored?	
Is scoring of RLD the same as test? (yes or no)	**RLD not scored**
Formulation is acceptable (yes or no)	**Yes**
If not acceptable, why?	

G. In Vitro Dissolution

NOTE: The dissolution data were reviewed originally in v:\firmsam\anchen\ltrs&rev\ 77284d0904.doc which found the dissolution testing **incomplete**. The DBE requested that the firm conduct additional dissolution testing using one of the FDA methods as well as in three dissolution media using the USP apparatus II (paddle) at 50 rpm. The firm submitted the requested dissolution data in the dissolution amendment dated May 16, 2005.

Source of Method	Firm's Proposed Method
Medium	0.1 N HCl
Volume (mL)	900 mL
USP Apparatus type	I(basket)
Rotation (rpm)	75
Firm's proposed specifications	2 hours: (b) (4) 4 hours: 8 hours: 16 hours %(Q)
FDA-recommended specifications based on the data submitted for the ANDA	2 hours: (b) (4) 4 hours: 8 hours: 16 hours: %(Q)

Comment: Currently, there are three different FDA-recommended dissolution methods recommended for the bupropion HCl ER tablet product. The firm was requested to conduct additional dissolution testing using one of the FDA-recommended method (900 mL of water, USP apparatus II(paddle) at 50 rpm). Compared with the data based on this FDA method, the firm's proposed method yielded better correlated data between the test and reference products (F2 >50). Both methods yielded correlated data between the 150 mg and 300 mg strengths of the test product (F2>50). Based on this comparison, the firm's proposed method was accepted.

H. Waiver Request(s)

Strengths for which waivers requested	300 mg
Regulation cited	21 CFR 320.22 (d)
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	See Deficiency Comments below.
Waiver granted (yes or no)	Yes

I. Deficiency Comments

The dissolution data as submitted are acceptable. The firm's proposed method is found to be more appropriate for the test product than the FDA-recommended method.

However, the specifications as recommended by the FDA, based on the data submitted, are different from the firm's proposed specifications. The firm is requested to acknowledge the FDA-recommended specifications.

The application is **incomplete** pending the firm's response concerning the dissolution specifications.

J. Recommendations

1. The single-dose, fasting bioequivalence and the single-dose, nonfasting bioequivalence study conducted by Anchen on the test product, Bupropion HCl Extended Release Tablets, 150 mg, lot # P000104-30, comparing it with the reference product, SmithKline Beecham's Wellbutrin XL® (bupropion HCl) Tablets, 150 mg, lot # 04B044P, have been found **acceptable** by the Division of Bioequivalence. The test product, Anchen's Bupropion HCl Extended Release Tablets, 150 mg, is bioequivalent to the reference product, Wellbutrin XL® (bupropion HCl) Tablets, 150 mg.

2. The dissolution testing conducted by Anchen on its Bupropion HCl 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:

2 hours: (b) (4)
4 hours:
8 hours:
16 hours: %(Q)

See revised specifications under subsequent review endorsed 7/15/05 Test

Since the above specifications are different from those proposed by the firm, we request that the firm provide acknowledgement of its acceptance of the DBE's recommended specifications.

3. The formulations of the 300 mg and 150 mg strengths of the test product are proportionally similar. The waiver request for the 300 mg strength of the test product is

granted. The test product, Anchen's Bupropion HCl Extended Release Tablets, 300 g, is deemed bioequivalent to the reference product, Wellbutrin XL® (bupropion HCl) Tablets, 300 mg.

The application is **incomplete** pending the firm's response concerning the recommended dissolution specifications.

6/21/05

Hoainhon Nguyen, Branch I, Date signed

6/21/2005

Shriniwas Nerurkar, Ph.D., Branch I, Date signed

6/21/05

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

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IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information	
Study Number	04083
Study Title	A Randomized, Two-Way Crossover, Single-Dose, Open-Label Study to Evaluate the 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 32 Fasted, Healthy, Adult Subjects
Clinical Site	Gateway Medical Research, St. Charles, MO
Principal Investigator	Steven Herrmann, M.D., Ph.D.
Study/Dosing Dates	Period I: 06/27/04; Period II: 07/18/04
Analytical Site	(b) (4)
Analytical Director	(b) (6) Ph.D.
Analysis Dates	07/29/04-08/08/04
Storage Period (no. of days from first sample to final analysis)	43 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Bupropion HCl ER Tablets	Wellbutrin XL® Tablets
Manufacturer	Anchen Pharmaceuticals	SmithKline Beecham
Batch/Lot No.	P000104-30	04B044P
Manufacture Date	05/19/04	
Expiration Date		06/05
Strength	150 mg	150 mg
Dosage Form	ER Tablets	ER Tablets
Batch Size	(b) (4)	
Potency	101.2%	99.6%
Content Uniformity	100.9%(RSD=0.9%)	Not provided
Formulation	See Appendix Section B	
Dose Administered	1x150 mg	1x150 mg
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	21 days
Randomization Scheme	Yes
Blood Sampling Times	0, 1.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 24, 36, 48, 72, 96, 120 and 144 hours postdose
Blood Volume Collected/Sample	7 mL/sample
Blood Sample Processing/Storage	Samples were collected in evacuated tubes containing EDTA. The samples were cooled in an ice bath until centrifuged and harvested for plasma. The plasma aliquots were transferred to a polypropylene tube containing 25 uL of 4 N HCl, and stored at -20°C until assayed.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	From 10 hours predose until 4 hours postdose
Length of Confinement	Approximately 10 hours predose until 24 hours postdose
Safety Monitoring	Blood pressure and pulse were measured at predose, and within ±30 minutes of post-dose Hours 3, 5, 8, and 24 hours.

Table 1 Demographics of Study Subjects (N=32)

Age		Weight, lbs		Age Groups		Gender		Race	
				Range		Sex		Category	
				<18	0			Caucasian	13(M) 9(F)
Mean	28.9 (M) 33.0 (F)	Mean	189.8 (M) 171.3 (F)	18-40	15(M) 11(F)	Male	17	Afr. Amer.	3(M) 6(F)
SD	9.1 (M) 14.4 (F)	SD	36.3 (M) 51.4 (F)	41-64	2(M) 4(F)	Female	15	Hispanic	1(M)
Range	19-51 (M) 19-59 (F)	Range	143-290(M) 123-283(F)	65-75	0			Asian	0
				>75	0			Others	0

NOTE: M: Male; F: Female

Study Results

Table 2 Dropout Information

There was no dropout.

Subject No N/A
Reason N/A
Period N/A
Replacement N/A

Was there a difference in side effects for the test versus the reference? The difference in adverse events between two treatments did not appear to be significant. Most adverse events ranged from moderate to severe.

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Headache	1	
Dizziness	1	
Chest pain		1
Nausea	1	1
Difficulty sleeping		1
Diarrhea		1
Total:	**3**	**4**

Was there a difference in protocol deviations for the test versus the reference?

Protocol Deviations

There was no significant protocol deviations that might have compromised the integrity of the study. There was no significant plasma sampling deviation.

Table 4 Assay Validation – Within Study

	Bupropion			Hydroxybupropion		
QC Conc. (ng/mL)	2.00 (n=32)	20.0 (n=32)	160 (n=32)	10.00 (n=32)	100.0 (n=32)	800 (n=32)
Inter day Precision (%CV)	5.38	4.79	10.7	6.72	4.05	6.41
Inter day Accuracy (%)	105	93.5	93.1	103	98.1	104
Cal. Standards Conc. (ng/mL)	1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 200.0			5.00, 10.0, 25.0, 50.0, 100, 250, 1000		
Inter day Precision (%CV)	1.58-6.33			0.791-10.0		
Inter day Accuracy (%)	94.8-112			92.8-105		
Linearity Range (range of R^2 values)	0.9969-0.9997			0.9994-0.9999		

Chromatograms: Any interfering peaks? There was no significant interfering peak.

Table 5 SOP's dealing with analytical repeats of study samples

None was submitted. Acceptance criteria were included in the analytical report.

SOP No.	Date of SOP	SOP Title

- **Comments on repeat assays.** Samples were repeated for analytical reasons only.
- **Comments on Within-Study Validation:** Acceptable.

Conclusion: Analytical method is acceptable.

Table 6 Arithmetic Mean Pharmacokinetic Parameters

Bupropion

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	Ng.hr/mL	633.5	38	621.1	37	1.02
AUC∞	Ng.hr/mL	710.0	36	680.2	36	1.04
Cmax	Ng/mL	61.61	37	55.46	35	1.11
Tmax	Hrs	5.00	13	5.03	30	0.99
T1/2	Hrs	37.53	58	30.85	50	1.22
kel	Hrs^{-1}	0.0281	78	0.0327	50	0.86

Hydroxybupropion

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	Ng.hr/mL	10,377	38	10,794	38	0.96
AUC∞	Ng.hr/mL	10,825	37	11,264	38	0.96
Cmax	Ng/mL	224.8	42	222.2	39	1.01
Tmax	Hrs	15.09	47	15.28	43	0.99
T1/2	Hrs	25.82	33	25.29	43	1.02
kel	Hrs^{-1}	0.0296	30	0.0303	32	0.98

Table 7 Least Square Geometric Means and 90% Confidence Intervals (N=32)

Bupropion

Parameter	Test	Reference	T/R	90% CI
AUC0-t	586.9	575.3	1.02	93.5-111.3
AUC∞	665.6	632.2	1.05	98.3-112.8
Cmax	57.17	51.87	1.10	99.1-122.6

Hydroxybupropion

Parameter	Test	Reference	T/R	90% CI
AUC_{0-t}	9736	10,004	0.97	88.9-106.5
AUC_{∞}	10,174	10,451	0.97	89.1-106.4
C_{max}	204.7	203.5	1.01	91.6-110.5

Table 8 Additional Study Information

Bupropion

Root mean square error, AUC_{0-t}	0.204744
Root mean square error, AUC_{∞}	0.162675
Root mean square error, C_{max}	0.250949
K_{el} and AUC_{∞} determined for how many subjects?	All
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as C_{max}	0
Were the subjects dosed as more than one group?	No

Hydroxybupropion

Root mean square error, AUC_{0-t}	0.212118
Root mean square error, AUC_{∞}	0.208761
Root mean square error, C_{max}	0.221861
K_{el} and AUC_{∞} determined for how many subjects?	All
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as C_{max}	0
Were the subjects dosed as more than one group?	No

Comments: The statistical and PK analysis is acceptable.

Conclusion: The single-dose fasting bioequivalence study is acceptable. The 90% confidence interval for lnAUC(0-T), lnAUC(0-Infinity) and lnCmax of bupropion and hydroxybupropion was within the acceptable limit of [0.80-1.25].

Table 9A Bupropion Mean Plasma Concentrations (ng/mL) Single-Dose Fasting Bioequivalence Study

Test Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	32	0.000	0.000	0.000	0.000
Hour1.50	32	1.867	3.487	0.000	15.800
Hour3	32	19.993	14.723	1.200	50.300
Hour4	32	38.143	20.763	6.090	85.200
Hour5	32	58.134	23.973	18.400	110.000
Hour6	32	46.325	21.202	13.000	95.800
Hour7	32	37.375	15.724	11.500	76.500
Hour8	32	32.569	13.588	11.000	60.800
Hour10	32	22.459	9.544	4.570	42.400
Hour12	32	18.521	7.773	4.300	34.400
Hour14	32	14.565	6.097	0.000	24.800
Hour24	32	6.513	2.788	1.900	13.100
Hour36	32	3.442	1.570	0.000	6.440
Hour48	32	2.597	1.477	0.000	5.770
Hour72	32	1.394	1.125	0.000	3.890
Hour96	32	0.708	0.887	0.000	2.670
Hour120	32	0.395	0.657	0.000	1.830
Hour144	32	0.174	0.473	0.000	1.590

Reference Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	32	0.000	0.000	0.000	0.000
Hour1.50	32	1.544	2.680	0.000	11.900
Hour3	32	22.193	17.855	0.000	70.500
Hour4	32	37.465	19.808	6.910	67.900
Hour5	32	51.003	20.574	15.500	92.100
Hour6	32	42.016	16.956	14.400	84.100
Hour7	32	33.450	12.745	13.600	69.900
Hour8	32	27.583	10.515	8.050	57.800
Hour10	32	21.601	7.394	8.370	35.900
Hour12	32	19.480	6.993	8.360	33.000
Hour14	32	14.925	5.755	5.640	24.400
Hour24	32	6.812	2.613	1.930	11.400
Hour36	32	3.590	2.218	0.000	10.000
Hour48	32	2.552	1.350	0.000	5.640
Hour72	32	1.483	1.187	0.000	4.360
Hour96	32	0.729	0.971	0.000	3.280
Hour120	32	0.401	0.712	0.000	2.440
Hour144	32	0.167	0.463	0.000	1.800

Table 9B Hydroxybupropion Mean Plasma Concentrations (ng/mL) Single-Dose Fasting Bioequivalence Study

Test Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	32	0.000	0.000	0.000	0.000
Hour1.50	32	6.910	13.535	0.000	55.900
Hour3	32	60.873	54.258	0.000	214.000
Hour4	32	118.006	66.636	17.200	254.000
Hour5	32	166.563	73.900	31.300	306.000
Hour6	32	180.653	77.330	43.300	340.000
Hour7	32	187.591	77.287	50.500	330.000
Hour8	32	197.872	84.232	59.400	393.000
Hour10	32	203.816	89.040	68.000	446.000
Hour12	32	193.228	82.549	61.000	385.000
Hour14	32	202.553	81.737	53.500	385.000
Hour24	32	194.525	80.843	70.500	410.000
Hour36	32	121.000	53.031	0.000	281.000
Hour48	32	92.966	35.286	40.900	181.000
Hour72	32	47.941	22.881	15.500	103.000
Hour96	32	24.518	15.319	6.370	62.100
Hour120	32	12.916	10.580	0.000	37.100
Hour144	32	6.180	8.283	0.000	29.300

Reference Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	32	0.000	0.000	0.000	0.000
Hour1.50	32	3.651	6.594	0.000	22.800
Hour3	32	58.006	47.969	0.000	142.000
Hour4	32	112.188	64.722	20.800	219.000
Hour5	32	161.191	74.303	39.800	317.000
Hour6	32	174.372	75.425	42.500	342.000
Hour7	32	179.763	75.276	43.600	374.000
Hour8	32	185.875	77.655	40.600	409.000
Hour10	32	196.766	82.464	39.400	425.000
Hour12	32	195.588	79.494	38.800	384.000
Hour14	32	200.381	75.072	36.700	383.000
Hour24	32	198.694	76.002	52.600	358.000
Hour36	32	126.069	59.301	0.000	246.000
Hour48	32	100.769	45.469	29.900	246.000
Hour72	32	53.978	29.562	17.000	140.000
Hour96	32	27.432	18.973	6.030	75.900
Hour120	32	13.449	14.149	0.000	57.600
Hour144	32	7.155	8.755	0.000	34.300

Figure 1A

Bupropion Mean Plasma Concentrations
Single Dose Fasting Study

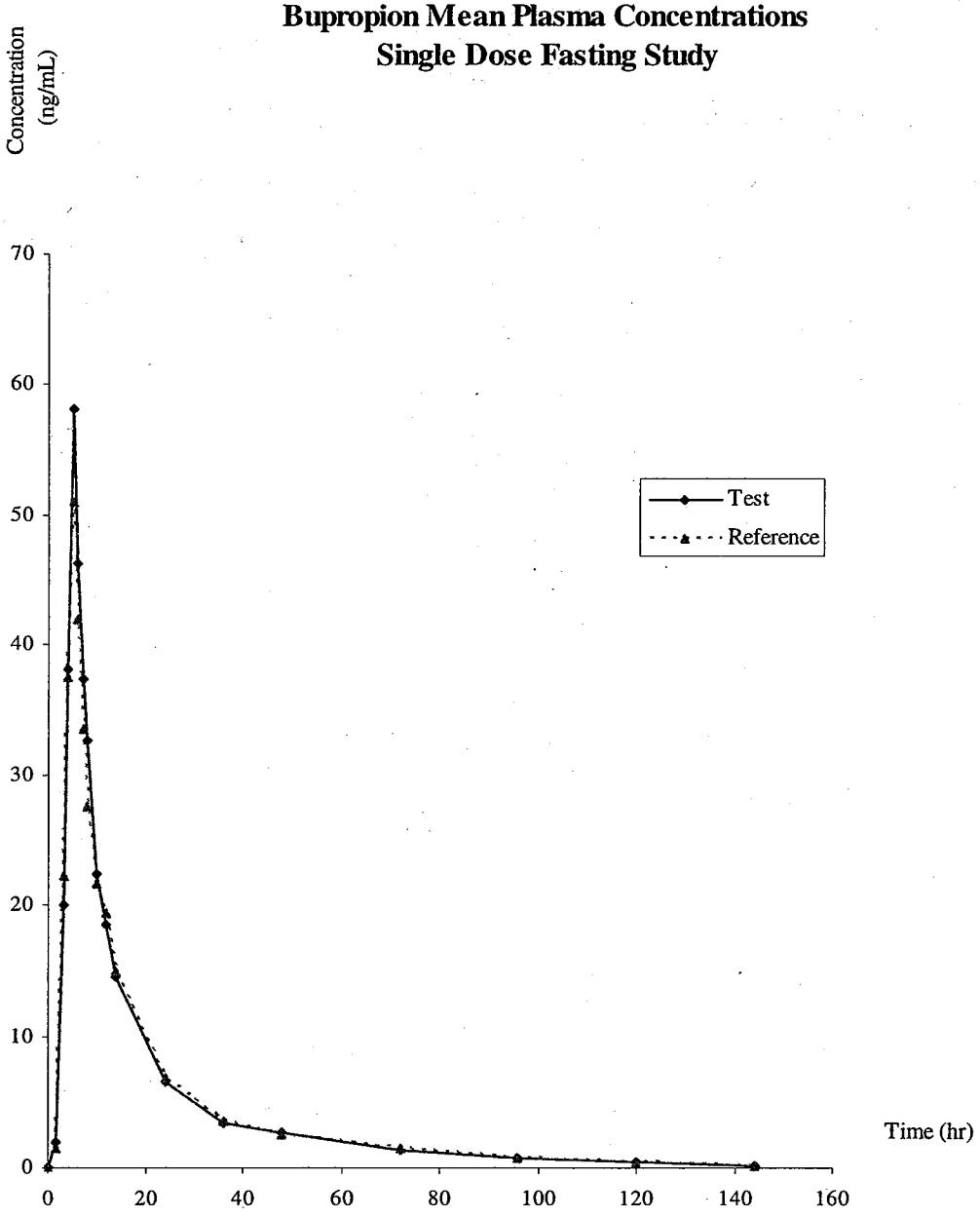
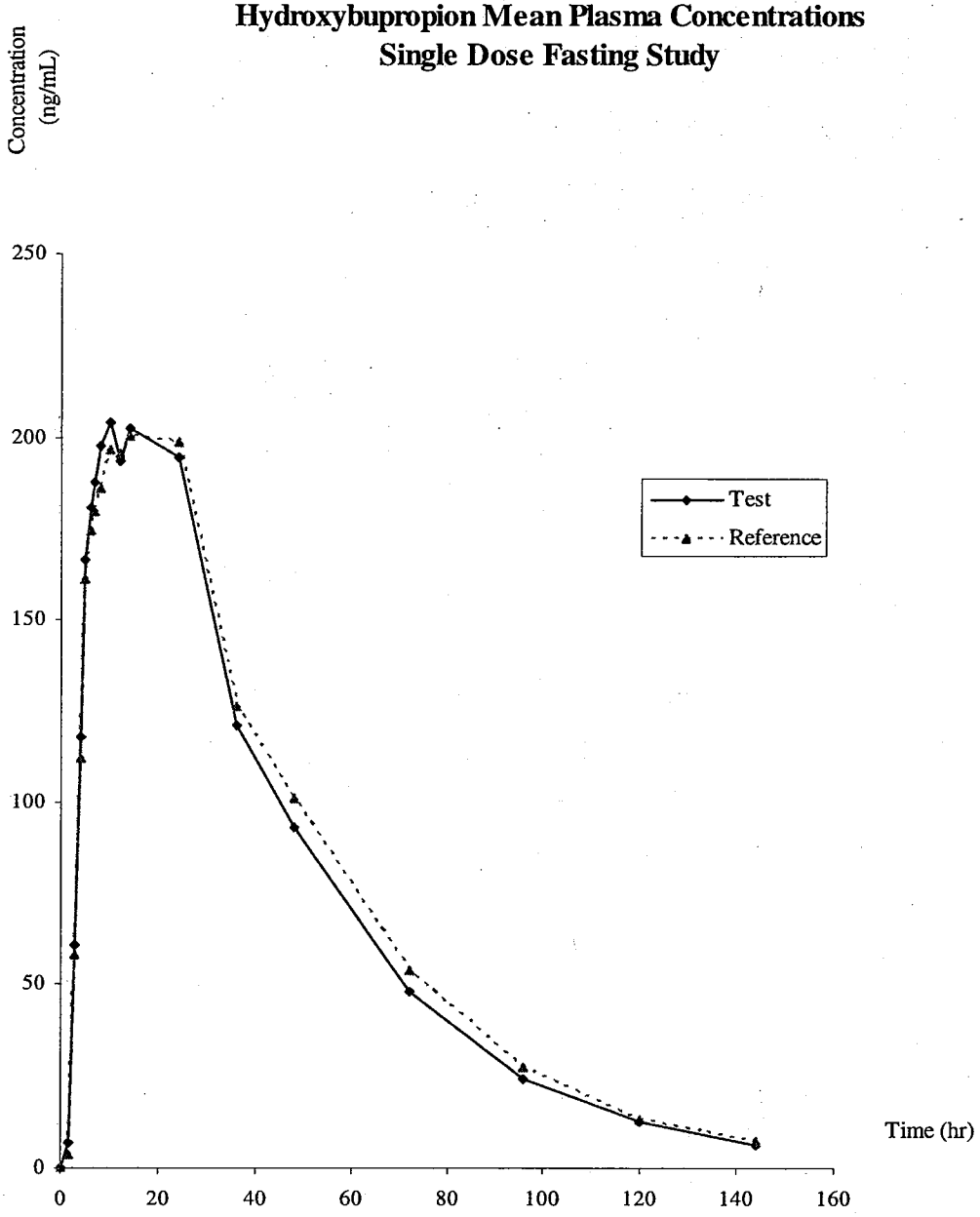


Figure 1B

Hydroxybupropion Mean Plasma Concentrations
Single Dose Fasting Study



2. Single-dose Fed Bioequivalence Study

Study Information	
Study Number	04100
Study Title	A Randomized, Two-Way Crossover, Single-Dose, Open-Label Study to Evaluate the 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 32 Fed, Healthy, Adult Subjects
Clinical Site	Gateway Medical Research, St. Charles, MO
Principal Investigator	Irwin Plisco, M.D.
Study/Dosing Dates	Period I: 06/27/03; Period II: 07/18/04
Analytical Site	(b) (4)
Analytical Director	(b) (6) Ph.D.
Analysis Dates	08/01/04-08/04/04
Storage Period (no. of days from first sample to final analysis)	38 days

Treatment ID	A	B
Test or Reference	Bupropion HCl ER Tablets	Wellbutrin XL® Tablets
Product Name	Anchen Pharmaceuticals	SmithKline Beecham
Manufacturer	P000104-30	04B044P
Batch/Lot No.	05/19/04	
Manufacture Date		06/05
Expiration Date	150 mg	150 mg
Strength	ER Tablets	ER Tablets
Dosage Form	(b) (4)	
Batch Size	101.2%	99.6%
Potency	100.9%(RSD=0.9%)	Not provided
Content Uniformity	See Appendix Section B	
Formulation	1x150 mg	1x150 mg
Dose Administered	Oral	
Route of Administration	Bupropion HCl ER Tablets	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	21 days
Randomization Scheme	Yes
Blood Sampling Times	0, 1.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 24, 36, 48, 72, 96, 120 and 144 hours postdose
Blood Volume Collected/Sample	7 mL/sample
Blood Sample Processing/Storage	Samples were collected in evacuated tubes containing EDTA. The samples were cooled in an ice bath until centrifuged and harvested for plasma. The plasma aliquots were transferred to a polypropylene tube containing 25 uL of 4 N HCl, and stored at -20°C until assayed.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 11
Length of Fasting*	From 10 hours predose until 4 hours postdose
Length of Confinement	Approximately 10 hours predose until 24 hours postdose
Safety Monitoring	Blood pressure and pulse were measured at predose, 2, 3, 8 and 24 hours postdose.

***NOTE:** At 30 minutes prior to dosing, the subjects were given a standardized breakfast consisting of two egg fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes, and eight ounces of whole milk. (970 total calories; 578.7 fat calories; 127.6 protein calories; 264 carbohydrate calories)

Table 10 Demographics of Study Subjects (N=31)

Age		Weight, lbs		Age Groups		Gender		Race	
				Range		Sex		Category	
				<18	0			Caucasian	14(M) 9(F)
Mean	28.7 (M) 29.4 (F)	Mean	191.7 (M) 171.1 (F)	18-40	15(M) 13 (F)	Male	17	Afr. Amer.	2 (M) 3 (F)
SD	10.7 (M) 6.9 (F)	SD	36.6 (M) 35.8 (F)	41-64	2(M) 1(F)	Female	14	Hispanic	2 (M)
Range	19-57 (M) 21-44 (F)	Range	68-77(M) 119-248(F)	65-75	0			Asian	
				>75	0			Others	

NOTE: M: Male; F: Female

Study Results

Table 11 Dropout Information

Subject No	24
Reason	Adverse event (headache, chills and shortness of breath)
Period	II
Replacement	No

Was there a difference in side effects for the test versus the reference? All adverse events were reported during the Reference treatment. The severity of the adverse events ranged from mild to moderate.

Table 12 Study Adverse Events

Adverse Event Description	**# in Test Group**	**# in Reference Group**
Headache		**2**
Lightheadedness		**1**
Sore throat		**1**
Congestion		**2**
Chills		**1**
Shortness of breath		**1**
Agitation		**1**
Sleeplessness		**1**
Total:		**10**

Was there a difference in protocol deviations for the test versus the reference? No.

Protocol Deviations There were no significant protocol deviations that might have compromised the integrity of the study. Any significant blood sampling deviations were corrected during the creation of PK data.

Table 13 Assay Validation – Within Study

	Bupropion			Hydroxybupropion		
QC Conc. (ng/mL)	2.00 (n=32)	20.0 (n=32)	160 (n=32)	10.00 (n=32)	100.0 (n=32)	800 (n=32)
Inter day Precision (%CV)	7.97	4.72	5.36	7.28	4.85	4.29
Inter day Accuracy (%)	104	92.5	95.0	102	100	102
Cal. Standards Conc. (ng/mL)	1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 200.0			5.00, 10.0, 25.0, 50.0, 100, 250, 1000		
Inter day Precision (%CV)	2.31-8.08			1.48-5.87		
Inter day Accuracy (%)	95.0-110			94.0-103.0		

Linearity Range (range of R^2 values)	0.9965-0.9998	0.9984-0.9999

Chromatograms: Any interfering peaks? No.

Table 14 SOP's dealing with analytical repeats

None was submitted. Acceptance criteria were included in the analytical report.

SOP No.	Date of SOP	SOP Title
N/A	N/A	N/A

There was no PK repeat sample.

Comments on Within-Study Validation: Acceptable.

Conclusion: Analytical method is acceptable.

Table 15 Arithmetic Mean Pharmacokinetic Parameters

Bupropion

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	Ng.hr/mL	863.7	29	876.6	32	0.98
AUC∞	Ng.hr/mL	938.6	31	934.7	31	1.00
Cmax	Ng/mL	63.14	33	64.93	38	0.97
Tmax	Hrs	6.45	29	7.23	32	0.89
T1/2	Hrs	34.79	51	32.83	43	1.06
kel	Hrs^{-1}	0.0249	51	0.0251	42	0.99

Hydroxybupropion

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	Ng.hr/mL	13,266	52	13,941	58	0.95
AUC∞	Ng.hr/mL	13,827	53	14,498	58	0.95
Cmax	Ng/mL	271.4	47	276.3	49	0.98
Tmax	Hrs	16.39	34	17.03	34	0.96
T1/2	Hrs	26.78	24	27.04	24	0.99
kel	Hrs^{-1}	0.0273	24	0.0270	24	1.01

Table 16 Geometric Means and 90% Confidence Intervals (N=31)

Bupropion

Parameter	Test	Reference	T/R	90% CI
AUC0-t	828.4	833.4	0.99	95.0-104.0
AUC∞	898.1	892.1	1.01	95.8-105.8
Cmax	60.05	60.79	0.99	93.2-104.7

Hydroxybupropion

Parameter	Test	Reference	T/R	90% CI
AUC0-t	11,780	12,155	0.97	91.6-102.6
AUC∞	12,259	12,619	0.97	91.9-102.7
Cmax	243.8	246.3	0.99	94.1-104.1

Table 17 Additional Study Information

Bupropion

Root mean square error, AUC0-t	0.104169
Root mean square error, AUC∞	0.114898
Root mean square error, Cmax	0.134590
Kel and AUC∞ determined for how many subjects?	All
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as Cmax	0
Were the subjects dosed as more than one group?	No

Hydroxybupropion

Root mean square error, AUC0-t	0.130973
Root mean square error, AUC∞	0.128917
Root mean square error, Cmax	0.116348
Kel and AUC∞ determined for how many subjects?	All
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as Cmax	0
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic and Statistical Analysis: The analysis is acceptable.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: The single-dose nonfasting bioequivalence study is acceptable. The 90% confidence interval for lnAUC(0-T), lnAUC(0-Infinity) and lnCmax of bupropion and hydroxybupropion was within the acceptable limit of [0.80-1.25].

Table 18A Bupropion Mean Plasma Concentrations, Single-Dose Fed Study

Test Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	31	0.000	0.000	0.000	0.000
Hour1.50	31	0.053	0.295	0.000	1.640
Hour3	31	5.766	7.406	0.000	39.400
Hour4	31	20.562	14.106	1.510	57.400
Hour5	31	53.626	16.978	18.400	92.800
Hour6	31	55.274	23.322	20.200	129.000
Hour7	31	50.687	21.641	17.800	106.000
Hour8	31	49.077	15.829	15.900	82.500
Hour10	31	39.952	12.221	11.500	64.400
Hour12	31	32.984	13.210	11.500	65.000
Hour14	31	25.241	9.578	7.780	48.800
Hour24	31	9.640	3.379	4.080	20.400
Hour36	31	5.055	1.776	0.000	8.890
Hour48	31	3.724	1.203	1.890	6.730
Hour72	31	1.877	0.986	0.000	3.890
Hour96	31	1.083	0.848	0.000	2.640
Hour120	31	0.540	0.860	0.000	3.720
Hour144	31	0.195	0.451	0.000	1.260

Reference Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	31	0.000	0.000	0.000	0.000
Hour1.50	31	0.034	0.187	0.000	1.040
Hour3	31	7.644	6.760	0.000	24.600
Hour4	31	26.322	19.721	2.450	76.200
Hour5	31	54.865	26.572	6.020	114.000
Hour6	31	52.148	25.125	18.200	113.000
Hour7	31	48.716	21.230	16.400	107.000
Hour8	31	49.161	23.179	13.600	142.000
Hour10	31	42.006	17.801	9.900	104.000
Hour12	31	34.925	13.473	7.760	66.400
Hour14	31	23.808	8.215	7.280	47.400
Hour24	31	9.902	3.920	4.360	19.600
Hour36	31	5.178	1.505	2.110	8.720
Hour48	31	3.674	1.342	1.650	6.660
Hour72	31	2.043	1.000	0.000	3.780
Hour96	31	1.086	0.886	0.000	2.420
Hour120	31	0.486	0.676	0.000	1.700
Hour144	31	0.216	0.449	0.000	1.200

Table 19B Hydroxybupropion Mean Plasma Concentrations, Single-Dose Fed Study

Test Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	31	0.000	0.000	0.000	0.000
Hour1.50	31	0.000	0.000	0.000	0.000
Hour3	31	8.643	10.139	0.000	36.000
Hour4	31	43.632	36.278	0.000	139.000
Hour5	31	97.277	50.357	27.100	214.000
Hour6	31	135.406	75.056	33.500	369.000
Hour7	31	170.239	88.712	36.400	398.000
Hour8	31	200.197	95.910	49.800	461.000
Hour10	31	238.168	115.890	61.600	531.000
Hour12	31	236.587	118.563	82.200	601.000
Hour14	31	258.239	125.997	83.700	611.000
Hour24	31	249.735	124.776	94.800	640.000
Hour36	31	161.784	91.356	0.000	452.000
Hour48	31	129.261	76.594	58.600	389.000
Hour72	31	62.110	41.407	0.000	180.000
Hour96	31	38.422	30.016	9.870	128.000
Hour120	31	20.524	18.115	0.000	80.000
Hour144	31	10.428	12.359	0.000	46.400

Reference Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	31	0.000	0.000	0.000	0.000
Hour1.50	31	0.000	0.000	0.000	0.000
Hour3	31	14.344	20.219	0.000	87.300
Hour4	31	53.649	45.926	0.000	199.000
Hour5	31	104.152	66.104	17.200	292.000
Hour6	31	134.419	78.074	35.900	335.000
Hour7	31	164.529	86.768	49.000	402.000
Hour8	31	197.539	103.240	75.400	552.000
Hour10	31	239.261	131.098	70.700	718.000
Hour12	31	247.706	129.988	80.800	703.000
Hour14	31	261.923	135.818	84.000	741.000
Hour24	31	255.581	130.792	78.500	716.000
Hour36	31	176.016	94.641	61.400	533.000
Hour48	31	134.326	85.372	42.100	455.000
Hour72	31	71.455	53.594	0.000	261.000
Hour96	31	39.025	30.890	8.670	143.000
Hour120	31	21.002	18.884	0.000	81.700
Hour144	31	11.295	12.505	0.000	51.400

Figure 2A

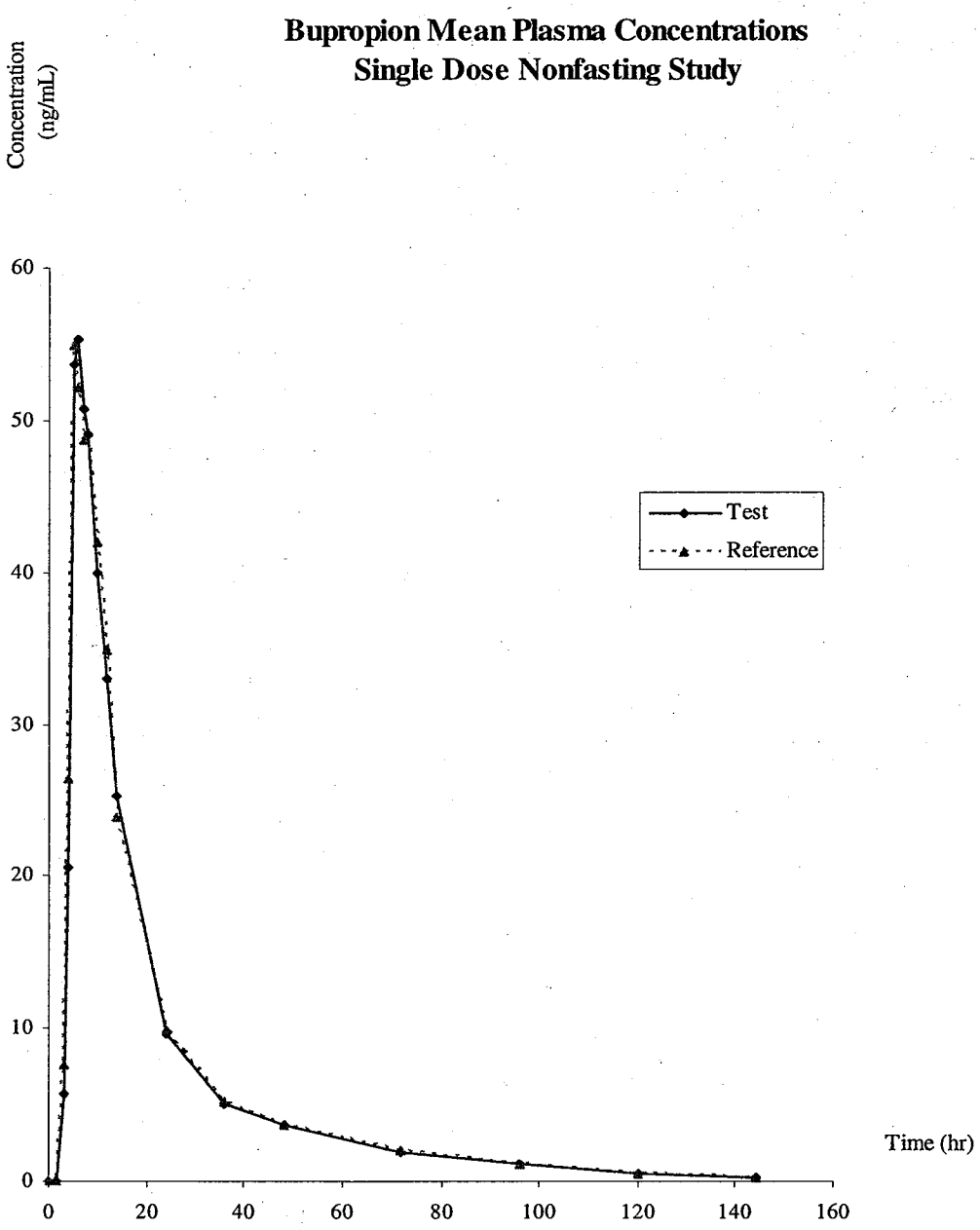
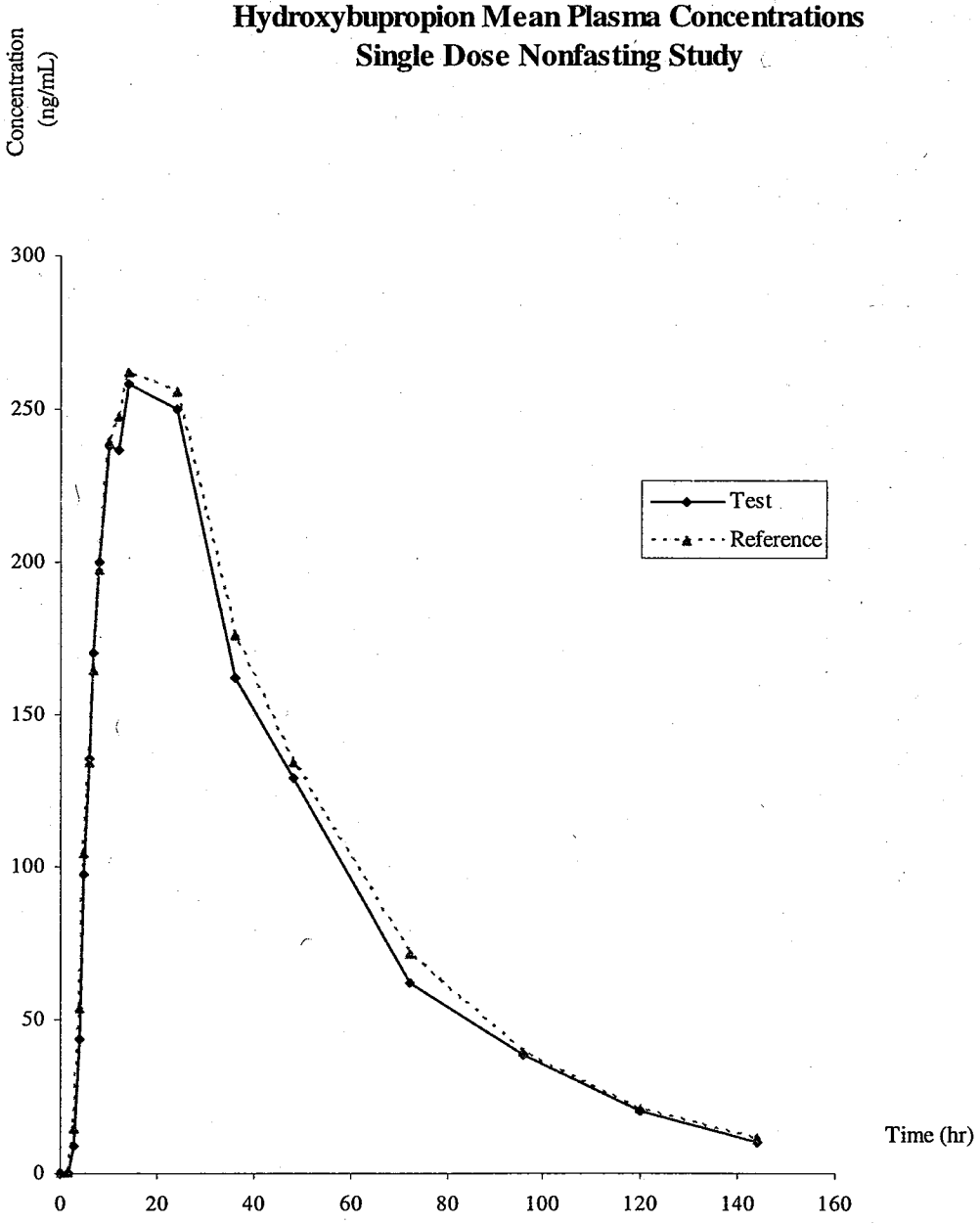

Bupropion Mean Plasma Concentrations
Single Dose Nonfasting Study
Concentration (ng/mL)
60
50
40
30
20
10
0
0
20
40
60
80
100
120
140
160
Time (hr)
Test
Reference

Figure 2B

Hydroxybupropion Mean Plasma Concentrations
Single Dose Nonfasting Study



B. Dissolution Data:

Testing Conditions:

From the dissolution review of the original submission dated September 21, 2004, v:\firmsam\anchen\ltrs&rev\77284d0904.doc:

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range)						Study Report Location
					60 min	120 min	240 min	360 min	480 min	960 min	
Not Provided (N.P.)	04B044P / GlaxoSmithKline K-32370	150 mg E.R. Tab	Dissolution: Apparatus 1 (USP) Speed of Rotation: 75 rpm Medium: 0.1 N HCl at 37°C	12	0 (b) (4)	2 (b) (4)	23	49	73	95 (b) (4)	V 1.1 p. 40
N.P.	P000104 / Anchen	150 mg E.R. Tab		12	0 (b) (4)	2 (b) (4)	27	52	70	98 (b) (4)	
N.P.	03K056P/ GlaxoSmithKline K-32369	300 mg E.R. Tab		12	0 (b) (4)	3 (b) (4)	29	51	70	95 (b) (4)	V 1.1 p. 43
N.P.	P000204/ Anchen	300 mg E.R. Tab		12	0 (b) (4)	2 (b) (4)	22	42	57	90 (b) (4)	

Similarity Factor F2 between the 150 mg of the test and reference products: 77.20

Similarity Factor F2 between the 300 mg of the test and reference products: 56.46

Similarity Factor F2 between the 150 mg and 300 mg strengths of the test product: 55.43

Source of Method	FDA
Medium	Water
Volume (mL)	900 mL
USP Apparatus type	II(paddle)
Rotation (rpm)	50 rpm

Table 19

Sampling Time (hours)	Test Product, Strength 300 mg Lot No. P000204-30			Reference Product, Strength 300 mg Lot No. 05B063P		
	Mean	SD	Range	Mean	SD	Range
1	1	1.0	(b) (4)	0	0	(b) (4)
2	3	1.8		1	0	
3	14	4.0		1	0.7	
4	28	5.0		5	1.2	
5	41	4.8		9	1.0	
6	52	4.3		14	1.4	
7	61	4.2		17	1.6	
8	69	4.1		22	1.8	
9	76	3.7		26	2.2	
10	82	3.1		30	2.5	
11	87	2.6		35	3.0	
16	99	1.6		56	4.1	

Similarity Factor F2 (between the test and reference products): 33.31

Table 20

Sampling Time (hours)	Test Product, Strength 150 mg Lot No. P000104-30			Reference Product, Strength 150 mg Lot No. 04B044P		
	Mean	SD	Range	Mean	SD	Range
1	1	1.0	(b) (4)	0	0	(b) (4)
2	4	2.2		1	0.5	
3	17	4.3		1	0.7	
4	35	4.9		3	1.6	
5	51	5.2		7	2.8	
6	63	4.5		11	3.4	
7	74	3.9		15	2.6	
8	82	3.5		19	2.6	
9	89	2.9		23	2.8	
10	94	2.5		27	2.9	
11	97	2.0		31	3.4	
16	97	1.4		51	5.4	

Similarity Factor F2 (between the test and reference products): 24.50

Similarity Factor F2 between the 150 mg and 300 mg strengths of the test product: 57.33

Source of Method	Varying pH media
Medium	0.1 N HCl
Volume (mL)	900 mL
USP Apparatus type	II(paddle)
Rotation (rpm)	50 rpm

Table 21

Sampling Time (hours)	Test Product, Strength 300 mg Lot No. P000204-30			Reference Product, Strength 300 mg Lot No. 05B063P		
	Mean	SD	Range	Mean	SD	Range
1	0	0	(b) (4)	0	0.4	(b) (4)
2	1	0.9		4	2.6	
3	6	3.1		17	3.5	
4	15	4.7		31	3.7	
5	25	5.2		44	3.5	
6	34	5.4		55	3.6	
7	42	5.1		65	3.7	
8	50	5.0		75	3.8	
9	56	4.9		82	3.8	
10	62	4.6		88	2.9	
16	86	2.9		98	1.5	

Similarity Factor F2: 44.07

Table 22

Sampling Time (hours)	Test Product, Strength 150 mg Lot No. P000104-30			Reference Product, Strength 150 mg Lot No. 04B044P		
	Mean	SD	Range	Mean	SD	Range
1	0	0	(b) (4)	0	0	(b) (4)
2	1	0.8		1	1.1	
3	8	3.5		8	5.5	
4	21	4.5		20	7.5	
5	33	4.7		34	7.1	
6	45	4.2		45	7.5	
7	54	4.0		57	7.2	
8	63	3.6		67	5.8	
9	70	3.2		76	4.0	
10	76	2.8		82	2.8	
11	81	2.4		86	2.1	
16	94	0.8		93	1.4	

Similarity Factor F2: 92.47

Source of Method	Varying pH media
Medium	pH 4.5
Volume (mL)	900 mL
USP Apparatus type	II(paddle)
Rotation (rpm)	50 rpm

Table 23

Sampling Time (hours)	Test Product, Strength 300 mg Lot No. P000204-30			Reference Product, Strength 300 mg Lot No. 05B063P		
	Mean	SD	Range	Mean	SD	Range
1	0	0	(b) (4)	0	0	(b) (4)
2	4	1.8		0	0.4	
3	16	3.7		1	0	
4	30	3.9		1	0.9	
5	42	3.9		4	1.7	
6	53	3.6		7	2.0	
7	62	3.5		11	1.9	
8	71	3.1		14	2.0	
9	77	2.8		18	2.4	
10	83	2.4		21	2.9	
11	88	2.2		25	3.4	
16	97	1.0		71	7.6	

Similarity Factor F2: 29.52

Table 24

Sampling Time (hours)	Test Product, Strength 150 mg Lot No. P000104-30			Reference Product, Strength 150 mg Lot No. 04B044P		
	Mean	SD	Range	Mean	SD	Range
1	0	0.5	(b) (4)	0	0	(b) (4)
2	4	2.2		0	0	
3	19	4.4		1	0	
4	37	4.5		1	0.4	
5	53	4.0		3	2.0	
6	67	3.7		6	3.2	
7	77	2.9		11	3.6	
8	85	2.4		14	3.6	
9	91	2.2		18	3.3	
16	99	1.9		75	5.5	

Similarity Factor F2: 21.68

Source of Method	Varying pH media
Medium	pH 6.8
Volume (mL)	900 mL
USP Apparatus type	II(paddle)
Rotation (rpm)	50 rpm

Table 25

Sampling Time (hours)	Test Product, Strength 300 mg Lot No. P000204-30			Reference Product, Strength 300 mg Lot No. 05B063P		
	Mean	SD	Range	Mean	SD	Range
1	13	0.7	(b) (4)	16	1.1	(b) (4)
2	30	1.2		34	0.9	
3	42	1.6		48	1.3	
4	51	1.9		57	1.4	
5	58	2.2		66	1.7	
6	65	2.4		72	1.7	
7	71	2.7		78	1.8	
8	76	2.8		83	1.9	
9	80	2.9		87	1.9	
10	83	2.8		89	2.0	
11	86	2.2		91	2.1	
16	91	1.2		95	2.2	

Similarity Factor F2: 63.15

Table 26

Sampling Time (hours)	Test Product, Strength 150 mg Lot No. P000104-30			Reference Product, Strength 150 mg Lot No. 04B044P		
	Mean	SD	Range	Mean	SD	Range
1	18	1.7	(b) (4)	18	2.0	(b) (4)
2	40	2.3		37	2.0	
3	55	2.2		51	1.9	
4	66	2.9		62	1.6	
5	76	3.3		69	1.5	
6	81	2.8		76	1.8	
7	87	2.5		81	1.8	
16	93	1.6		92	2.1	

Similarity Factor F2: 66.16

Following this page, 2 pages withheld in full-(b)(4) CCI/TS (formulation data)

Comments on Formulations: The same inactive ingredients are used in the 150 mg and 300 mg formulations and the ingredients are within the IIG approved ranges. The ingredients of the (b) (4) tablets of the 150 mg and 300 mg formulations are proportional. The total difference in the amount of the ingredients in the (b) (4) (b) (4) between the two strengths is (b) (4) %. The difference is within the SUPAC-specified change of release controlling excipients for Level 1 and "*unlikely to have any detectable impact on formulation quality and performance*" per the SUPAC guidance for MR products. The formulations of the two strengths are considered proportionally similar and **acceptable.**

C. SAS Output

1. Fasting Study:

Bupropion

77284FASTBU.txt

Hydroxybupropion

77284FASTHYDROXY
.txt

2. Nonfasting Study:

Bupropion

77284FEDBU.txt

Hydroxybupropion

77284FEDHYDROXY.
txt

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-284 APPLICANT: Anchen Pharmaceuticals

DRUG PRODUCT: Bupropion HCl Extended Release Tablets, 150 mg & 300 mg

The Division of Bioequivalence (DBE) has completed its review and has the following comments:

We agree that the dissolution testing for the test product should be conducted using your proposed dissolution 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.

However, based on the dissolution data submitted, the DBE recommends the following specifications:

	(b) (4)
2 hours:	
4 hours:	
8 hours:	
16 hours:	%(Q)

Since the above specifications are different from those proposed by you, please provide your acknowledgement of the DBE's proposed specifications.

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 77-284
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ SNerurkar

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ SNerurkar
HFD-617/ A. Sigler
HFD-650/ D. Conner 6/21/05

6/21/05

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BIOEQUIVALENCE - ACCEPTABLE
DISSOLUTION - **INCOMPLETE**

Submission date: 09-21-04
& 05-16-05

1. FASTING STUDY (STF) — Strength: 150 mg
   Clinical: Gateway Medical Research — **Outcome: AC**
   Analytical: (b)(4)

2. NONFASTING STUDY (STP) — Strength: 150 mg
   Clinical: Gateway Medical Research — **Outcome: AC**
   Analytical: (b)(4)

3. DISSOLUTION WAIVER (DIW) — Strength: 300 mg
   Outcome: AC

4. DISSOLUTION AMENDMENT (OTH) — **Strengths: 150 mg & 300 mg**
Outcome: IC

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable **NC** - No credit

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-284
Drug Product Name	Bupropion HCl ER Tablets
Strength	150 mg & 300 mg
Applicant Name	Anchen Pharmaceutical
Address	Irvine, CA
Submission Date(s)	September 21, 2004
Amendment Date(s)	May 16, 2005
Reviewer	Hoainhon Nguyen
First Generic	Yes
File Location	**V:\firmsam\anchen\ltrs&rev\77284n0904.doc**

I. Executive Summary

The firm has submitted a single-dose, 2-way crossover fasting bioequivalence study and a single-dose, 2-way crossover nonfasting bioequivalence study comparing the test product, Bupropion HCl Extended Release Tablets, 150 mg, with the RLD product, SmithKline Beecham's Wellbutrin XL® (bupropion HCl) Tablets, 150 mg. The fasting study was performed in 17 normal males and 15 normal females at a dose of 1x150 mg and resulted in acceptable data (point-estimate, 90% CI) that demonstrate BE in the fasted state (Bupropion: AUCt 1.02, 93.5-111.3; AUCinf 1.05, 98.3-112.8; Cmax 1.10, 99.1-122.6. Hydroxybupropion: AUCt 0.97, 88.9-106.5; AUCinf 0.97, 89.1-106.4; Cmax 1.01, 91.6-110.5). The nonfasting study was performed in 17 normal males and 14 normal females at a dose of 1x150 mg and resulted in acceptable data (point-estimate, 90% CI) that demonstrate BE in the fed state (Bupropion: AUCt 0.99, 95.0-104.0; AUCinf 1.01, 95.8-105.8; Cmax 0.99, 93.2-104.7. Hydroxybupropion: AUCt 0.97, 91.6-102.6; AUCinf 0.97, 91.9-102.7; Cmax 0.99, 94.1-104.1).

The comparative dissolution data comparing both strengths of the test product with the reference product were acceptable. The firm's proposed dissolution method was acceptable. The firm's proposed dissolution specifications are acceptable.

The formulations of the 150 mg and 300 mg strengths of the test product are proportionally similar. The waiver request for the 300 mg strength is granted.

The application is **complete** with no further bioequivalence deficiency at this time.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Bupropion HCl ER Tablets, 150 mg & 300 mg
Reference Product	Wellbutrin XL® (bupropion HCl) Tablets, 150 mg & 300 mg
RLD Manufacturer	SmithKline Beecham
NDA No.	21-515
RLD Approval Date	08/28/2003
Indication	indicated for the treatment of major depressive disorder

B. PK/PD Information (Reference: PDR 2005)

Bioavailability	Not yet determined
Food Effect	Food did not affect the C_{max} or AUC of bupropion.
Tmax	5 hours for bupropion; approximately 6 hours for the three active metabolites.
Metabolism	Bupropion is extensively metabolized in humans. There are three active metabolites: hydroxybupropion and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via hydroxylation of the *tert* -butyl group of bupropion and/or reduction of the carbonyl group. 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.
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. The fraction of the oral dose of bupropion excreted unchanged was only 0.5%.
Half-life	21 hours for bupropion; 20 hours for hydroxybupropion, 37 hours for threohydrobupropion, and 33 hours for erythrohydrobupropion

Relevant OGD or DBE History

1. Prior to the issuance of the general BA/BE guidance in October 2000, the DBE had recommended the following for the drug product: a single-dose fasting bioequivalence study, a single-dose nonfasting bioequivalence study and a multiple-dose bioequivalence study. Bupropion, hydroxybupropion and a combination of threohydrobupropion and erythrobupropion were measured for the studies. The sampling schedule was generally up to 168 hours or 192 hours for single-dose studies. The practice was reflected in the reviews of the following documents: Protocol #98-021 ((b) (4); 07/20/98), Control Documents #98-200 ((b) (4); 05/21/98) and 99-009 (Apotex; 01/06/99), ANDA (b) (4) ((b) (4); 06/17/99), ANDA (b) (4) ((b) (4); 09/10/99), ANDA #75-932 (Eon; 07/26/2000) and ANDA (; 06/30/2000).

2. Control Document #97-285 ((b) (4); 10/02/97) and 98-018 ((b) (4); 01/21/98): The DBE recommended the following: *" Wellbutrin SR® and Zyban® are considered separate reference listed drug products and cannot be considered to be therapeutically equivalent to each other because the products have different labeled indications. However, an in vivo bioequivalence study conducted on Wellbutrin SR® (Bupropion Hydrochloride Extended-release Tablets, 150 mg) may be referenced to support a request for a waiver of evidence of in vivo bioequivalence for Zyban® (Bupropion Hydrochloride Extended-release Tablets, 150 mg) or vice versa."* In addition, *"A separate abbreviated new drug application is required for each of these reference listed drug products."*

The above recommendation was applied to the waiver request of the following ANDAs: # (b) (4) ((b) (4); 08/10/99), ANDA # (b) (4) ((b) (4); 06/30/2000) and ANDA #75-913 (Impax; 06/22/2000).

3. Control Document #01-068 ((b) (4) 02/06/2001): The DBE had revised the recommendations concerning the bioequivalence requirements for the drug product based on the general BA/BE guidance (issued 10/2000). A single dose, replicate, fasting bioequivalence study on the highest strength, and a single dose, two way crossover, nonfasting bioequivalence study on the same strength were recommended. Measurement of bupropion and hydroxybupropion were requested but only bupropion data should be subject to the confidence interval criteria.

4. Control Document #01-149 ((b) (4) 03/08/2001): As the general BA/BE guidance was revised, the DBE revised its recommendations accordingly: A single dose, **nonreplicate**, fasting bioequivalence study on the highest strength, 150 mg, and a single dose, two way crossover, nonfasting bioequivalence study on the same strength were recommended. Measurement of bupropion and hydroxybupropion which is formed presystemically were requested. A biowaiver may be granted for the lower strength, 100 mg, based on formulation proportionality, comparable dissolution profiles between strengths and acceptable bioequivalence studies on the 150 mg.

5. The RLD product, Wellbutrin XL® Tablet, 150 mg and 300 mg, (NDA 21-515) were approved on 08/28/03 to provide improved once-daily formulations for patients who have been treated with Wellbutrin SR® Tablet, which was approved (06/14/02). The two formulations and their release-controlling technologies are different. NDA 21-515 was approved based on a confirmatory bioequivalence study comparing this formulation with Wellbutrin® Tablets (immediate-release formulation). Since the 150 mg and 300 mg strengths are not formulation proportional, a steady-state bioequivalence study comparing the two strengths using 300 mg dosage was also submitted for NDA 21-515. It should be noted that Wellbutrin SR® Tablet product was approved based on a bioequivalence study comparing this formulation with Wellbutrin® Tablets (immediate-release formulation) also. The interchangeability of Wellbutrin® products is addressed in the labeling of Wellbutrin XL®. According to this labeling, *"When switching patients from WELLBUTRIN Tablets to WELLBUTRIN XL or from WELLBUTRIN SR Sustained-Release Tablets to WELLBUTRIN XL, give the same total daily dose when possible. Patients who are currently being treated with WELLBUTRIN Tablets at 300 mg/day (for example, 100 mg 3 times a day) may be switched to WELLBUTRIN XL 300 mg once daily. Patients who are currently being treated with WELLBUTRIN SR Sustained-Release Tablets at 300 mg/day (for example, 150 mg twice daily) may be switched to WELLBUTRIN XL 300 mg once daily."*

The labeling of Wellbutrin XL® Tablets also recommends that *"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."* The 150 mg strength, therefore, is designated in the Orange Book as the RLD strength. Due to the safety concern, the 300 mg strength of the generic version can be waived of *in vivo* bioequivalence testing provided that the formulation of the higher strength is proportionally similar to that of the 150 mg strength, and the dissolution profiles of the two strengths are comparable.

6. Three different dissolution methods have been recommended for different

ANDAs of bupropion HCl ER products.
Method 1: USP Apparatus II (paddle) at 50 rpm, with 900 mL of water (recommended for ANDAs #75-913, 75-914, (b) (4))
Method 2: USP Apparatus II (paddle) at 50 rpm, with 900 mL of pH 1.5 SGF (without enzyme) (recommended for ANDA # (b) (4))
Method 3: USP Apparatus I(basket) at 50 rpm, with 900 mL of 0.1 N HCl, pH 1.5 (recommended for ANDA #75-932)

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	1
Waiver requests	Yes	1
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments		

D. Pre-Study Bioanalytical Method Validation

	Parent	Metabolite
Analyte name	Bupropion	Hydroxybupropion
Internal Standard	(b) (4)	Same
Method description	LC/MS/MS	Same
QC range	1.00-160 ng/mL	5.00-800 ng/mL
Standard curve range	1.00-200 ng/mL	5.00-1000 ng/mL
Limit of quantitation	1.00 ng/L	5.00 ng/ml
Average recovery of Drug (%)	91.3%	95.0%
Average Recovery of Int. Std (%)	92.2%	Same
Intraday precision range (%CV)	1.71-7.48%	1.68-2.60%
Intraday accuracy range (%)	98.5-110%	101-113%
Interday precision range (%CV)	2.28-5.37%	2.56-4.96%
Interday accuracy range (%)	101-110%	104-110%
Bench-top stability (hrs)	6 hours	6 hours
Stock stability (days)	16 hours (RT); 94 days* (4°C)	16 hours (RT); 94 days* (4°C)
Processed stability (hrs)	48 hours	48 hours
Freeze-thaw stability (cycles)	3	3
Long-term storage stability (days)	56 days	56 days
Dilution integrity	10-fold, 98.8%	10-fold, 101%
Specificity	Yes	Yes
SOPs submitted	Yes	Yes
Bioanalytical method is acceptable	Yes	Yes
20% Chromatograms included (Y/N)	Yes	Yes
Random Selection of Serial Chrom	Yes	Yes

*Data were submitted in the amendment dated 05/16/05

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	04083
Study Design	Two-way randomized crossover
No. of subjects enrolled	32
No. of subjects completing	32
No. of subjects analyzed	32
Subjects (Normal/Patients?)	Normal healthy subjects
Sex(es) included (how many?)	Male: 17 Female: 15
Test product	Anchen's Bupropion HCl ER Tablets, 150 mg
Reference product	Wellbutrin XL® Tablets, 150 mg
Strength tested	150 mg
Dose	1x150 mg

Summary of Statistical Analysis : Bupropion (N=32) Additional Information in Appendix, Table 6 and Table 7		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.02	93.5-111.3
AUC_{∞}	1.05	98.3-112.8
C_{max}	1.10	99.1-122.6

Summary of Statistical Analysis : Hydroxybupropion (N=32) Additional Information in Appendix, Table 6 and Table 7		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	0.97	88.9-106.5
AUC_{∞}	0.97	89.1-106.4
C_{max}	1.01	91.6-110.5

Reanalysis of Study Samples Additional information in Appendix, Table 5								
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**
All samples were reassayed for analytical reasons only.								
Total								

Did use of recalculated plasma concentration data change study outcome? N/A

Comments on Fasting Study:

2. Single-dose Fed Bioequivalence Study

Study No.	04100
Study Design	Two-way, randomized, crossover
No. of subjects enrolled	32
No. of subjects completing	31
No. of subjects analyzed	31
Subjects (Normal/Patients?)	Normal healthy subjects
Sex(es) included (how many?)	Male: 17 Female: 14
Test product	Anchen's Bupropion HCl ER Tablets, 150 mg
Reference product	Wellbutrin XL® Tablets, 150 mg
Strength tested	150 mg
Dose	1x150 mg

Summary of Statistical Analysis: Bupropion (N=31) Additional Information in Appendix, Table 15 and Table 17		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	0.99	95.0-104.0
AUC_{∞}	1.01	95.8-105.8
C_{max}	0.99	93.2-104.7

Summary of Statistical Analysis: Hydroxybupropion (N=31) Additional Information in Appendix, Table 15 and Table 17		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	0.97	91.6-102.6
AUC_{∞}	0.97	91.9-102.7
C_{max}	0.99	94.1-104.1

Reanalysis of Study Samples Additional information in Appendix, Table 14								
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**
All samples were reassayed for analytical reasons only.								
Total								

Did use of recalculated plasma concentration data change study outcome? N/A

Comments on fed study: The study is acceptable.

F. Formulation

Location in appendix	Section B, Page 29
Inactive ingredients within IIG Limits (yes or no)	**Yes**
If no, list ingredients outside of limits	
If a tablet, is the product scored? (yes or no)	**No**
If yes, which strengths are scored?	
Is scoring of RLD the same as test? (yes or no)	**RLD not scored**
Formulation is acceptable (yes or no)	**Yes**
If not acceptable, why?	

G. In Vitro Dissolution

NOTE: The dissolution data were reviewed originally in v:\firmsam\anchen\ltrs&rev\ 77284d0904.doc which found the dissolution testing **incomplete**. The DBE requested that the firm conduct additional dissolution testing using one of the FDA methods as well as in three dissolution media using the USP apparatus II (paddle) at 50 rpm. The firm submitted the requested dissolution data in the dissolution amendment dated May 16, 2005.

Source of Method	Firm's Proposed Method
Medium	0.1 N HCl
Volume (mL)	900 mL
USP Apparatus type	I(basket)
Rotation (rpm)	75
Firm's proposed specifications	2 hours: (b) (4) 4 hours: 8 hours: 16 hours: %(Q)
FDA-recommended specifications based on the data submitted for the ANDA	Same as the firm's proposed specifications.

Comment: Currently, there are three different FDA-recommended dissolution methods recommended for the bupropion HCl ER tablet product. The firm was requested to conduct additional dissolution testing using one of the FDA-recommended method (900 mL of water, USP apparatus II(paddle) at 50 rpm). Compared with the data based on this FDA method, the firm's proposed method yielded better correlated data between the test and reference products (F2 >50). Both methods yielded correlated data between the 150 mg and 300 mg strengths of the test product (F2>50). Based on this comparison, the firm's proposed method was accepted.

H. Waiver Request(s)

Strengths for which waivers requested	300 mg
Regulation cited	21 CFR 320.22 (d)
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	See Deficiency Comments below.
Waiver granted (yes or no)	Yes

I. Comments

The dissolution data as submitted are acceptable. The firm's proposed method is found to be more appropriate for the test product than the FDA-recommended method.

The firm's proposed specifications are acceptable.

The application is **complete** with no further bioequivalence deficiency.

J. Recommendations

1. The single-dose, fasting bioequivalence and the single-dose, nonfasting bioequivalence study conducted by Anchen on the test product, Bupropion HCl Extended Release Tablets, 150 mg, lot # P000104-30, comparing it with the reference product, SmithKline Beecham's Wellbutrin XL® (bupropion HCl) Tablets, 150 mg, lot # 04B044P, have been found **acceptable** by the Division of Bioequivalence. The test product, Anchen's Bupropion HCl Extended Release Tablets, 150 mg, is bioequivalent to the reference product, Wellbutrin XL® (bupropion HCl) Tablets, 150 mg.

2. The dissolution testing conducted by Anchen on its Bupropion HCl 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:

2 hours: (b) (4)
4 hours:
8 hours:
16 hours: %(Q)

3. The formulations of the 300 mg and 150 mg strengths of the test product are proportionally similar. The waiver request for the 300 mg strength of the test product is granted. The test product, Anchen's Bupropion HCl Extended Release Tablets, 300 g, is deemed bioequivalent to the reference product, Wellbutrin XL® (bupropion HCl) Tablets, 300 mg.

The application is **complete** with no further bioequivalence deficiency at this time.

7/15/05

Hoaithon Nguyen, Branch I, Date signed

7/15/2005

Shriniwas Nerurkar, Ph.D., Branch I, Date signed

7/15/05

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

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IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information	
Study Number	04083
Study Title	A Randomized, Two-Way Crossover, Single-Dose, Open-Label Study to Evaluate the 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 32 Fasted, Healthy, Adult Subjects
Clinical Site	Gateway Medical Research, St. Charles, MO
Principal Investigator	Steven Herrmann, M.D., Ph.D.
Study/Dosing Dates	Period I: 06/27/04; Period II: 07/18/04
Analytical Site	(b) (4)
Analytical Director	(b) (6) Ph.D.
Analysis Dates	07/29/04-08/08/04
Storage Period (no. of days from first sample to final analysis)	43 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Bupropion HCl ER Tablets	Wellbutrin XL® Tablets
Manufacturer	Anchen Pharmaceuticals	SmithKline Beecham
Batch/Lot No.	P000104-30	04B044P
Manufacture Date	05/19/04	
Expiration Date		06/05
Strength	150 mg	150 mg
Dosage Form	ER Tablets	ER Tablets
Batch Size	(b) (4)	
Potency	101.2%	99.6%
Content Uniformity	100.9%(RSD=0.9%)	Not provided
Formulation	See Appendix Section B	
Dose Administered	1x150 mg	1x150 mg
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	21 days
Randomization Scheme	Yes
Blood Sampling Times	0, 1.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 24, 36, 48, 72, 96, 120 and 144 hours postdose
Blood Volume Collected/Sample	7 mL/sample
Blood Sample Processing/Storage	Samples were collected in evacuated tubes containing EDTA. The samples were cooled in an ice bath until centrifuged and harvested for plasma. The plasma aliquots were transferred to a polypropylene tube containing 25 uL of 4 N HCl, and stored at -20°C until assayed.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	From 10 hours predose until 4 hours postdose
Length of Confinement	Approximately 10 hours predose until 24 hours postdose
Safety Monitoring	Blood pressure and pulse were measured at predose, and within ±30 minutes of post-dose Hours 3, 5, 8, and 24 hours.

Table 1 Demographics of Study Subjects (N=32)

Age		Weight, lbs		Age Groups		Gender		Race	
				Range		Sex		Category	
				<18	0			Caucasian	13(M) 9(F)
Mean	28.9 (M) 33.0 (F)	Mean	189.8 (M) 171.3 (F)	18-40	15(M) 11(F)	Male	17	Afr. Amer.	3(M) 6(F)
SD	9.1 (M) 14.4 (F)	SD	36.3 (M) 51.4 (F)	41-64	2(M) 4(F)	Female	15	Hispanic	1(M)
Range	19-51 (M) 19-59 (F)	Range	143-290(M) 123-283(F)	65-75	0			Asian	0
				>75	0			Others	0

NOTE: M: Male; F: Female

Study Results

Table 2 Dropout Information

There was no dropout.

Subject No	N/A
Reason	N/A
Period	N/A
Replacement	N/A

Was there a difference in side effects for the test versus the reference? The difference in adverse events between two treatments did not appear to be significant. Most adverse events ranged from moderate to severe.

Table 3 Study Adverse Events

Adverse Event Description	**# in Test Group**	**# in Reference Group**
Headache	1	
Dizziness	1	
Chest pain		1
Nausea	1	1
Difficulty sleeping		1
Diarrhea		1
Total:	**3**	**4**

Was there a difference in protocol deviations for the test versus the reference?

Protocol Deviations

There was no significant protocol deviations that might have compromised the integrity of the study. There was no significant plasma sampling deviation.

Table 4 Assay Validation – Within Study

	Bupropion			Hydroxybupropion		
QC Conc. (ng/mL)	2.00 (n=32)	20.0 (n=32)	160 (n=32)	10.00 (n=32)	100.0 (n=32)	800 (n=32)
Inter day Precision (%CV)	5.38	4.79	10.7	6.72	4.05	6.41
Inter day Accuracy (%)	105	93.5	93.1	103	98.1	104
Cal. Standards Conc. (ng/mL)	1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 200.0			5.00, 10.0, 25.0, 50.0, 100, 250, 1000		
Inter day Precision (%CV)	1.58-6.33			0.791-10.0		
Inter day Accuracy (%)	94.8-112			92.8-105		
Linearity Range (range of R^2 values)	0.9969-0.9997			0.9994-0.9999		

Chromatograms: Any interfering peaks? There was no significant interfering peak.

Table 5 SOP's dealing with analytical repeats of study samples

None was submitted. Acceptance criteria were included in the analytical report.

SOP No.	Date of SOP	SOP Title

- **Comments on repeat assays.** Samples were repeated for analytical reasons only.
- **Comments on Within-Study Validation:** Acceptable.

Conclusion: Analytical method is acceptable.

Table 6 Arithmetic Mean Pharmacokinetic Parameters

Bupropion

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	Ng.hr/mL	633.5	38	621.1	37	1.02
AUC∞	Ng.hr/mL	710.0	36	680.2	36	1.04
Cmax	Ng/mL	61.61	37	55.46	35	1.11
Tmax	Hrs	5.00	13	5.03	30	0.99
T1/2	Hrs	37.53	58	30.85	50	1.22
kel	Hrs^{-1}	0.0281	78	0.0327	50	0.86

Hydroxybupropion

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	Ng.hr/mL	10,377	38	10,794	38	0.96
AUC∞	Ng.hr/mL	10,825	37	11,264	38	0.96
Cmax	Ng/mL	224.8	42	222.2	39	1.01
Tmax	Hrs	15.09	47	15.28	43	0.99
T1/2	Hrs	25.82	33	25.29	43	1.02
kel	Hrs^{-1}	0.0296	30	0.0303	32	0.98

Table 7 Least Square Geometric Means and 90% Confidence Intervals (N=32)

Bupropion

Parameter	Test	Reference	T/R	90% CI
AUC0-t	586.9	575.3	1.02	93.5-111.3
AUC∞	665.6	632.2	1.05	98.3-112.8
Cmax	57.17	51.87	1.10	99.1-122.6

Hydroxybupropion

Parameter	Test	Reference	T/R	90% CI
AUC_{0-t}	9736	10,004	0.97	88.9-106.5
AUC_{∞}	10,174	10,451	0.97	89.1-106.4
C_{max}	204.7	203.5	1.01	91.6-110.5

Table 8 Additional Study Information

Bupropion

Root mean square error, AUC_{0-t}	0.204744
Root mean square error, AUC_{∞}	0.162675
Root mean square error, C_{max}	0.250949
K_{el} and AUC_{∞} determined for how many subjects?	All
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as C_{max}	0
Were the subjects dosed as more than one group?	No

Hydroxybupropion

Root mean square error, AUC_{0-t}	0.212118
Root mean square error, AUC_{∞}	0.208761
Root mean square error, C_{max}	0.221861
K_{el} and AUC_{∞} determined for how many subjects?	All
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as C_{max}	0
Were the subjects dosed as more than one group?	No

Comments: The statistical and PK analysis is acceptable.

Conclusion: The single-dose fasting bioequivalence study is acceptable. The 90% confidence interval for lnAUC(0-T), lnAUC(0-Infinity) and lnCmax of bupropion and hydroxybupropion was within the acceptable limit of [0.80-1.25].

Table 9A Bupropion Mean Plasma Concentrations (ng/mL) Single-Dose Fasting Bioequivalence Study

Test Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	32	0.000	0.000	0.000	0.000
Hour1.50	32	1.867	3.487	0.000	15.800
Hour3	32	19.993	14.723	1.200	50.300
Hour4	32	38.143	20.763	6.090	85.200
Hour5	32	58.134	23.973	18.400	110.000
Hour6	32	46.325	21.202	13.000	95.800
Hour7	32	37.375	15.724	11.500	76.500
Hour8	32	32.569	13.588	11.000	60.800
Hour10	32	22.459	9.544	4.570	42.400
Hour12	32	18.521	7.773	4.300	34.400
Hour14	32	14.565	6.097	0.000	24.800
Hour24	32	6.513	2.788	1.900	13.100
Hour36	32	3.442	1.570	0.000	6.440
Hour48	32	2.597	1.477	0.000	5.770
Hour72	32	1.394	1.125	0.000	3.890
Hour96	32	0.708	0.887	0.000	2.670
Hour120	32	0.395	0.657	0.000	1.830
Hour144	32	0.174	0.473	0.000	1.590

Reference Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	32	0.000	0.000	0.000	0.000
Hour1.50	32	1.544	2.680	0.000	11.900
Hour3	32	22.193	17.855	0.000	70.500
Hour4	32	37.465	19.808	6.910	67.900
Hour5	32	51.003	20.574	15.500	92.100
Hour6	32	42.016	16.956	14.400	84.100
Hour7	32	33.450	12.745	13.600	69.900
Hour8	32	27.583	10.515	8.050	57.800
Hour10	32	21.601	7.394	8.370	35.900
Hour12	32	19.480	6.993	8.360	33.000
Hour14	32	14.925	5.755	5.640	24.400
Hour24	32	6.812	2.613	1.930	11.400
Hour36	32	3.590	2.218	0.000	10.000
Hour48	32	2.552	1.350	0.000	5.640
Hour72	32	1.483	1.187	0.000	4.360
Hour96	32	0.729	0.971	0.000	3.280
Hour120	32	0.401	0.712	0.000	2.440
Hour144	32	0.167	0.463	0.000	1.800

Table 9B Hydroxybupropion Mean Plasma Concentrations (ng/mL) Single-Dose Fasting Bioequivalence Study

Test Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	32	0.000	0.000	0.000	0.000
Hour1.50	32	6.910	13.535	0.000	55.900
Hour3	32	60.873	54.258	0.000	214.000
Hour4	32	118.006	66.636	17.200	254.000
Hour5	32	166.563	73.900	31.300	306.000
Hour6	32	180.653	77.330	43.300	340.000
Hour7	32	187.591	77.287	50.500	330.000
Hour8	32	197.872	84.232	59.400	393.000
Hour10	32	203.816	89.040	68.000	446.000
Hour12	32	193.228	82.549	61.000	385.000
Hour14	32	202.553	81.737	53.500	385.000
Hour24	32	194.525	80.843	70.500	410.000
Hour36	32	121.000	53.031	0.000	281.000
Hour48	32	92.966	35.286	40.900	181.000
Hour72	32	47.941	22.881	15.500	103.000
Hour96	32	24.518	15.319	6.370	62.100
Hour120	32	12.916	10.580	0.000	37.100
Hour144	32	6.180	8.283	0.000	29.300

Reference Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	32	0.000	0.000	0.000	0.000
Hour1.50	32	3.651	6.594	0.000	22.800
Hour3	32	58.006	47.969	0.000	142.000
Hour4	32	112.188	64.722	20.800	219.000
Hour5	32	161.191	74.303	39.800	317.000
Hour6	32	174.372	75.425	42.500	342.000
Hour7	32	179.763	75.276	43.600	374.000
Hour8	32	185.875	77.655	40.600	409.000
Hour10	32	196.766	82.464	39.400	425.000
Hour12	32	195.588	79.494	38.800	384.000
Hour14	32	200.381	75.072	36.700	383.000
Hour24	32	198.694	76.002	52.600	358.000
Hour36	32	126.069	59.301	0.000	246.000
Hour48	32	100.769	45.469	29.900	246.000
Hour72	32	53.978	29.562	17.000	140.000
Hour96	32	27.432	18.973	6.030	75.900
Hour120	32	13.449	14.149	0.000	57.600
Hour144	32	7.155	8.755	0.000	34.300

Figure 1A

Bupropion Mean Plasma Concentrations
Single Dose Fasting Study

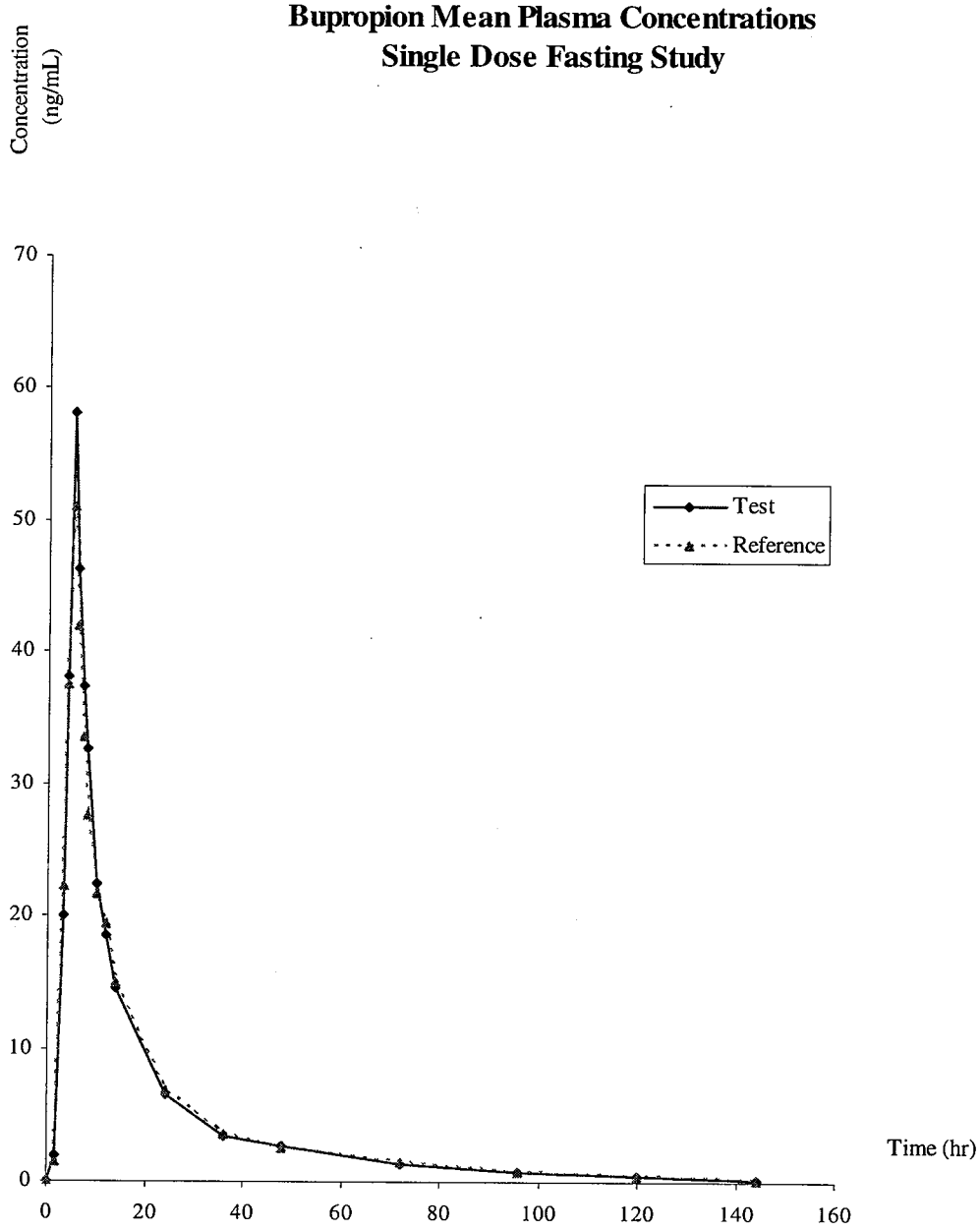
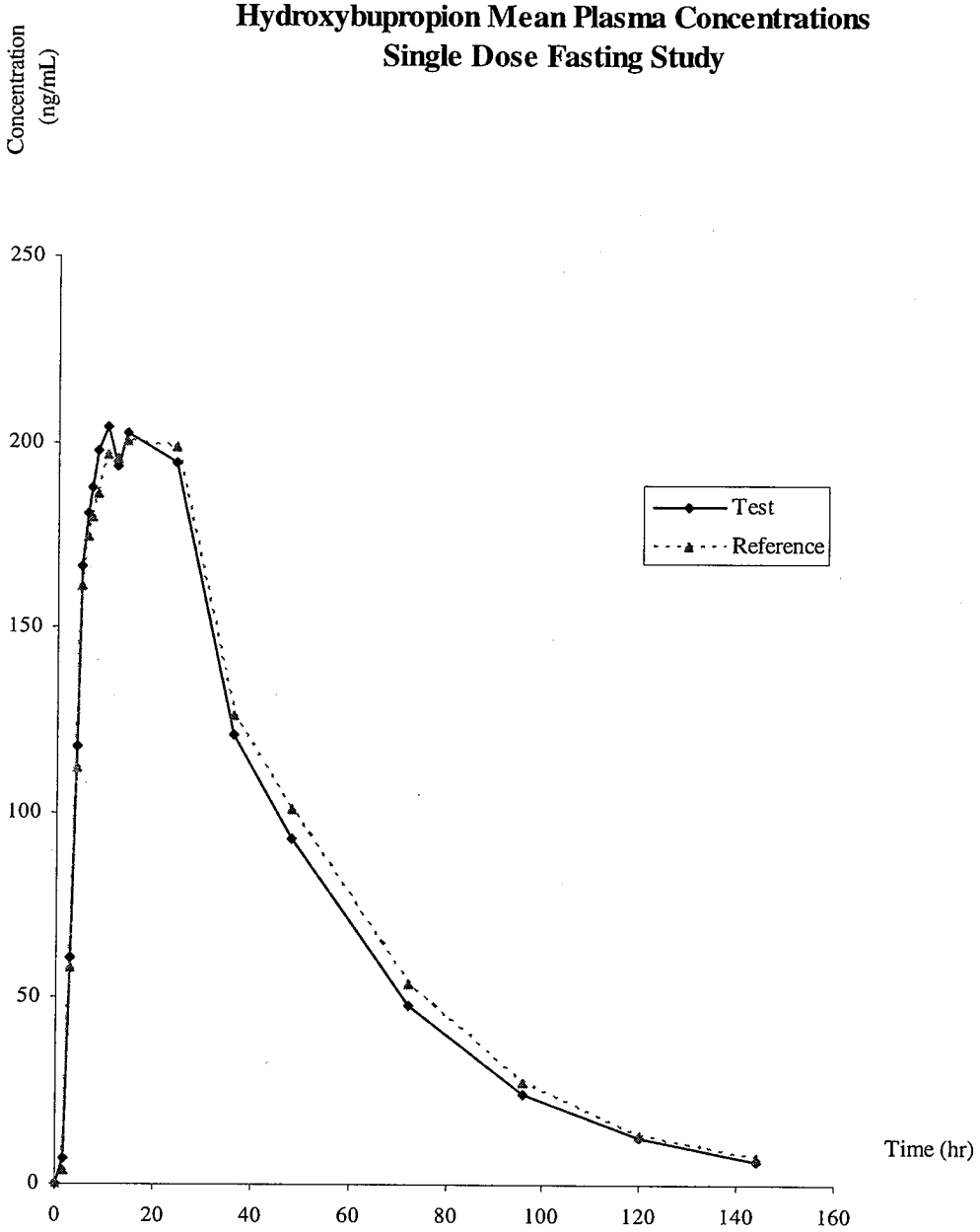


Figure 1B

Hydroxybupropion Mean Plasma Concentrations
Single Dose Fasting Study



2. Single-dose Fed Bioequivalence Study

Study Information	
Study Number	04100
Study Title	A Randomized, Two-Way Crossover, Single-Dose, Open-Label Study to Evaluate the 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 32 Fed, Healthy, Adult Subjects
Clinical Site	Gateway Medical Research, St. Charles, MO
Principal Investigator	Irwin Plisco, M.D.
Study/Dosing Dates	Period I: 06/27/03; Period II: 07/18/04
Analytical Site	(b) (4)
Analytical Director	(b) (6) Ph.D.
Analysis Dates	08/01/04-08/04/04
Storage Period (no. of days from first sample to final analysis)	38 days

Treatment ID	A	B
Test or Reference	Bupropion HCl ER Tablets	Wellbutrin XL® Tablets
Product Name	Anchen Pharmaceuticals	SmithKline Beecham
Manufacturer	P000104-30	04B044P
Batch/Lot No.	05/19/04	
Manufacture Date		06/05
Expiration Date	150 mg	150 mg
Strength	ER Tablets	ER Tablets
Dosage Form	(b) (4)	
Batch Size	101.2%	99.6%
Potency	100.9%(RSD=0.9%)	Not provided
Content Uniformity	See Appendix Section B	
Formulation	1x150 mg	1x150 mg
Dose Administered	Oral	
Route of Administration	Bupropion HCl ER Tablets	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	21 days
Randomization Scheme	Yes
Blood Sampling Times	0, 1.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 24, 36, 48, 72, 96, 120 and 144 hours postdose
Blood Volume Collected/Sample	7 mL/sample
Blood Sample Processing/Storage	Samples were collected in evacuated tubes containing EDTA. The samples were cooled in an ice bath until centrifuged and harvested for plasma. The plasma aliquots were transferred to a polypropylene tube containing 25 uL of 4 N HCl, and stored at -20°C until assayed.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 11
Length of Fasting*	From 10 hours predose until 4 hours postdose
Length of Confinement	Approximately 10 hours predose until 24 hours postdose
Safety Monitoring	Blood pressure and pulse were measured at predose, 2, 3, 8 and 24 hours postdose.

***NOTE:** At 30 minutes prior to dosing, the subjects were given a standardized breakfast consisting of two egg fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes, and eight ounces of whole milk. (970 total calories; 578.7 fat calories; 127.6 protein calories; 264 carbohydrate calories)

Table 10 Demographics of Study Subjects (N=31)

Age		Weight, lbs		Age Groups		Gender		Race	
				Range		Sex		Category	
				<18	0			Caucasian	14(M) 9(F)
Mean	28.7 (M) 29.4 (F)	Mean	191.7 (M) 171.1 (F)	18-40	15(M) 13 (F)	Male	17	Afr. Amer.	2 (M) 3 (F)
SD	10.7 (M) 6.9 (F)	SD	36.6 (M) 35.8 (F)	41-64	2(M) 1(F)	Female	14	Hispanic	2 (M)
Range	19-57 (M) 21-44 (F)	Range	68-77(M) 119-248(F)	65-75	0			Asian	
				>75	0			Others	

NOTE: M: Male; F: Female

Study Results

Table 11 Dropout Information

Subject No	24
Reason	Adverse event (headache, chills and shortness of breath)
Period	II
Replacement	No

Was there a difference in side effects for the test versus the reference? All adverse events were reported during the Reference treatment. The severity of the adverse events ranged from mild to moderate.

Table 12 Study Adverse Events

Adverse Event Description	**# in Test Group**	**# in Reference Group**
Headache		**2**
Lightheadedness		**1**
Sore throat		**1**
Congestion		**2**
Chills		**1**
Shortness of breath		**1**
Agitation		**1**
Sleeplessness		**1**
Total:		**10**

Was there a difference in protocol deviations for the test versus the reference? No.

Protocol Deviations There were no significant protocol deviations that might have compromised the integrity of the study. Any significant blood sampling deviations were corrected during the creation of PK data.

Table 13 Assay Validation – Within Study

	Bupropion			Hydroxybupropion		
QC Conc. (ng/mL)	2.00 (n=32)	20.0 (n=32)	160 (n=32)	10.00 (n=32)	100.0 (n=32)	800 (n=32)
Inter day Precision (%CV)	7.97	4.72	5.36	7.28	4.85	4.29
Inter day Accuracy (%)	104	92.5	95.0	102	100	102
Cal. Standards Conc. (ng/mL)	1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 200.0			5.00, 10.0, 25.0, 50.0, 100, 250, 1000		
Inter day Precision (%CV)	2.31-8.08			1.48-5.87		
Inter day Accuracy (%)	95.0-110			94.0-103.0		

Linearity Range (range of R^2 values)	0.9965-0.9998	0.9984-0.9999

Chromatograms: Any interfering peaks? No.

Table 14 SOP's dealing with analytical repeats

None was submitted. Acceptance criteria were included in the analytical report.

SOP No.	Date of SOP	SOP Title
N/A	N/A	N/A

There was no PK repeat sample.

Comments on Within-Study Validation: Acceptable.

Conclusion: Analytical method is acceptable.

Table 15 Arithmetic Mean Pharmacokinetic Parameters

Bupropion

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	Ng.hr/mL	863.7	29	876.6	32	0.98
AUC∞	Ng.hr/mL	938.6	31	934.7	31	1.00
Cmax	Ng/mL	63.14	33	64.93	38	0.97
Tmax	Hrs	6.45	29	7.23	32	0.89
T1/2	Hrs	34.79	51	32.83	43	1.06
kel	Hrs^{-1}	0.0249	51	0.0251	42	0.99

Hydroxybupropion

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	Ng.hr/mL	13,266	52	13,941	58	0.95
AUC∞	Ng.hr/mL	13,827	53	14,498	58	0.95
Cmax	Ng/mL	271.4	47	276.3	49	0.98
Tmax	Hrs	16.39	34	17.03	34	0.96
T1/2	Hrs	26.78	24	27.04	24	0.99
kel	Hrs^{-1}	0.0273	24	0.0270	24	1.01

Table 16 Geometric Means and 90% Confidence Intervals (N=31)

Bupropion

Parameter	Test	Reference	T/R	90% CI
AUC0-t	828.4	833.4	0.99	95.0-104.0
AUC∞	898.1	892.1	1.01	95.8-105.8
Cmax	60.05	60.79	0.99	93.2-104.7

Hydroxybupropion

Parameter	Test	Reference	T/R	90% CI
AUC0-t	11,780	12,155	0.97	91.6-102.6
AUC∞	12,259	12,619	0.97	91.9-102.7
Cmax	243.8	246.3	0.99	94.1-104.1

Table 17 Additional Study Information

Bupropion

Root mean square error, AUC0-t	0.104169
Root mean square error, AUC∞	0.114898
Root mean square error, Cmax	0.134590
Kel and AUC∞ determined for how many subjects?	All
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as Cmax	0
Were the subjects dosed as more than one group?	No

Hydroxybupropion

Root mean square error, AUC0-t	0.130973
Root mean square error, AUC∞	0.128917
Root mean square error, Cmax	0.116348
Kel and AUC∞ determined for how many subjects?	All
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as Cmax	0
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic and Statistical Analysis: The analysis is acceptable.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: The single-dose nonfasting bioequivalence study is acceptable. The 90% confidence interval for lnAUC(0-T), lnAUC(0-Infinity) and lnCmax of bupropion and hydroxybupropion was within the acceptable limit of [0.80-1.25].

Table 18A Bupropion Mean Plasma Concentrations, Single-Dose Fed Study

Test Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	31	0.000	0.000	0.000	0.000
Hour1.50	31	0.053	0.295	0.000	1.640
Hour3	31	5.766	7.406	0.000	39.400
Hour4	31	20.562	14.106	1.510	57.400
Hour5	31	53.626	16.978	18.400	92.800
Hour6	31	55.274	23.322	20.200	129.000
Hour7	31	50.687	21.641	17.800	106.000
Hour8	31	49.077	15.829	15.900	82.500
Hour10	31	39.952	12.221	11.500	64.400
Hour12	31	32.984	13.210	11.500	65.000
Hour14	31	25.241	9.578	7.780	48.800
Hour24	31	9.640	3.379	4.080	20.400
Hour36	31	5.055	1.776	0.000	8.890
Hour48	31	3.724	1.203	1.890	6.730
Hour72	31	1.877	0.986	0.000	3.890
Hour96	31	1.083	0.848	0.000	2.640
Hour120	31	0.540	0.860	0.000	3.720
Hour144	31	0.195	0.451	0.000	1.260

Reference Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	31	0.000	0.000	0.000	0.000
Hour1.50	31	0.034	0.187	0.000	1.040
Hour3	31	7.644	6.760	0.000	24.600
Hour4	31	26.322	19.721	2.450	76.200
Hour5	31	54.865	26.572	6.020	114.000
Hour6	31	52.148	25.125	18.200	113.000
Hour7	31	48.716	21.230	16.400	107.000
Hour8	31	49.161	23.179	13.600	142.000
Hour10	31	42.006	17.801	9.900	104.000
Hour12	31	34.925	13.473	7.760	66.400
Hour14	31	23.808	8.215	7.280	47.400
Hour24	31	9.902	3.920	4.360	19.600
Hour36	31	5.178	1.505	2.110	8.720
Hour48	31	3.674	1.342	1.650	6.660
Hour72	31	2.043	1.000	0.000	3.780
Hour96	31	1.086	0.886	0.000	2.420
Hour120	31	0.486	0.676	0.000	1.700
Hour144	31	0.216	0.449	0.000	1.200

Table 19B Hydroxybupropion Mean Plasma Concentrations, Single-Dose Fed Study

Test Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	31	0.000	0.000	0.000	0.000
Hour1.50	31	0.000	0.000	0.000	0.000
Hour3	31	8.643	10.139	0.000	36.000
Hour4	31	43.632	36.278	0.000	139.000
Hour5	31	97.277	50.357	27.100	214.000
Hour6	31	135.406	75.056	33.500	369.000
Hour7	31	170.239	88.712	36.400	398.000
Hour8	31	200.197	95.910	49.800	461.000
Hour10	31	238.168	115.890	61.600	531.000
Hour12	31	236.587	118.563	82.200	601.000
Hour14	31	258.239	125.997	83.700	611.000
Hour24	31	249.735	124.776	94.800	640.000
Hour36	31	161.784	91.356	0.000	452.000
Hour48	31	129.261	76.594	58.600	389.000
Hour72	31	62.110	41.407	0.000	180.000
Hour96	31	38.422	30.016	9.870	128.000
Hour120	31	20.524	18.115	0.000	80.000
Hour144	31	10.428	12.359	0.000	46.400

Reference Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	31	0.000	0.000	0.000	0.000
Hour1.50	31	0.000	0.000	0.000	0.000
Hour3	31	14.344	20.219	0.000	87.300
Hour4	31	53.649	45.926	0.000	199.000
Hour5	31	104.152	66.104	17.200	292.000
Hour6	31	134.419	78.074	35.900	335.000
Hour7	31	164.529	86.768	49.000	402.000
Hour8	31	197.539	103.240	75.400	552.000
Hour10	31	239.261	131.098	70.700	718.000
Hour12	31	247.706	129.988	80.800	703.000
Hour14	31	261.923	135.818	84.000	741.000
Hour24	31	255.581	130.792	78.500	716.000
Hour36	31	176.016	94.641	61.400	533.000
Hour48	31	134.326	85.372	42.100	455.000
Hour72	31	71.455	53.594	0.000	261.000
Hour96	31	39.025	30.890	8.670	143.000
Hour120	31	21.002	18.884	0.000	81.700
Hour144	31	11.295	12.505	0.000	51.400

Figure 2A

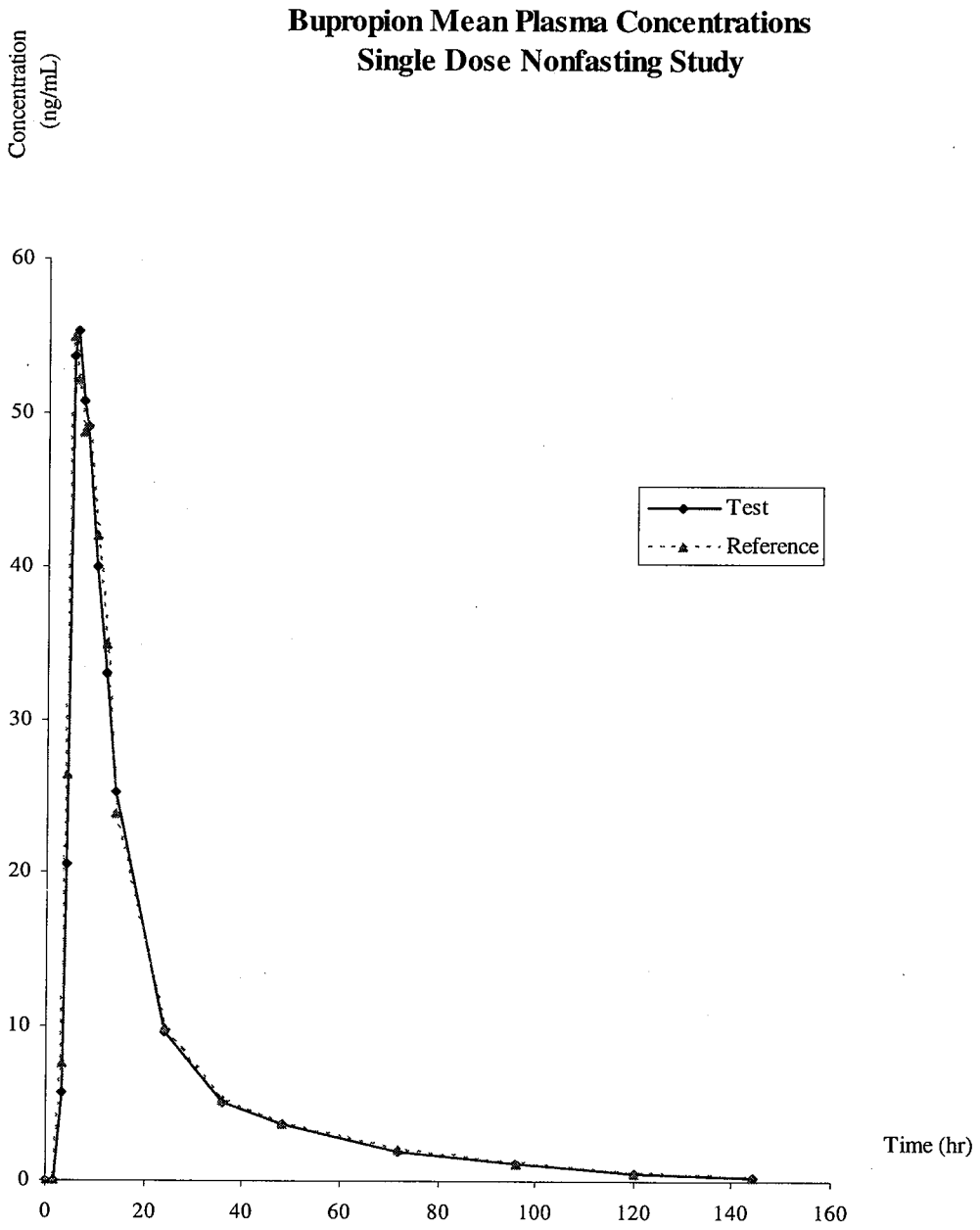
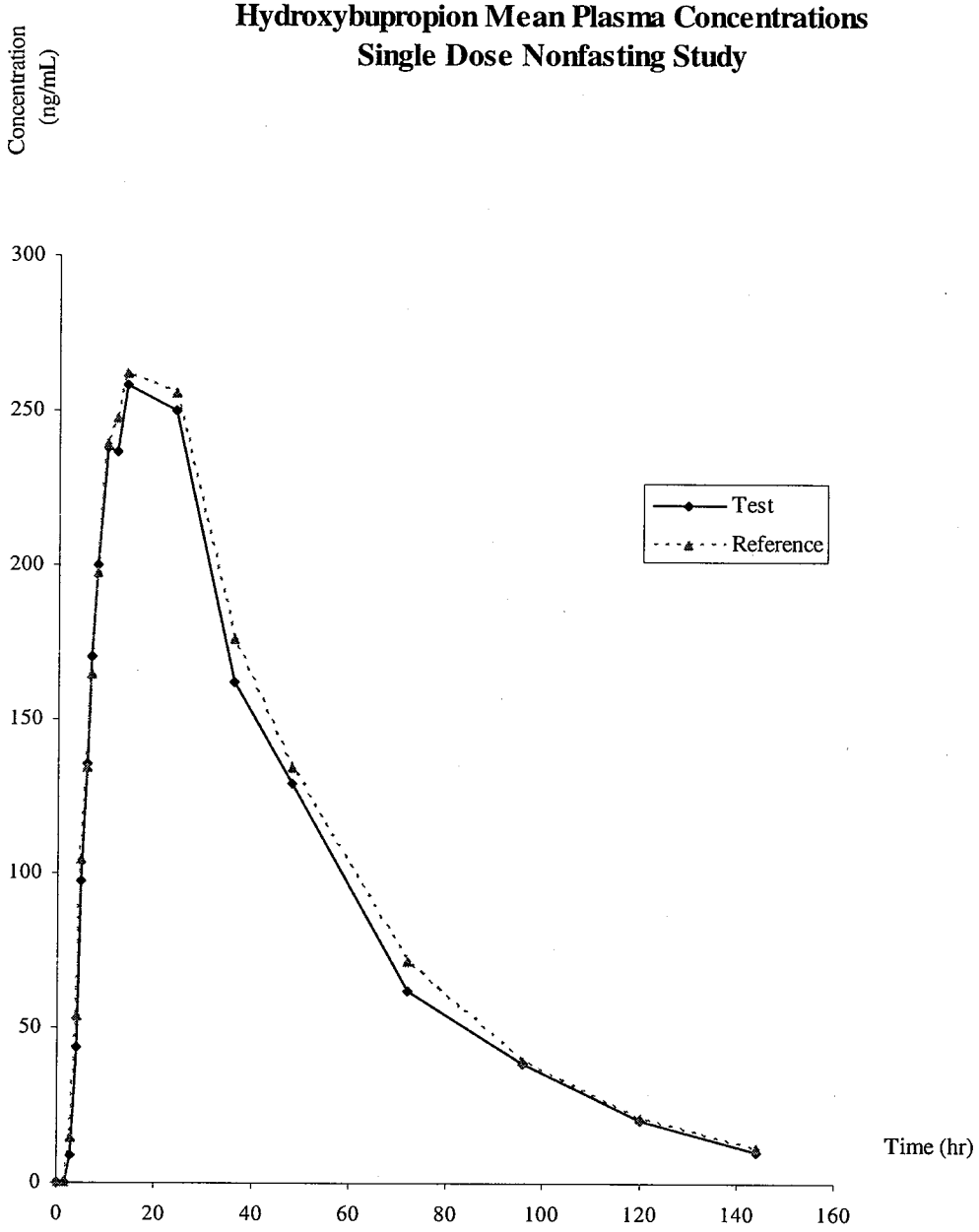

Bupropion Mean Plasma Concentrations
Single Dose Nonfasting Study
Concentration (ng/mL)
60
50
40
30
20
10
0
0
20
40
60
80
100
120
140
160
Time (hr)
Test
Reference

Figure 2B

Hydroxybupropion Mean Plasma Concentrations
Single Dose Nonfasting Study



B. Dissolution Data:

Testing Conditions:

From the dissolution review of the original submission dated September 21, 2004, v:\firmsam\anchen\ltrs&rev\77284d0904.doc:

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range)						Study Report Location
					60 min	120 min	240 min	360 min	480 min	960 min	
Not Provided (N.P.)	04B044P / GlaxoSmithKline K-32370	150 mg E.R. Tab	Dissolution: Apparatus 1 (USP) Speed of Rotation: 75 rpm Medium: 0.1 N HCl at 37°C	12	0 (b) (4)	2 (b) (4)	23	49	73	95 (b) (4)	V 1.1 p. 40
N.P.	P000104 / Anchen	150 mg E.R. Tab		12	0 (b) (4)	2 (b) (4)	27	52	70	98 (b) (4)	
N.P.	03K056P/ GlaxoSmithKline K-32369	300 mg E.R. Tab		12	0 (b) (4)	3 (b) (4)	29	51	70	95 (b) (4)	V 1.1 p. 43
N.P.	P000204/ Anchen	300 mg E.R. Tab		12	0 (b) (4)	2 (b) (4)	22	42	57	90 (b) (4)	

Similarity Factor F2 between the 150 mg of the test and reference products: 77.20

Similarity Factor F2 between the 300 mg of the test and reference products: 56.46

Similarity Factor F2 between the 150 mg and 300 mg strengths of the test product: 55.43

Source of Method	FDA
Medium	Water
Volume (mL)	900 mL
USP Apparatus type	II(paddle)
Rotation (rpm)	50 rpm

Table 19

Sampling Time (hours)	Test Product, Strength 300 mg Lot No. P000204-30			Reference Product, Strength 300 mg Lot No. 05B063P		
	Mean	SD	Range	Mean	SD	Range
1	1	1.0	(b) (4)	0	0	(b) (4)
2	3	1.8		1	0	
3	14	4.0		1	0.7	
4	28	5.0		5	1.2	
5	41	4.8		9	1.0	
6	52	4.3		14	1.4	
7	61	4.2		17	1.6	
8	69	4.1		22	1.8	
9	76	3.7		26	2.2	
10	82	3.1		30	2.5	
11	87	2.6		35	3.0	
16	99	1.6		56	4.1	

Similarity Factor F2 (between the test and reference products): 33.31

Table 20

Sampling Time (hours)	Test Product, Strength 150 mg Lot No. P000104-30			Reference Product, Strength 150 mg Lot No. 04B044P		
	Mean	SD	Range	Mean	SD	Range
1	1	1.0	(b) (4)	0	0	(b) (4)
2	4	2.2		1	0.5	
3	17	4.3		1	0.7	
4	35	4.9		3	1.6	
5	51	5.2		7	2.8	
6	63	4.5		11	3.4	
7	74	3.9		15	2.6	
8	82	3.5		19	2.6	
9	89	2.9		23	2.8	
10	94	2.5		27	2.9	
11	97	2.0		31	3.4	
16	97	1.4		51	5.4	

Similarity Factor F2 (between the test and reference products): 24.50

Similarity Factor F2 between the 150 mg and 300 mg strengths of the test product: 57.33

Source of Method	Varying pH media
Medium	0.1 N HCl
Volume (mL)	900 mL
USP Apparatus type	II(paddle)
Rotation (rpm)	50 rpm

Table 21

Sampling Time (hours)	Test Product, Strength 300 mg Lot No. P000204-30			Reference Product, Strength 300 mg Lot No. 05B063P		
	Mean	SD	Range	Mean	SD	Range
1	0	0	(b) (4)	0	0.4	(b) (4)
2	1	0.9		4	2.6	
3	6	3.1		17	3.5	
4	15	4.7		31	3.7	
5	25	5.2		44	3.5	
6	34	5.4		55	3.6	
7	42	5.1		65	3.7	
8	50	5.0		75	3.8	
9	56	4.9		82	3.8	
10	62	4.6		88	2.9	
16	86	2.9		98	1.5	

Similarity Factor F2: 44.07

Table 22

Sampling Time (hours)	Test Product, Strength 150 mg Lot No. P000104-30			Reference Product, Strength 150 mg Lot No. 04B044P		
	Mean	SD	Range	Mean	SD	Range
1	0	0	(b) (4)	0	0	(b) (4)
2	1	0.8		1	1.1	
3	8	3.5		8	5.5	
4	21	4.5		20	7.5	
5	33	4.7		34	7.1	
6	45	4.2		45	7.5	
7	54	4.0		57	7.2	
8	63	3.6		67	5.8	
9	70	3.2		76	4.0	
10	76	2.8		82	2.8	
11	81	2.4		86	2.1	
16	94	0.8		93	1.4	

Similarity Factor F2: 92.47

Source of Method	Varying pH media
Medium	pH 4.5
Volume (mL)	900 mL
USP Apparatus type	II(paddle)
Rotation (rpm)	50 rpm

Table 23

Sampling Time (hours)	Test Product, Strength 300 mg Lot No. P000204-30			Reference Product, Strength 300 mg Lot No. 05B063P		
	Mean	SD	Range	Mean	SD	Range
1	0	0	(b) (4)	0	0	(b) (4)
2	4	1.8		0	0.4	
3	16	3.7		1	0	
4	30	3.9		1	0.9	
5	42	3.9		4	1.7	
6	53	3.6		7	2.0	
7	62	3.5		11	1.9	
8	71	3.1		14	2.0	
9	77	2.8		18	2.4	
10	83	2.4		21	2.9	
11	88	2.2		25	3.4	
16	97	1.0		71	7.6	

Similarity Factor F2: 29.52

Table 24

Sampling Time (hours)	Test Product, Strength 150 mg Lot No. P000104-30			Reference Product, Strength 150 mg Lot No. 04B044P		
	Mean	SD	Range	Mean	SD	Range
1	0	0.5	(b) (4)	0	0	(b) (4)
2	4	2.2		0	0	
3	19	4.4		1	0	
4	37	4.5		1	0.4	
5	53	4.0		3	2.0	
6	67	3.7		6	3.2	
7	77	2.9		11	3.6	
8	85	2.4		14	3.6	
9	91	2.2		18	3.3	
16	99	1.9		75	5.5	

Similarity Factor F2: 21.68

Source of Method	Varying pH media
Medium	pH 6.8
Volume (mL)	900 mL
USP Apparatus type	II(paddle)
Rotation (rpm)	50 rpm

Table 25

Sampling Time (hours)	Test Product, Strength 300 mg Lot No. P000204-30			Reference Product, Strength 300 mg Lot No. 05B063P		
	Mean	SD	Range	Mean	SD	Range
1	13	0.7	(b) (4)	16	1.1	(b) (4)
2	30	1.2		34	0.9	
3	42	1.6		48	1.3	
4	51	1.9		57	1.4	
5	58	2.2		66	1.7	
6	65	2.4		72	1.7	
7	71	2.7		78	1.8	
8	76	2.8		83	1.9	
9	80	2.9		87	1.9	
10	83	2.8		89	2.0	
11	86	2.2		91	2.1	
16	91	1.2		95	2.2	

Similarity Factor F2: 63.15

Table 26

Sampling Time (hours)	Test Product, Strength 150 mg Lot No. P000104-30			Reference Product, Strength 150 mg Lot No. 04B044P		
	Mean	SD	Range	Mean	SD	Range
1	18	1.7	(b) (4)	18	2.0	(b) (4)
2	40	2.3		37	2.0	
3	55	2.2		51	1.9	
4	66	2.9		62	1.6	
5	76	3.3		69	1.5	
6	81	2.8		76	1.8	
7	87	2.5		81	1.8	
16	93	1.6		92	2.1	

Similarity Factor F2: 66.16

Following this page, 2 pages withheld in full (b)(4)-CCI/TS (formulation data)

Comments on Formulations: The same inactive ingredients are used in the 150 mg and 300 mg formulations and the ingredients are within the IIG approved ranges. The ingredients of the (b) (4) tablets of the 150 mg and 300 mg formulations are proportional. The total difference in the amount of the ingredients in the (b) (4) (b) (4) between the two strengths is (b) (4)%. The difference is within the SUPAC-specified change of release controlling excipients for Level 1 and *"unlikely to have any detectable impact on formulation quality and performance"* per the SUPAC guidance for MR products. The formulations of the two strengths are considered proportionally similar and **acceptable.**

C. SAS Output

1. Fasting Study:

Bupropion


77284FASTBU.txt

Hydroxybupropion


77284FASTHYDROXY
.txt

2. Nonfasting Study:

Bupropion


77284FEDBU.txt

Hydroxybupropion


77284FEDHYDROXY.
txt

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-284 APPLICANT: Anchen Pharmaceuticals

DRUG PRODUCT: Bupropion HCl Extended Release Tablets, 150 mg & 300 mg

The Division of Bioequivalence (DBE) has completed its review and has no further questions at this time. Please note there were errors concerning the specifications recommended in the letter dated 06/29/05 from the DBE. Please disregard this earlier letter.

We agree that the dissolution testing for the test product should be conducted using your proposed dissolution 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 product should meet the following specifications:

2 hours:	(b) (4)
4 hours:	
8 hours:	
16 hours:	%(Q)

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 77-284
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ SNerurkar

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ SNerurkar 7/15/05
HFD-617/ A. Sigler
HFD-650/ D. Conner 7/15/05

V:\FIRMSAM\anchen\ltrs&rev\77284n0904.doc
Printed in final on / /

BIOEQUIVALENCE - ACCEPTABLE
DISSOLUTION - **ACCEPTABLE**

Submission date: 09-21-04
& 05-16-05

1. FASTING STUDY (STF)
   Clinical: Gateway Medical Research
   Analytical: (b) (4)
   Strength: 150 mg
   ✓ **Outcome: AC**

2. NONFASTING STUDY (STP)
   Clinical: Gateway Medical Research
   Analytical: (b) (4)
   Strength: 150 mg
   ✓ **Outcome: AC**

3. DISSOLUTION WAIVER (DIW)
   Strength: 300 mg
   ✓ **Outcome: AC**

4. DISSOLUTION AMENDMENT (OTH)
Strengths: 150 mg & 300 mg
✓ **Outcome: AC**

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable **NC** - No credit

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #:	77-284	**SPONSOR:**	Anchen Pharmaceuticals
DRUG & DOSAGE FORM:	Bupropion HCl ER Tablets		
STRENGTH(S):	150 mg & 300 mg		
TYPES OF STUDIES:	Fasting and Nonfasting Studies (150 mg)		
CLINICAL STUDY SITE(S):	Gateway Medical Research		
ANALYTICAL SITE(S):	(b) (4)		
STUDY SUMMARY:	Acceptable		
DISSOLUTION:	Acceptable		

DSI INSPECTION STATUS

		Inspection status:	**Inspection results:**
Inspection needed:	NO		
First Generic	YES		
New facility			
For cause			
Other			

Proposed Dissolution Method and Specifications from Original Submission Acceptable?

Yes X No _____ (If no, project Manager should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Specifications acknowledged by firm? Yes ___ No ___

AMENDMENT DATE: _____

PROJECT MANAGER: _____ **DATE:** _____

PRIMARY REVIEWER: Hoainhon Nguyen **BRANCH:** I
INITIAL: HNC DATE: 7/15/05

TEAM LEADER: Shriniwas Nerurkar, Ph.D. **BRANCH:** I
INITIAL: _____ DATE: 7/15/2005

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: _____ DATE: 7/15/05

DIVISION OF BIOEQUIVALENCE REVIEW - ADDENDUM

ANDA No.	77-284
Drug Product Name	Bupropion HCl ER Tablets
Strength	150 mg & 300 mg
Applicant Name	Anchen Pharmaceutical
Address	Irvine, CA
Submission Date(s)	September 21, 2004
Amendment Date(s)	May 16, 2005
Reviewer	Hoainhon Nguyen
First Generic	Yes
File Location	**V:\firmsam\anchen\ltrs&rev\77284a0904.doc**

I. Executive Summary

This is an addendum to the review V:\firmsam\anchen\ltrs&rev\77284n0904.doc. 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 are described for the additional testing.

The application has previously been found **complete** with other bioequivalence requirement aspects (See the review V:\firmsam\anchen\ltrs&rev\77284n0904.doc).

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Bupropion HCl ER Tablets, 150 mg & 300 mg
Reference Product	Wellbutrin XL® (bupropion HCl) Tablets, 150 mg & 300 mg
RLD Manufacturer	SmithKline Beecham
NDA No.	21-515
RLD Approval Date	08/28/2003
Indication	indicated for the treatment of major depressive disorder

B. Original Submission Review

See the review V:\firmsam\anchen\ltrs&rev\77284n0904.doc

C. 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, 0.1 N HCl, apparatus 1 (basket) @ 75 rpm, with and without the alcohol (see below):

Test 1: 12 units tested 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 analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV on both strengths.

D. Recommendations

The dissolution testing conducted by Anchen on its Bupropion HCl 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.

7/6/06

Hoaimon Nguyen, Branch I, Date signed

7/6/06

Moheb H. Makary, Ph.D., Branch I, Date signed

7/7/06

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

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HFD-652/ HNguyen
HFD-652/ MMakary

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ MMakary 7/6/06
HFD-617/ A. Sigler
HFD-650/ D. Conner 7/7/06

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BIOEQUIVALENCE - ACCEPTABLE
DISSOLUTION - **INCOMPLETE**

Submission date: 09-21-04
& 05-16-05

1. US Document (Review Addendum)

Strength: 150 mg & 300 mg
Outcome: IC

OUTCOME DECISIONS: **IC** - Incomplete

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-284
Drug Product Name	Bupropion HCl ER Tablets
Strength	150 mg & 300 mg
Applicant Name	Anchen Pharmaceutical
Address	Irvine, CA
Submission Date(s)	August 9, 2006
Amendment Date(s)	
Reviewer	Hoainhon Nguyen
First Generic	Yes
File Location	**V:\firmsam\anchen\ltrs&rev\77284a0806.doc**

I. Executive Summary

This is a review of an amendment. Due to concern of dose dumping for the drug product, the Agency has currently requested that the firm conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium. The testing conditions were described for the additional testing.

In the current amendment, the firm has submitted the additional dissolution data as requested. The data showed that there was no dumping in any additional media tested at 120 minutes of testing.

The application has previously been found **complete** with other bioequivalence requirement aspects (See the review V:\firmsam\anchen\ltrs&rev\77284n0904.doc).

The application is **complete.**

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Bupropion HCl ER Tablets, 150 mg & 300 mg
Reference Product	Wellbutrin XL® (bupropion HCl) Tablets, 150 mg & 300 mg
RLD Manufacturer	SmithKline Beecham
NDA No.	21-515
RLD Approval Date	08/28/2003
Indication	indicated for the treatment of major depressive disorder

B. Original Submission Review

See the review V:\firmsam\anchen\ltrs&rev\77284n0904.doc

C. Additional Dissolution Data

Due to concern of dose dumping for the drug product, the Agency has currently requested that the firm conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus 1 (basket) @ 75 rpm, with and without the alcohol (see below):

Test 1: 12 units tested 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 analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

In the current amendment, the firm has submitted the additional dissolution data as requested. The dissolution data are summarized as follows:


Test1with150mg.pdf

Test1with300mg.pdf

Test2with150mg.pdf

Test2with300mg.pdf


Test3with150mg.pdf

Test3with300mg.pdf

Test4with150mg.pdf

Test4with300mg.pdf

***NOTE:** Anchen Lot Nos. P000104-500 (150 mg) and P000204-500 (300 mg) both had proposed expiry date of 04/06. The test lots were past expiry date at the time of testing. The firm believes that this simulates worst case scenario for the Anchen product. The Lot Nos. 06E072P (150 mg) and 06E085P (300 mg) of the reference product, Wellbutrin XL®, had the expiry dates of 09/07 and 10/07, respectively.

D. Comments

Although the drug release rate was increased with the concentration of alcohol added to the medium, not more than 20% of the labeled amount of the drug was released at 120 minutes in the medium with the highest concentration of alcohol (40% v/v). The dissolution profiles of the first 2 hours of the test and reference product of both strengths are comparable, with no significant dose dumping.

	Mean % Drug Release (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	1	2	13	20
Reference	1	3	11	15
300 mg				
Test	1	2	10	15
Reference	2	4	11	18

E. Recommendations

The additional dissolution testing conducted by Anchen on its Bupropion HCl Extended Release Tablets, 150 mg and 300 mg, as requested by the DBE, is **acceptable.**

8/24/06

Hoainhon Nguyen, Branch I, Date signed

Moheb H. Makary 8/24/06

Moheb H. Makary, Ph.D., Branch I, Date signed

Barbara M Davit 8/24/06

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

v:\firmsam\anchen\77284a00806.doc

BIOEQUIVALENCE COMMENTS

ANDA: 77-284 APPLICANT: Anchen Pharmaceuticals

DRUG PRODUCT: Bupropion HCl Extended Release Tablets, 150 mg & 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 product is conducted using the following dissolution 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 product should meet the following specifications:

	(b) (4)
2 hours:	
4 hours:	
8 hours:	
16 hours:	%

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,

for Barbara McDavit

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

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HFD-652/ HNguyen
HFD-652/ MMakary

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ MMakary 8/24/06
HFD-617/ A. Sigler
HFD-650/ D. Conner BHD 8/24/06

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Printed in final on / /

BIOEQUIVALENCE - ACCEPTABLE
DISSOLUTION - ACCEPTABLE

Submission date: 08-09-06

1. Dissolution Amendment (OTH)

Strength: 150 mg & 300 mg
Outcome: AC

OUTCOME DECISIONS: **AC** - Acceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #:	77-284	**SPONSOR:**	Anchen Pharmaceuticals
DRUG & DOSAGE FORM:	Bupropion HCl ER Tablets		
STRENGTH(S):	150 mg & 300 mg		
TYPES OF STUDIES:	Fasting and Nonfasting Studies (150 mg)		
CLINICAL STUDY SITE(S):	Gateway Medical Research		
ANALYTICAL SITE(S):	(b) (4)		
STUDY SUMMARY:	Acceptable		
DISSOLUTION:	Incomplete		

DSI INSPECTION STATUS

Inspection needed:	NO	**Inspection status:**	**Inspection results:**
First Generic	YES		
New facility			
For cause			
Other			

Proposed Dissolution Method and Specifications from Original Submission Acceptable?
Yes X No _____ (If no, project Manager should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Specifications acknowledged by firm? Yes ____ No ____

AMENDMENT DATE: _____

PROJECT MANAGER: _____ **DATE:** _____

PRIMARY REVIEWER: Hoainhon Nguyen **BRANCH:** I
INITIAL: HNC DATE: 8/24/06

TEAM LEADER: Moheb H. Makary, Ph.D. **BRANCH:** I
INITIAL: MHM DATE: 8/24/06

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: BHD DATE: 8/24/06

DIVISION OF BIOEQUIVALENCE REVIEW ADDENDUM

ANDA No.	77-284
Drug Product Name	Bupropion HCl ER Tablets
Strength	150 mg & 300 mg
Applicant Name	Anchen Pharmaceutical
Address	Irvine, CA
Submission Date(s)	September 21, 2004
Amendment Date(s)	May 16, 2005
Reviewer	Hoainhon Nguyen
First Generic	Yes

This is an addendum to the original review v:\firmsam\anchen\ltrs&rev\77284n0904.doc. The purpose of the addendum is to revise the sections of the review concerning approval of the 300 mg strength of the test product.

1. The **Executive Summary** on page 1 of the original review should *now* read as follows:

"The firm has submitted a single-dose, 2-way crossover fasting bioequivalence study and a single-dose, 2-way crossover nonfasting bioequivalence study comparing the test product, Bupropion HCl Extended Release Tablets, 150 mg, with the RLD product, SmithKline Beecham's Wellbutrin XL® (bupropion HCl) Tablets, 150 mg. The fasting study was performed in 17 normal males and 15 normal females at a dose of 1x150 mg and resulted in acceptable data (point-estimate, 90% CI) that demonstrate BE in the fasted state (Bupropion: AUCt 1.02, 93.5-111.3; AUCinf 1.05, 98.3-112.8; Cmax 1.10, 99.1-122.6. Hydroxybupropion: AUCt 0.97, 88.9-106.5; AUCinf 0.97, 89.1-106.4; Cmax 1.01, 91.6-110.5). The nonfasting study was performed in 17 normal males and 14 normal females at a dose of 1x150 mg and resulted in acceptable data (point-estimate, 90% CI) that demonstrate BE in the fed state (Bupropion: AUCt 0.99, 95.0-104.0; AUCinf 1.01, 95.8-105.8; Cmax 0.99, 93.2-104.7. Hydroxybupropion: AUCt 0.97, 91.6-102.6; AUCinf 0.97, 91.9-102.7; Cmax 0.99, 94.1-104.1).

The comparative dissolution data comparing both strengths of the test product with the reference product were acceptable. The firm's proposed dissolution method was acceptable. The firm's proposed dissolution specifications are acceptable.

The formulations of the 150 mg and 300 mg strengths of the test product are proportionally similar. The 300 mg strength of the test product is deemed bioequivalent to the 300 mg strength of the RLD product, SmithKline Beecham's Wellbutrin XL® (bupropion HCl) Tablets per 21 CFR 320.24(b)(6).

The application is **complete** with no further bioequivalence deficiency at this time."

2. The **Waiver Request** section on page 9 of the original review should *now* read as follows:

Strengths for which waivers requested	300 mg
Regulation cited	21 CFR 320.24(b)(6)
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	Yes

***NOTE:** The *in vivo* bioequivalence testing for the 300 mg strength was not requested due to safety concerns for testing with any strength higher than 150 mg (See the clinical consult for the Control Document No. 02-712 ([(b) (4)]; 12/04/2002) in the review file: cdsnas\ogds11\[(b) (4)]\controls\ 02-712md.doc)).

3. The **Recommendations** section on page 9 of the original review should *now* read as follows:

"1. The single-dose, fasting bioequivalence study and the single-dose, nonfasting bioequivalence study conducted by Anchen on the test product, Bupropion HCl Extended Release Tablets, 150 mg, lot # P000104-30, comparing it with the reference product, SmithKline Beecham's Wellbutrin XL® (bupropion HCl) Tablets, 150 mg, lot # 04B044P, have been found **acceptable** by the Division of Bioequivalence. The test product, Anchen's Bupropion HCl Extended Release Tablets, 150 mg, is bioequivalent to the reference product, Wellbutrin XL® (bupropion HCl) Tablets, 150 mg.

2. The dissolution testing conducted by Anchen on its Bupropion HCl 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 specifications:

2 hours:	[(b) (4)]
4 hours:	
8 hours:	
16 hours	%

3. The formulations of the 300 mg and 150 mg strengths of the test product are proportionally similar. The test product, Anchen's Bupropion HCl Extended Release Tablets, 300 g, is deemed bioequivalent to the reference product, Wellbutrin XL® (bupropion HCl) Tablets, 300 mg, per 21 CFR 320.24(b)(6).

The application is **complete** with no further bioequivalence deficiency at this time."

ANDA 77-284

BIOEQUIVALENCE - ACCEPTABLE
DISSOLUTION - **ACCEPTABLE**

Submission dates: 09-21-04 & 05-16-05

1. ADDENDUM (OTH)

Strength: 300 mg
Outcome: WC

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

/s/

Hoainhon T. Nguyen
12/13/2006 04:07:52 PM
BIOPHARMACEUTICS

Moheb H. Makary
12/13/2006 04:09:26 PM
BIOPHARMACEUTICS

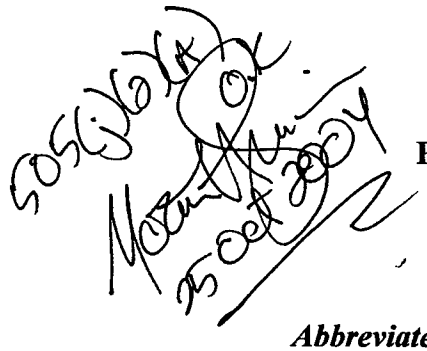
Barbara Davit
12/13/2006 04:15:26 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077284

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS



Anchen
Pharmaceuticals, Inc.

September 21, 2004

Abbreviated New Drug Application

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

77-284

RE: **Bupropion Hydrochloride Extended Release (ER) Tablets**
150 mg and 300 mg

Dear Mr. Buehler:

Anchen Pharmaceuticals, Inc. (Anchen) submits herein an original Abbreviated New Drug Application for Bupropion Hydrochloride ER Tablets, 150 mg and 300 mg.

The drug product described above is the same as the Reference Listed Drug (RLD) Wellbutrin XL™ (bupropion hydrochloride extended-release tablets) 150 mg and 300 mg by GlaxoSmithKline (GSK), the NDA holder (please note SmithKline Beecham is listed as the NDA holder in the Orange Book). We have submitted comparative information to indicate that our product is the same as the RLD. This information is presented in tabular form in Section IV, comparing active ingredients, inactive ingredients, condition of use, route of administration, dosage form, strength, bioequivalence, and labeling for the products as supplied by Anchen and by GlaxoSmithKline.

Anchen commits to resolve any issues identified in the method validation process after approval.

In accordance with the electronic labeling rule published on Dec. 11, 2003 (68FR 69009), Anchen provides one (1) computer diskette (CD) of Anchen proposed labeling in PDF and WORD format. This CD is located at the front of Volume 1 of the Archival copy of this ANDA.

The bioanalytical study reports and method validation are included in Section XXI of this submission. In addition, we have included two (2) computer diskettes with the analytical data and bioavailability parameters in the format prescribed by FDA. The diskettes are located at the front of Volume 1 of the Orange Review Copy of this application.

One archival and one review copy of this ANDA are included. In accordance with 21 CFR 314.94(d)(5), one (1) field copy of the application will be forwarded to the Los Angeles District Office. Anchen certifies that the Field Copy is a true copy of the technical sections contained in the archival and review copies of this ANDA.

5 Goodyear . Irvine, CA 92618 . (949) 837-6178 . Fax (949) 837-6120

As required, two (2) additional separately bound copies of the analytical methods and descriptive information needed to perform the tests on the active pharmaceutical ingredient and finished products are included in this ANDA. These are in plain blue pressboard covers.

The number of volumes in the archival, review, and field copies of the ANDA are as follows:

Blue Archival Copy	- 8 volumes
Orange Review Copy	- 6 volumes
Red Review Copy	- 2 volumes
Burgundy Field Copy	- 2 volumes

We trust the information submitted is sufficient for this Abbreviated New Drug Application to be evaluated. Please contact me by phone at (949) 837-6178 ext. 102 or by fax at (949) 837-6120 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Maggie Chang, Ph.D.
Vice President, Quality Affairs

Bio

(P)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : September 23, 2004

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 77-284 for Bupropion Extended-release Tablets, 150 mg and 300 mg **(the 300 mg is a new strength)** to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv).

Anchen Pharmaceuticals Inc. has submitted ANDA 77-284 for Bupropion Extended-release Tablets, 150 mg and 300 mg **(the 300 mg is a new strength)**. The ANDA contains a certification pursuant to 21 USC 355(j)(5)(B)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Anchen Pharmaceuticals Inc. on September 21, 2004 for its Bupropion product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 77-284 **FIRM NAME Anchen Pharmaceuticals, Inc.**

DRUG NAME Bupropion Hydrochloride

DOSAGE FORM Extended release tablets, 150 mg and 300 mg
SUBJ: Request for examination of: Bioequivalence Study

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☒	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

Shirley Lu Date: 9/29/04
Reviewer

Kuldeep Dhariwal Date: 9/29/04
Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			p. 247-263, p. 1467-1488
Assay Methodology	☒	☐			p. 732-749
Procedure SOP	☒	☐			p. 732-738
Methods Validation	☒	☐			p. 714-753
Study Results Ln/Lin	☒	☐			p. 6-11, p. 1231-1236
Adverse Events	☒	☐			p. 242, p. 1462
IRB Approval	☒	☐			p. 282
Dissolution Data	☒	☐			p. 39-56
Pre-screening of Patients	☒	☐			vol. 2, vol. 5
Chromatograms	☒	☐			vol. 3, vol. 6
Consent Forms	☒	☐			p. 301
Composition	☒	☐			p. 84-87
Summary of Study	☒	☐			p. 1021-1047
Individual Data & Graphs, Linear & Ln	☒	☐			p. 56-119, p. 165-228, p. 1280-1341, p. 1387-1448
PK/PD Data Disk Submitted)	☒	☐			in EDR
Randomization Schedule	☒	☐			p. 1029
Protocol Deviations	☒	☐			p. 249, p. 1462
Clinical Site	☒	☐			p. 28
Analytical Site	☒	☐			p. 28
Study Investigators	☒	☐			p. 31

Medical Records	☒	☐			vol. 2, vol. 5
Clinical Raw Data	☒	☐			vol. 2, vol. 5
Test Article Inventory	☒	☐			p. 307-309, p. 1527-1529
BIO Batch Size	☒	☐			p. 84
Assay of Active Content Drug	☒	☐			p. 60, p. 65
Content Uniformity	☒	☐			p. 60, p. 65
Date of Manufacture	☒	☐			p. 34
Exp. Date of RLD	☒	☐			p. 34
BioStudy Lot Numbers	☒	☐			p. 307, p. 1527
Statistics	☒	☐			p. 6-11, p. 1231-1236
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			p. 1032, p. 1042
Waiver requests for other strengths / supporting data	☒	☐			p. 32

Additional Comments regarding the ANDA:

The firm conducted fasting and fed studies on the 150 mg strength and is requesting a waiver for the 300 mg strength. The firm also measured both the parent drug (bupropion) and the main active metabolite (hydroxybupropion) in plasma. This was done in accordance with a controlled document dated May 18, 2004, which was included with the application on page 36.

Telecon Record

Date: 10/13/04

ANDA: 77-284

Firm: Anchen Pharmaceuticals, Inc.

Drug: Bupropion Hydrochloride Extended-release Tablets USP, 150mg and 300mg

FDA Participants: Iain Margand

Industry Participants: Connie Chang

Phone: 949-837-6178

Agenda:

1. Iain requested the following:

   Provide a Form 356H with original signature.

   Change the established name of drug on 356H Form to designate product as a USP product (Bupropion Extended-release listed in USP website).

   Provide protocol information for stability data.

   Provide Certificates of Analysis from supplier and applicant for (b) (4) (b) (4) and (b) (4) in the inactive ingredient section.

Anchen

Pharmaceuticals, Inc.

Archival Copy

October 15, 2004

Telephone Amendment

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/MC

RE: **ANDA 77-284**
Bupropion Hydrochloride Extended Release (ER) Tablets
150 mg and 300 mg

Dear Mr. Buehler:

Anchen Pharmaceuticals, Inc. (Anchen) is submitting this telephone amendment in response to the request from Mr. Iain Margand, Office of Generic Drugs, Regulatory Support Branch, on October 13, 2004. For convenience of review, your comments are provided in bold face type, followed by our responses.

Comment 1: Please provide original signed copy of FDA 356h Form. Also please include "USP" in your product name in the Established Name section of the FDA Form 356h.

We have revised the FDA Form 356h to include "USP" in the Established Name section as requested by the Agency (see **Exhibit 1**).

Please note that Anchen's Bupropion Hydrochloride Extended Release Tablets, 150 mg and 300 mg, the subject of this application is the same as Wellbutrin XL ™. In our opinion, bupropion hydrochloride extended release tablets, USP referenced in the USP27/NF22 is for Wellbutrin SR.

Comment 2: Please provide detailed proposed stability protocol.

We have included a revised proposed stability protocol with detail of test specifications, test interval, packaging material and manufacturing site (see **Exhibit 2**).

Comment 3: Please provide information related to raw material (b) (4) **and** (b) (4).

We have provided information related to raw material (b) (4) and (b) (4) in **Exhibit 3**.

RECEIVED

OCT 18 2004

OGD / CDER

5 Goodyear . Irvine, CA 92618 . (949) 837-6178 . Fax (949) 837-6120

We believe that this response adequately addresses OGD's comments. Should any additional information be required, please contact me at (949) 837-6178 ext. 102 or by fax at (949) 837-6120.

Sincerely,

Maggie Chang, Ph.D.
Vice President, Quality Affairs

ANDA 77-284 Final Check List for Branch Chief

✓ 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.

✓ 3) Check for gross errors in letter.

✓ 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)

✓ 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.

✓ 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 150 mg

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.

✓ 14) Review Basis for Submission. 21-515 wellbutrin XL 150 & 300 mg

✓ 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 A. Johnson date 25 Oct 2004

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 77-284 **FIRM NAME**: ANCHEN PHARMACEUTICALS INC.

RELATED APPLICATION(S): NA

First Generic Product Received? YES ON 300 MG ONLY

DRUG NAME: BUPROPION HYDROCHLORIDE
DOSAGE FORM: TABLETS, 150 MG AND 300 MG

Bio Assignments:	☐ **Micro Review**
☒ **BPH**	
☐ **BCE**	
☐ **BST**	

Random Queue: 10
Chem Team Leader: Rosencrance, Susan PM: Tom Hinchliffe Labeling Reviewer: Michelle Dillahunt

Letter Date: SEPTEMBER 21, 2004	**Received Date**: SEPTEMBER 21, 2004
Comments: EC- 2 YES **On Cards:** YES **Therapeutic Code:** 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) YES (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 Iain Margand** **Date 10/18/04**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date:	**Date:** 25 Oct 2004
ADDITIONAL COMMENTS REGARDING THE ANDA: **See T-con dated 10/13/04**	
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 XL 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 2. Expiration of Patent: 10-30-2018 A. Pediatric Exclusivity Submitted? N/A B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement:** YES	☒
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Y 2. Active ingredients Y 3. Route of administration Y 4. Dosage Form Y 5. Strength Y	☒
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL Y 2. 1 RLD label and 1 RLD container label Y 3. 1 side by side labeling comparison with all differences annotated and explained Y 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 **2. Request for Waiver of In-Vivo Study(ies): YES ON 300 MG** **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) **4. Lot Numbers of Products used in BE Study(ies): 150mg: P000104 300mg: P000204** 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 (SEE REFERENCE NUMBER # (OGD# 04-344) LETTER DATED: 4-06-04 AND STAMP DATE: 5-18-04) a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) Both Bupropion and Hydroxybupropion measured b. EDR Email: Data Files Submitted: YES SENT TO EDR c. In-Vitro Dissolution: YES Starts Pg. 39	☒

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 Pg. 84-88 2. Inactive ingredients as appropriate Excipients acceptable per IIG	☒

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers Y b. Type II DMF authorization letters or synthesis DMF# (b) (4) c. COA(s) specifications and test results from drug substance mfgr(s) Y d. Applicant certificate of analysis e. Testing specifications and data from drug product manufacturer(s) Y f. Spectra and chromatograms for reference standards and test samples Y g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified Y b. Testing specifications (including identification and characterization) Y c. Suppliers' COA (specifications and test results) Y d. Applicant certificate of analysis Y	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) Y 2. CGMP Certification: YES 3. CFN numbers	☒
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address Y 2. Functions Y 3. CGMP Certification/GLP Y 4. CFN numbers	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) Y 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified 150mg : (b) (4) 300mg: (b) (4) 3.If sterile product: Aseptic fill / Terminal sterilization N/A 4.Filter validation (if aseptic fill) N/A 5. Reprocessing Statement Y Pg.452	☒
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 Y Ty: 150mg- (b) (4) 300mg- (b) (4) Ay: Packaged: 30's- (b) (4) (b) (4) 30's- (b) (4) (b) (4)	☒
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) Y 2. Components Specification and Test Data (Type III DMF References) Y 3. Packaging Configuration and Sizes 30 and (b) (4) count bottle size 4. Container/Closure Testing Y 5. Source of supply and suppliers address Y	☒

Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data Y 2. Certificate of Analysis for Finished Dosage Form Y	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted Y 2. Post Approval Commitments Pg. 941 3. Expiration Dating Period 24 months 4. Stability Data Submitted a. 3 month accelerated stability data Y b. Batch numbers on stability records the same as the test batch 150mg: P000104 300mg: P000204	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance Y 2. Finished Dosage Form Y 3. Same lot numbers Y	☒
Sec. XVII	**Environmental Impact Analysis Statement Y Pg. 1011**	☒
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other**: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A 2. Debarment Certification (original signature): YES 3. List of Convictions statement (original signature) N/A 4. Field Copy Certification (original signature) Y (in cover letter)	☒

OGD Template Revised 04/01/2004 /T.Hinchliffe

ANDA 77-284

Anchen Pharmaceuticals, Inc.
Attention: Maggie Chang, Ph.D.
5 Goodyear
Irvine, CA 92618

NOV 10 2004

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated October 13, 2004 and your correspondence dated October 15, 2004.

NAME OF DRUG: Bupropion Hydrochloride Extended-release Tablets USP, 150 mg and 300 mg

DATE OF APPLICATION: September 21, 2004

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 21, 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 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:

Tom 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

cc: ANDA 77-284
DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/G. Davis
HFD-92

Endorsement: HFD-615/MShimer, Chief, RSB _____ date 8 Nov 2004
HFD-615/IMargand, CSO _____ date 10/25/04
Word File V:\Filesam\Anchen\Ltrs&rev\77284.ack
FT/ 10/18/04
ANDA Acknowledgment Letter!

Anchen

Pharmaceuticals, Inc.

Archival Copy

January 13, 2005

N|xP

Patent Amendment

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: **ANDA 77-284**
Bupropion Hydrochloride Extended Release (ER) Tablets, USP
150 mg and 300 mg

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application, ANDA No. **77-284** for Bupropion Hydrochloride Extended Release (ER) Tablets, USP 150 mg and 300 mg.

Anchen Pharmaceuticals, Inc. (Anchen) is amending the above application in accordance with 21 C.F.R. § 314.95(e) to include documentation of receipt of the notice required under paragraph (a) of this section by each person provided the notice. Anchen certifies that the documentation of receipt of notice requirements stated in 21 C.F.R. § 314.95(e) have been satisfied. On 11/12/04 a notice-of-paragraph-IV-certification letter was sent to GlaxoSmithKline and Biovail Laboratories Inc., in accordance with 21 C.F.R. § 314.95(a). Biovail Laboratories Inc., is the owner of United States Patent No. 6,096,341 and 6,143,327. GlaxoSmithKline is the holder of the approved NDA No. 21-515 under § 505(b) of the Federal Food, Drug and Cosmetic Act for the listed drug, Wellbutrin XL™, for which Anchen is seeking approval. United States Patent No. 6,096,341 and 6,143,327 are the subject of Anchen's Paragraph IV Certification. The content of the notice letter complied with the requirements set forth in 21 C.F.R. § 314.95(c). The letters were sent by certified Mail.

In accordance with 21 C.F.R. § 314.95(e), Anchen encloses, as proof of receipt of notification, the following documentation:

As proof of receipt of notice by GlaxoSmithKline (**Exhibit 1**):

a. a copy of the certified mail receipt sent to GlaxoSmithKline
b. a copy of the certified mail postcard received from GlaxoSmithKline, indicating delivery on 11/17/04

5 Goodyear . Irvine, CA 92618 . (949) 837-6178 . Fax (949) 837-6120

As proof of receipt of notice by Biovail Laboratories Inc., (**Exhibit 2**):

a. Mail sent to Biovail c/o Alston & Bird LLP in Charlotte, North Carolina
   1. a copy of the certified mail receipt sent to Alston & Bird LLP.
   2. a copy of the certified mail postcard received from Alston & Bird LLP, indicating delivery on 11/15/04
b. Mail sent to Biovail in St. Michael, Barbados
   1. a copy of the certified mail receipt sent to Biovail on 11/12/04
   2. a copy of the certified mail receipt (a re-sent mail) to Biovail on 11/30/04
   3. a copy of the certified mail postcard received from Biovail Laboratories Inc., indicating delivery on 12/14/04
c. Mail sent to Biovail in Ontario, Canada
   1. a copy of the certified mail receipt sent to Biovail on 11/12/04
   2. a copy of the transmission from the U.S. Postal Service indicating that the item was delivered in Canada on 11/22/04.

Additionally, we have received a notification from United States District Court Central District of California indicating that Biovail Laboratories Inc., and SmithKline Beecham Corp. filed a complaint for patent infringement against Anchen Pharmaceuticals, Inc., A copy of the notification is included for your reference (**Exhibit 3**).

One archival and one review copy of this amendment is included. In accordance with 21 CFR 314.96(b), one (1) field copy of the application will be forwarded to the Los Angeles District Office. Anchen Pharmaceuticals, Inc. certifies that the Field Copy is a true copy of the technical sections contained in the archival and review copies of this ANDA.

Please contact me at (949) 837-6178 ext. 102 or by fax at (949) 837-6120, if you have any questions or require additional information.

Sincerely,

Maggie Chang, Ph.D.
Vice President, Quality Affairs

ORIG AMENDMENT

N/AM

Anchen Pharmaceuticals, Inc.

Archival Copy

April 07, 2005

Minor CMC Amendment

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 77-284
Bupropion Hydrochloride Extended Release (ER) Tablets, USP
150 mg and 300 mg

Dear Mr. Buehler:

Anchen Pharmaceuticals, Inc. (Anchen) is submitting the minor amendment in response to your comments received on March 10, 2005 (see attached). For convenience of review, your comments are provided in bold face type, followed by our responses.

A. Deficiencies:

1. (b) (4)

2.

5 Goodyear . Irvine, CA 92618 . (949) 837-6178 . Fax (949) 837-6120

RECEIVED
APR 08 2005
OGD/CDER

Following this page, 6 pages withheld in full (b)(4)-CCI/TS (CMC deficiencies)

(b) (4)

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

1. The test specification and test method for Drug Release will be evaluated by the Division of Bioequivalence, comments, if any, will be provided to you separately.

Anchen acknowledges that the test specification and test method for drug release will be evaluated by the Division of Bioequivalence that will be provided to us separately.

2. Please provide all available room temperature stability data in your next amendment.

Nine (9) months Controlled Room Temperature is provided in **Exhibit 12a-12d**. All data meet specifications.

We believe that this response adequately addresses OGD's comments. Should any additional information be required, please contact me at (949) 837-6178 ext. 102 or by fax at (949) 837-6120.

Sincerely,

Maggie Chang, Ph.D.
Vice President, Quality Affairs

Anchen

Pharmaceuticals, Inc.

ORIG AMENDMENT

Archival Copy

May 16, 2005

Bioequivalency Amendment

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 77-284
Bupropion Hydrochloride Extended Release (ER) Tablets, USP
150 mg and 300 mg

Dear Mr. Buehler:

Anchen Pharmaceuticals, Inc. (Anchen) is submitting the Bioequivalency Amendment in response to your comments received on April 18, 2005 (see attached). For convenience of review, your comments are provided in bold face type, followed by our responses.

1. ***Please conduct comparative dissolution testing using 12 dosage units of the test and reference products using the following USP method:***

Medium:	***water***
Volume:	***900 mL***
Temperature:	***37°C***
Apparatus:	***Apparatus II (paddle)***
Rotation:	***50 rpm***
Specification:	(b) (4) ***% in 1 hour***
	% in 4 hours
	in 8 hours

We have conducted the comparative drug release testing as requested and the testing results are provided in **Exhibit 1**. Please note that the Wellbutrin XL™ 300 mg, Lot # 03K056P used in the original drug release testing expired in 02/05, therefore, a new lot of 300 mg Lot #05B063P was used in this comparative drug release testing study.

Based on the data provide in **Exhibit 1** for Wellbutrin XL™ and Anchen product, both Wellbutrin XL™ and Anchen product are not the same as the extended-release product cited in the USP monograph, which is controlled by a different release mechanism. Therefore, we would like to propose the following drug release specifications for the routine monitoring of our product:

5 Goodyear . Irvine, CA 92618 . (949) 837-6178 . Fax (949) 837-6120

Medium:	***0.1 N HCl***
Volume:	***900 mL***
Temperature:	***37°C***
Apparatus:	***Apparatus I (Basket)***
Rotation:	***75 rpm***
Specification:	(b) (4) ***% in 2 hours***
	(b) (4) ***% in 4 hours***
	% in 8 hours
	(b) (4) ***% in 16 hours***

Anchen commits to revise the finished product release specification once the Agency accepts our proposed specification.

2. ***In additional, please conduct dissolution testing in at least three other dissolution media (e.g. pH 1.2, 4.5, and 6.8) using the USP apparatus II (paddle) at 50 rpm.***

We have conducted the comparative drug release testing with the drug release media such as 0.1 N HCl, pH 4.5 Acetate Buffer and pH 6.8 Phosphate Buffer as requested and the testing results are provided in **Exhibit 2.**

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.

Anchen provides one (1) computer diskette (CD) that contains electronic data including the in-vivo study data, dissolution data and formulation data in the format specified by the Agency. The CD is located at the front of the Archival copy of this amendment.

In addition, we received an updated bio-analytical method validation report "Addendum D" from (b) (4) for the bio-analytical method "AN LC/MS/MS METHOD FOR THE DETERMINATION OF BUPROPION AND HYDROXYBUPROPION IN HUMAN EDTA PLASMA SAMPLES SPIKED WITH HYDROCHLORIC ACID" dated 9/14/04. This Addendum (**Exhibit 3**) is to provide stability data of the standard stock solutions of bupropion and hydroxybupropion to 94 days when stored in a refrigerator. The method validation report (report number 000-04005V) was filed in the original ANDA submission Volume 5 of 8 on page 706.

We believe that this response adequately addresses OGD's comments. Should any additional information be required, please contact me at (949)-837-6178 ext. 102 or by fax at (949)-837-6120.

Sincerely,

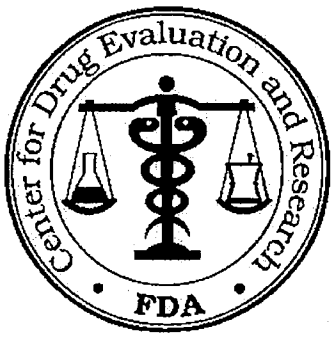
Maggie Chang, Ph. D.
Vice President, Quality Affairs

BIOEQUIVALENCY AMENDMENT

ANDA 77-284

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUN 29 2005



APPLICANT: Anchen Pharmaceuticals, Inc.

TEL: 949-837-6178 x102

ATTN: Maggie Chang

FAX: 949-837-6120

FROM: Aaron Sigler AS

PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on September 21, 2004, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Extended-release Tablets USP, 150 mg and 300 mg.

Reference is also made to your amendment dated May 16, 2005.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 1 page. 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:

JUN 29 2005

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-284 APPLICANT: Anchen Pharmaceuticals

DRUG PRODUCT: Bupropion HCl Extended Release Tablets, 150 mg & 300 mg

The Division of Bioequivalence (DBE) has completed its review and has the following comments:

We agree that the dissolution testing for the test product should be conducted using your proposed dissolution 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.

However, based on the dissolution data submitted, the DBE recommends the following specifications:

2 hours:	(b) (4)
4 hours:	
8 hours:	
16 hours:	%(Q)

Since the above specifications are different from those proposed by you, please provide your acknowledgement of the DBE's proposed specifications.

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

Anchen ANCHEN PHARMACEUTICALS, INC.

Archival Copy

ORIG AMENDMENT
N/AF

August 18, 2005

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Labeling Amendment
FINAL PRINTED LABELING INCLUDED

RE: ANDA 77-284
Bupropion Hydrochloride Extended Release (ER) Tablets (XL), USP
150 mg and 300 mg

Dear Mr. Buehler:

Anchen Pharmaceuticals, Inc. (Anchen) is submitting the Labeling Amendment in response to your comments received on June 17, 2005 (see attached). For convenience of review, your comments are provided in bold face type, followed by our responses.

General

- **The Division of Neuropharmacological Drug Products and the Office of New Drug Evaluation I have determined that, in order to ensure that safety information is provided with all antidepressant products, the products are ONLY to be distributed in unit-of-use packages with each package having a MedGuide affixed to the container. The unit-of-use packages should be designed for direct dispensing to the patient, with child-resistant closures, and with package sizes based on monthly usage (30's, 60's, 90's, etc.) up to a three months supply. Please note that you should transition to the unit of use packaging by January 2006.**

We will package and distribute our product in unit-of-use of package sizes, 30's, 60's and 90's. Each package size will have a Medication Guide affixed to the container as requested by the Agency.
Container labels for the 30's and 90's for both strengths are included electronically in the Computer Diskette (CD) at the front of the Archival Copy. *Please refer to the Table of Contents (TOC) of the CD for details.* The "HOW SUPPLY" section of the package insert was revised accordingly (*please refer to the TOC of the CD for the path to the revised insert*). In addition, final printed version of the Medication Guide is also provided (please refer to the TOC of the CD).

- **This drug product appears to be a subject of USP 28 monograph. Please include the term "USP" in association with the established name.**

We have included "USP" with the established name as requested in all of our final printed labeling. *Please refer to TOC of the CD.*

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- **Submit your proposal for dissemination of the medication guide for review.**

We have included our final printed medication guide for your review. Each package size will have a Medication Guide affixed to the container

- **Reformat your principal display panel to include all the information shown below as an example.**

Once Daily **BUPROPION HCL** **EXTENDED-RELEASE TABLETS (XL)** **XXX mg** **Warning: Do not use in combination with ZYBAN® or any other medicines that contain bupropion hydrochloride.** **XXX** Tablets Rx only **ATTENTION: Dispense with Medication Guide**

We have revised our container labels as requested. *Please refer to TOC of the CD for the path to the container labels.*

CONTAINER: 30s and (b) (4) (150 mg & 300 mg)

- **See comments under GENERAL**

We have revised our container labels as requested. *Please refer to TOC of the CD for the path to the container labels.*

PHYSICIAN INSERT/MEDICATION GUIDE

- **Update your labeling based on the attached approved labeling for the reference listed drug, Wellbutrin XL, approved January 12, 2005.**

We have revised our package insert in accordance with the Wellbutrin XL as requested.

In addition, we have revised the "Description" Section in the Physician Insert to include the solvent ethyl alcohol and the storage statement to "**Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature]**" as committed in our CMC amendment dated April 7, 2005.

The final printed labeling are provided as electronic format per the electronic labeling rule published in December 11, 2003 (68 FR 69009), effective 6/8/04. The labeling is provided in MS Word and pdf formats to assist your review.

In order to further facilitate review of our amendment, we have provide a side-by-side comparison of our proposed outsert labeling with the attached reference listed drug labeling (approved January 12, 2005) and our proposed container labels with the one submitted in the original ANDA (Sept, 21, 2004). All differences are highlighted, annotated and explained.

We acknowledge that it may be necessary to further revise our labeling subsequent to approved changes for the reference listed drug prior approval.

Anchen provides one (1) computer diskette (CD) that contains electronic final printed labeling located at the front of the Archival copy of this amendment.

We believe that this response adequately addresses OGD's comments. Should any additional information be required, please contact me at (949)-837-6178 ext. 127 or by fax at (949)-837-6120.

Sincerely,

M. Choy

Margaret Choy, M.S.
Vice President, Regulatory Affairs

FDA FAX

ANDA 77-284

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: Anchen Pharmaceuticals, Inc.

TEL: 949-837-6178 x127

ATTN: Margaret Choy

FAX: 949-837-6120

FROM:

PROJECT MANAGER:

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated September 21, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Extended-release Tablets USP, 150 mg and 300 mg.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

*You should respond to these deficiencies with a "**Telephone Amendment**" within ten days. If you have questions regarding these deficiencies please contact the Project Manager, Tom Hinchliffe, at 301-827-5771. Please submit documentation by fax to the attention of the Project Manager at 301-443-3839. Please also submit official hard copies of any faxed documentation to the Document Room.*

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-284

APPLICANT: Anchen Pharmaceuticals, Inc.

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

*The deficiencies presented below represent MINOR deficiencies and the current review cycle will remain open. You should respond to these deficiencies with a "**Telephone Amendment**" within ten days. If you have questions regarding these deficiencies please contact the Project Manager, Tom Hinchliffe, at 301-827-5771. Please submit documentation by fax to the attention of the Project Manager at 301-443-3839. Please also submit official hard copies of any faxed documentation to the Document Room.*

A. Deficiencies:

1. (b) (4)

2.

3.

(b) (4)

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

Please revise and submit the Description section and storage statement when you respond to the labeling deficiencies.

Anchen ANCHEN PHARMACEUTICALS, INC.

Archival Copy

ORIG AMENDMENT
N/AM

September 8, 2005

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Telephone Amendment

RE: ANDA 77-284
Bupropion Hydrochloride Extended-Release (ER) Tablets (XL), USP
150 mg and 300 mg

Dear Mr. Buehler:

Anchen Pharmaceuticals, Inc. (Anchen) is submitting the Telephone Amendment in response to your comments received on September 1, 2005 (see attached). For convenience of review, your comments are provided in bold face type, followed by our responses.

A. Deficiencies:

1. (b) (4)

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2. (b) (4)

3.

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

Please revise and submit the Description section and storage statement when you respond to the labeling deficiencies.

We have submitted the Labeling amendment to the Agency on August 18, 2005 which included the revised Description section and storage statement as requested in the labeling deficiencies.

One archival and one review copy of this amendment is included. In accordance with 21 CFR 314.96(b), one (1) field copy of the application will be forwarded to the Los Angeles District Office. Anchen Pharmaceuticals, Inc. certifies that the Field Copy is a true copy of the technical sections contained in the archival and review copies of this ANDA.

We believe that this response adequately addresses OGD's comments. Should any additional information be required, please contact me at (949) 837-6178 ext. 127 or by fax at (949) 837-6120.

Sincerely,

Margaret L. Choy, M.S.
Vice President, Regulatory Affairs

Archival Copy

ANCHEN PHARMACEUTICALS, INC.

ORIG AMENDMENT

October 11, 2005

N/AF

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Labeling Amendment
FINAL PRINTED LABELING INCLUDED

RE: ANDA 77-284
Bupropion Hydrochloride Extended Release (ER) Tablets USP (XL)
150 mg and 300 mg

Dear Mr. Buehler:

Anchen Pharmaceuticals, Inc. (Anchen) is submitting the Labeling Amendment in response to your comments received on September 28, 2005 (see attached). For convenience of review, your comments are provided in bold face type, followed by our responses.

General

- **This drug product appears to be a subject of USP 28 monograph. Please include the term "USP" in association with the established name as follows:**
  "Bupropion Hydrochloride Extended Release Tablets USP (XL)"

We have revised our labeling to include "USP" with the established name in the exact format and order as requested in our final printed labeling. *Please refer to the Table of Contents (TOC) of the CD for details.*

- **Your proposal for dissemination of the medication guide is acceptable.**

We acknowledge that our proposal for dissemination of the medication guide is acceptable.

Container: 30s and (b) (4) (150 mg & 300 mg)

- **See comments under General.**

We have revised our container labels for the 30s, 60s, and 90s as requested. Please note that we will not be marketing the (b) (4) as requested by the Agency in your comments received on September 28, 2005. *Please refer to TOC of the CD for path to the container labels.*

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OCT 12 2005
OGD/CDER

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- **As requested previously, reformat your principal display panel to include all the information shown below as an example. The "Attention:" statement could be located on the side panel if there is not enough space on the principal display panel.**

Once Daily **BUPROPION HCL** **EXTENDED-RELEASE TABLETS USP (XL)** **XXX mg** **Warning: Do not use in combination with ZYBAN® or any other medicines that contain bupropion hydrochloride.** **XXX** Tablets Rx only **ATTENTION: Dispense with Medication Guide**

We have revised our container labels as requested to display "Warning: Do not use in combination of ZYBAN® or any other medicines that contain bupropion hydrochloride" on the principal display panel and "Attention: Dispense with Medication Guide" on the side panel due to space limitation. *Please refer to TOC of the CD for the path to the container labels.*

PHYSICIAN INSERT/MEDICATION GUIDE

- **Under PRECAUTIONS: Cardiovascular Effect, 2nd paragraph, 4th sentence.**

  Replace "sustained-release formulation of bupropion" with "Zyban" as appears on the RLD.

We have revised our insert to include the requested replacement in our final printed labeling. *Please refer to TOC of the CD.*

The final printed labeling are provided as electronic format per the electronic labeling rule published in December 11, 2003 (68 FR 69009), effective 6/8/04. The labeling is provided in MS Word and pdf formats to assist your review.

We acknowledge that it may be necessary to further revise our labeling subsequent to approved changes for the reference listed drug prior approval.

Anchen provides one (1) computer diskette (CD) that contains electronic final printed labeling located at the front of the Archival copy of this amendment.

We believe that this response adequately addresses OGD's comments. Should any additional information be required, please contact me at (949)-837-6178 ext. 127 or by fax at (949)-837-6120.

Sincerely,

M. Choy

Margaret Choy, M.S.
Vice President, Regulatory Affairs

Anchen ANCHEN PHARMACEUTICALS, INC.

Archival Copy

November 7, 2005

ORIG AMENDMENT
N/Am

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Telephone Amendment

RE: ANDA 77-284
Bupropion Hydrochloride Extended-Release (ER) Tablets USP (XL)
150 mg and 300 mg

Dear Mr. Buehler:

Anchen Pharmaceuticals, Inc. (Anchen) is submitting this Telephone Amendment in response to comments provided by the Agency in our telephone conversation between Dr. Florence Fang, Dr. Bingyuan Wu and Margaret Choy on November 7, 2005. For convenience of review, your comments are provided in bold face type, followed by our responses.

Comment:

1. (b) (4)

2.

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One archival and one review copy of this amendment is included. In accordance with 21 CFR 314.96(b), one (1) field copy of the application will be forwarded to the Los Angeles District Office. Anchen Pharmaceuticals, Inc. certifies that the Field Copy is a true copy of the technical sections contained in the archival and review copies of this ANDA.

We believe that this response adequately addresses OGD's comments. Should any additional information be required, please contact me at (949) 837-6178 ext. 127 or by fax at (949) 837-6120.

Sincerely,

M. Choy

Margaret L. Choy, M.S.
Vice President, Regulatory Affairs

Anchen ANCHEN PHARMACEUTICALS, INC.

Archival Copy

November 9, 2005

ORIG AMENDMENT
N/AM

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Telephone Amendment

RE: ANDA 77-284
Bupropion Hydrochloride Extended-Release (ER) Tablets USP (XL)
150 mg and 300 mg

Dear Mr. Buehler:

Anchen Pharmaceuticals, Inc. (Anchen) is submitting this Telephone Amendment in response to comments provided by the Agency in our telephone conversation between Dr. Florence Fang, Dr. Bingyuan Wu and Margaret Choy on November 9, 2005. For convenience of review, your comments are provided in bold face type, followed by our responses.

Comment:

1. (b) (4)

[redacted]

One archival and one review copy of this amendment is included. In accordance with 21 CFR 314.96(b), one (1) field copy of the application will be forwarded to the Los Angeles District Office. Anchen Pharmaceuticals, Inc. certifies that the Field Copy is a true copy of the technical sections contained in the archival and review copies of this ANDA.

We believe that this response adequately addresses OGD's comments. Should any additional information be required, please contact me at (949) 837-6178 ext. 127 or by fax at (949) 837-6120.

RECEIVED
NOV 10 2005
OGD / CDER

5 Goodyear, Irvine • CA 92618 U.S.A. • Tel: +1 949-837-6178 • Fax: +1 949-837-6120

Sincerely,

M. Choy

Margaret L. Choy, M.S.
Vice President, Regulatory Affairs

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-284 Applicant Anchen Pharmaceuticals, Inc
Drug Bupropion HCl Extended-release Tablets USP Strength(s) 150mg + 300mg

APPROVAL ☐ **TENTATIVE APPROVAL** ☑ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: | **DRAFT Package** | **FINAL Package**

1. Martin Shimer
Chief, Reg. Support Branch

Date 31 Oct 2005 Initials MMS | Date 11/14/05 Initials for

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = Wellbutrin XL NDA# 21-515 150mg + 300mg
Patent/Exclusivity Certification: Yes ☑ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☑ No ☐
Was applicant sued w/in 45 days: Yes ☑ No ☐
Has case been settled: Yes ☐ No ☑ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐ (not determined)
Date Checked
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐
Type of Letter: PIV to both '341 & '327 patents. CN-SNEV04-1468-JVS(Rax) filed on 12/23/04
Comments: for infringement of both the '341 & '327 patents 30 month = 6/14/07

2. Project Manager, THinchliffe Team 10
Review Support Branch

Date 10/24/05 Initials | Date 10/31/05 Initials

Original Rec'd date 9-21-04
Date Acceptable for Filing 9-21-04 ✓
Patent Certification (type) IV
Date Patent/Exclus.expires 10-30-18
Citizens' Petition/Legal Case Yes ☐ No ☐
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Acceptable Bio reviews tabbed Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 2-7-05 (folder)
Date of Office Bio Review 7-15-05 (V 3.1)
Date of Labeling Approv. Sum 10/20/05
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☒

Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def. /NA Minor issued ☐ Date
Comments:

3. David Read **(PP IVs Only)**
OGD Regulatory Counsel,
Comments:

Pre-MMA Language included ☐
Post-MMA Language Included ☑
see revised version.

Date 10/28/05 Initials DR

4. Div. Dir./Deputy Dir.
Chemistry Div. I II OR III
Comments:

Concerns regarding the [redacted] (b)(4) were addressed in 11/7 and 11/9/05 amendments.

CMC OK

Date 11/09/05 Initials

REVIEWER: **FINAL ACTION**

5. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)
Multiple ANDAs for Wellbutrin SR tablets (Bupropion HCl Extended-release tablets (SR) have been approved).

6. Vacant RCD = Wellbutrin XL® Extended-release Tablets NDA 21-515 (001, 003) 150mg, 300mg
Deputy Dir., DLPS Date_____
GlaxoSmithKline = GlaxoSmithKline Beecham Corp. Initials_____

7. Peter Rickman Date 11/14/05
Director, DLPS Initials
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable 225 dated 2/7/05 (Verified 11/14/05) No OAI. Clerks noted - Bioequivalence review of dissolution data found acceptable 6/16/05. Bio studies (fasting and non-fasting) also found acceptable for the 150mg strength. Waiver granted for 300mg tablet strength. Bio study test sites have acceptable determination. States Office dwt bio endorsed 2/15/05 - labeling found acceptable for TA on 6/16/05 - GMP found acceptable 10/28/05 - Methods validation was not requested. Recommend for approval

8. Robert L. West Date 11/14/2005
Deputy Director, OGD Initials
Para.IV Patent Cert: Yes ☒ No ☐; Pending Legal Action: Yes ☒ No ☐; Petition: Yes ☐ No ☐
Comments: Amchem made paragraph IV certifications to both the '341 and '327 patents currently listed in the "Orange Book". Amchem was sued for infringement of both the '341 and '327 patents. The 30-month period expires on 4/14/07. There are no other patents presently listed in the current "Orange Book" for this drug product.
This NDA is recommended for tentative approval.

9. Gary Buehler Date 11/14/05
Director, OGD Initials GB
Comments: Tentative
First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
(for 150mg and 300mg Once-A-Day dosing)

10. Project Manager, Team Tom Hinchliffe Date 11/14
Review Support Branch Initials
NH Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
11:30 am Time notified of approval by phone 11 am Time approval letter faxed
FDA Notification:
11/14 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
11/14 Date Approval letter copied to \\CDS014\DRUGAPP\ directory. File V:/division/dlps/approvrou8.doc

Anchen **ANCHEN PHARMACEUTICALS, INC.**

February 23, 2006

N/MC

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Controlled Correspondence

RE: ANDA 77-284
Bupropion Hydrochloride Extended-Release (ER) Tablets USP (XL)
150 mg and 300 mg

Dear Mr. Buehler:

Anchen Pharmaceuticals, Inc. (Anchen) is submitting this Controlled Correspondence in response to comments provided by the Agency in our telephone conversation between Ms. Hyojong Kwon, OGD and Margaret Choy, Anchen on Febrauary 16, 2006 regarding drug release data in alcohol for our product. As discussed, Anchen had generated drug release data in 40% alcohol for our product to demonstrated that our drug product maintains its extended-release properties in the presence of 40% alcohol over a 16 hours period. No dose dumping was observed for our drug product. A report entitled, "Drug Release Test of Anchen's Bupropion HCl Extended-Released Tablets (150 an 300 mg) in 40% Alcohol vs. Water" is attached with details of the experiement for your reference.

We believe that this response adequately addresses OGD's request. Should any additional information be required, please contact me at (949) 837-6178 ext. 127 or by fax at (949) 837-6120.

Sincerely,

M. Choy

Margaret L. Choy, M.S.
Vice President, Regulatory Affairs

ANCHEN PHARMACEUTICALS, INC.

Archival Copy

ORIG AMENDMENT
N/AM

June 23, 2006

Minor CMC/Labeling Amendment

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 77-284
Bupropion Hydrochloride Extended Release (ER) Tablets USP (XL)
150 mg and 300 mg

Dear Mr. Buehler:

Anchen Pharmaceuticals, Inc. (Anchen) is submitting this minor amendment to amend the ANDA 77-284 to include the following in the packaging outsert:

1. Include "hydrochloric acid" as an ingredient of the tablet in the Description section.
2. Include the following sentence to the Description section (last paragraph, after the last sentence): "USP drug release testing is pending." as previously committed.

In addition:

3. Revise Section IV Comparison Between ANDA Drug and Reference Listed Drug to include "hydrochloric acid" as an ingredient.

Please note that this Amendment does not change the formulation of the tablet products, or the proposed drug release test.

(b) (4) Hydrochloric Acid (b) (4), NF is identified in the ANDA as an inactive ingredient that functions as a '(b) (4)'. (ANDA Section VII.2, ANDA Page 91, for a copy please refer to **Exhibit I**) (b) (4)

Anchen is providing the following revised documents:

1. Revise Section IV Comparison Between ANDA Drug and Reference Listed Drug (see **Exhibit IV**) to include "hydrochloric acid" as an ingredient.

RECEIVED
JUN 26 2006
OGD / CDER

5 Goodyear . Irvine, CA 92618 . (949) 837-6178 . Fax (949) 837-6120

In addition, as per our previous commitments *(October 21 and 24, 2005)*, Anchen takes this opportunity to include the following additional changes to the Final Printed Labeling. (See **Exhibit III** and **IV** for marked-up representative labeling. Revised Final Printed labeling will be submitted at time of Final Approval request.)

- Include the sentence "USP drug release testing is pending." into the Description section of the Package Outsert.
- Use of Tall-man labeling for all container labeling: Originally printed as "Bupropion HCl" will now read as "BuPROPion HCl".

We believe that this amendment adequately addresses Anchen's proposed changes. Should any additional information be required, please contact me at (949) 837-6178 ext. 127 or by fax at (949) 837-6120.

Sincerely,

M. Choy

Margaret Choy, M.S.
Vice President, Regulatory Affairs

BIOEQUIVALENCY AMENDMENT

N/US

JUL 25 2006

ANDA 77-284

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: Anchen Pharmaceuticals, Inc. TEL: 949-837-6178 x127

ATTN: Margaret Choy FAX: 949-837-6120

FROM: Aaron Sigler PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on September 21, 2004, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Extended-release Tablets USP, 150 mg and 300 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 page. 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

ANDA: 77-284 APPLICANT: Anchen Pharmaceuticals

DRUG PRODUCT: Bupropion HCl Extended Release Tablets, 150 mg & 300 mg

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

Due to concern of dose dumping for the drug product, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus 1 (basket) @ 75 rpm, with and without the alcohol:

Test 1: 12 units tested 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 analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV on both strengths.

Sincerely yours,

Barbara M Davit

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

Anchen ANCHEN PHARMACEUTICALS, INC.

Archival Copy

August 9, 2006

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Bioequivalency Amendment

ORIG AMENDMENT
N/AP

RE: ANDA 77-284
Bupropion Hydrochloride Extended-Release (ER) Tablets USP (XL)
150 mg and 300 mg

Dear Mr. Buehler:

Anchen Pharmaceuticals, Inc. (Anchen) is submitting the Bioequivalency Amendment in response to your Bioequivalence Deficiency Letter received on July 25, 2006 (see attached). For convenience of review, your comments are provided in bold face type, followed by our responses.

Bioequivalence Deficiencies

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

Due to concern of dose dumping for the drug product, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus 1 (basket) @ 75 rpm, with and without the alcohol:

Test 1: **12 units tested 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 analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.**

Test 3: **12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.**

Test 4: **12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.**

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV on both strengths.

In response to the Agency's concern about dose dumping, Anchen has performed the testing of Bupropion HCl Extended-Release (ER) Tablets USP (XL) as recommended by the Agency. The study was performed as recommended above on the 150 mg (Anchen Lot# P000104-500 proposed expiry date 04/06 and Wellbutrin XL™ Lot# 06E072P expiry date 09/07) and 300 mg (Anchen Lot# P000204-500 proposed expiry date 04/06 and Wellbutrin XL™ Lot# 06E085P expiry date 10/07). The drug

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release data and profiles of Anchen's Bupropion ER Tablets (150 mg and 300 mg) in 0.1 N HCl with and without the presence of alcohol are provided in **Exhibit 1 and 2,** respectively. The Anchen and RLD drug release profiles both showed comparable profiles for each media tested. Both the Anchen and RLD drug release profiles showed a slight increase in drug release as the percentage of alcohol increased, with the maximum % drug release seen in the 40% (v/v) alcohol in 0.1 N HCl (see Table 1).

Table 1: Two (2) Hour Dissolution Testing - Mean % Drug Release

	Mean % Drug Release (2 hours)			
	0.1N HCl	**5% Alcohol in 0.1N HCl**	**20% Alcohol in 0.1N HCl**	**40% Alcohol in 0.1N HCl**
150 mg Bupropion ER Tablets:				
Anchen *(Lot# P000104-500)*	1	2	13	20
RLD *(Lot# 06E072P)*	1	3	11	15
300 mg Bupropion ER Tablets:				
Anchen *(Lot# P000204-500)*	1	2	10	15
RLD *(Lot# 06E085P)*	2	4	11	18

Based on the drug release data and profiles, Anchen believes that there is no dose dumping observed for Anchen's ANDA batches of Bupropion HCl ER Tablets (150 mg and 300 mg) in 0.1 N HCl with and without the presence of alcohol.

One archival and one review copy of this amendment is included. In accordance with 21 CFR 314.96(b), one (1) field copy of the application will be forwarded to the Los Angeles District Office. Anchen Pharmaceuticals, Inc. certifies that the Field Copy is a true copy of the technical sections contained in the archival and review copies of this ANDA.

We believe that this response adequately addresses OGD's comments. Should any additional information be required, please contact me at (949) 837-6178 ext. 127 or by fax at (949) 837-6120.

Sincerely,

M. Choy

Margaret L. Choy, M.S.
Vice President, Regulatory Affairs

ANCHEN PHARMACEUTICALS, INC.

Archival Copy

MC.

August 11, 2006

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Exclusivity Statement

RE: **ANDA 77-284**
Bupropion Hydrochloride Extended Release (ER) Tablets USP (XL)
150 mg and 300 mg

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application, ANDA No. **77-284** for Bupropion Hydrochloride Extended Release (ER) Tablets USP (XL) 150 mg and 300 mg.

Anchen Pharmaceuticals, Inc. (Anchen) submits the enclosed Exclusivity Statement (see **Exhibit I**) in response to the recent exclusivity obtained by the RLD product (NDA 21-515 Wellbutrin XL™, 150 mg and 300 mg).

One archival and one review copy of this submission is included. In accordance with 21 CFR 314.96(b), one (1) field copy of the application will be forwarded to the Los Angeles District Office. Anchen Pharmaceuticals, Inc. certifies that the Field Copy is a true copy of the technical sections contained in the archival and review copies of this ANDA.

Please contact me at (949) 837-6178 ext. 127 or by fax at (949) 837-6120, if you have any questions or require additional information.

Sincerely,

M. Choy

Margaret L. Choy, M.S.
Vice President, Regulatory Affairs

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AUG 14 2006
OGD / CDER

ANCHEN PHARMACEUTICALS, INC.

August 11, 2006

Alonza E. Cruse
District Director (HFR-PA200)
Los Angeles District Office, FDA
19701 Fairchild Rd.
Irvine, CA 92612-2506

Field Copy
Exclusivity Statement

RE: ANDA 77-284
Bupropion Hydrochloride Extended-Release (ER) Tablets USP (XL)
150 mg and 300 mg

Dear Mr. Cruse:

On August 11, 2006, Anchen Pharmaceuticals, Inc. (Anchen) submitted to the Office of Generic Drugs an Exclusivity Statement in reference to ANDA #77-284 for Bupropion HCl ER Tablets USP (XL), 150 mg and 300 mg.

In accordance with 21 CFR 314.96(b), Anchen is hereby providing the Field Copy to the Los Angeles District Office. Anchen Pharmaceuticals, Inc. certifies that this Field Copy is a true copy of the response submitted to OGD.

Should you require additional information, please contact me by telephone at (949) 837-6178 ext. 127, or by fax at (949) 837-6120.

Sincerely,

M. Choy

Margaret L. Choy, M.S.
Vice President, Regulatory Affairs

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Anchen ANCHEN PHARMACEUTICALS, INC.

Archival Copy

ORIG AMENDMENT
N/AF

August 17, 2006

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Labeling Amendment
FINAL PRINTED ELECTRONIC LABELING

RE: ANDA 77-284
Bupropion Hydrochloride Extended Release (ER) Tablets USP (XL)
150 mg and 300 mg

Dear Mr. Buehler:

Anchen Pharmaceuticals, Inc. (Anchen) is submitting this Labeling Amendment in response to your comments received on August 7, 2006 (see attached). For convenience of review, your comments are provided in bold face type, followed by our responses.

Labeling Deficiencies:

A. General:

1. **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.**

   Anchen has previously provided the Exclusivity Statement to the Agency in a submission dated August 11, 2006. For ease of review, Anchen has provided a copy of the Exclusivity Statement in **Exhibit I**.

2. **Please provide chemistry data for your package sizes of 60s and 90s, if you have not already done so.**

   Please note that the container configuration originally proposed for the 30-count bottle (data provided in the original ANDA dated September 21, 2004, page 636) is the same container configuration proposed for the 60- and 90-count bottle. All the specifications and technical data (i.e. bottle resins and colorants) are the same for the 30s, 60s, and 90s package sizes.

(b) (4)

[redacted]

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B. CONTAINER (30s, 60s, 90s)

Satisfactory in draft as of the June 23, 2006 amendment.

Anchen acknowledges that as of the June 23, 2006 amendment our container labeling is satisfactory as drafted. Anchen is now providing final print labeling for all container configurations, please refer to the Table of Contents contained on the enclosed CD ROM for access to the files and directory pathways.

C. INSERT

Due to changes in the insert labeling for the reference listed drug, Wellbutrin XL® Tablets (NDA 21-515/S-018), approved June 12, 2006, please revise your labeling to be in accordance. This labeling can be found on the following website; http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
You should address all exclusivities and patents listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") and revise your insert labeling accordingly.

Due to the changes in the insert labeling for the reference listed drug, Wellbutrin XL® Tablets (NDA 21-515/S-018), approved June 12, 2006, Anchen has revised the outsert labeling for Bupropion Hydrochloride Extended Release (ER) Tablets USP (XL). In accordance with the Exclusivity Statement submitted by Anchen on August 11, 2006, Anchen did not include information regarding the indication for the prevention of seasonal major depressive episodes in patients with seasonal affective disorder. Please refer to the Table of Contents contained on the enclosed CD ROM for access to the files and directory pathways.

The final printed labeling are provided as electronic format per the electronic labeling rule published in December 11, 2003 (68 FR 69009), effective 6/8/04. To assist in your review and in accordance with Docket 92S-0251, Memorandum 32, effective October 31, 2005, the electronic labeling formats provided are *spl*, *doc (MS Word)*, and *pdf*.

In order to facilitate review of our amendment, we have provide a side-by-side comparison of our proposed outsert labeling (version 08/06) with the previously submitted labeling (version 10/05). All differences are highlighted, annotated and explained.

Anchen is providing one (1) computer CD ROM that is located at the front of the Archival Copy of this amendment. Please refer to the Table of Contents contained on the enclosed CD ROM for access to the files and directory pathways.

Anchen acknowledges that it may be necessary to further revise our labeling subsequent to approved changes for the reference listed drug prior approval.

We believe that this response adequately addresses OGD's comments. Should any additional information be required, please contact me at (949)-837-6178 ext. 127 or by fax at (949)-837-6120.

Sincerely,

M. Choy

Margaret Choy, M.S.
Vice President, Regulatory Affairs

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Anchen ANCHEN PHARMACEUTICALS, INC.

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August 21, 2006

ORIG AMENDMENT

N/AM

Minor Amendment-
Final Approval Requested

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 77-284
Bupropion Hydrochloride Extended-Release (ER) Tablets USP (XL) 150 mg and 300 mg

Dear Mr. Buehler:

Anchen Pharmaceuticals, Inc. (Anchen) is submitting this Minor Amendment to request final approval to our tentatively approved application, Bupropion Hydrochloride Extended-Release (ER) Tablets USP (XL) 150 mg and 300 mg (ANDA 77-284).

As stated in the Tentative Approval Letter of November 14, 2005, final approval of the application can be granted when there is a court decision on the non-infringement or invalidity of the patents that Anchen included in our paragraph IV certification. On August 1, 2006, the United States District Court granted Anchen's Motion for Summary judgment of Non-Infringement of all asserted claims of United States Patent No. 6,096,341. A copy of the court decision can be found at **Exhibit 1**. Biovail Laboratories, Inc. previously dismissed with prejudice all claims for infringement of United States Patent No. 6,143,327. A copy of the Stipulated Dismissal Order entered by the United States District Court on February 3, 2006, can be found at **Exhibit 2**.

Anchen has adequately addressed all outstanding deficiencies. Bioequivalency deficiency dated July 25, 2006 was responded on August 9, 2006 and Labeling deficiency dated August 7, 2006 was responded August 17, 2006. There are no other changes made to the application.

One archival and one review copy of this amendment is included. In accordance with 21 CFR 314.96(b), one (1) field copy of the application will be forwarded to the Los Angeles District Office. Anchen Pharmaceuticals, Inc. certifies that the Field Copy is a true copy of the technical sections contained in the archival and review copies of this ANDA.

We believe that this amendment adequately addresses all the requirements for final approval. Should any additional information be required, please contact me at (949) 837-6178 ext. 127 or by fax at (949) 837-6120.

Sincerely,

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AUG 22 2006
CDER

M. Choy

Margaret L. Choy, M.S.
Vice President, Regulatory Affairs

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Anchen ANCHEN PHARMACEUTICALS, INC.

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August 28, 2006

ORIG AMENDMENT
NDA M

Minor Amendment-
Final Approval Requested

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 77-284
Bupropion Hydrochloride Extended-Release (ER) Tablets USP (XL) 150 mg and 300 mg

Dear Mr. Buehler:

Anchen Pharmaceuticals, Inc. (Anchen) is submitting this Minor Amendment to our request for final approval to our tentatively approved application, Bupropion Hydrochloride Extended-Release (ER) Tablets USP (XL) 150 mg and 300 mg (ANDA 77-284) dated August 21, 2006.

Please note on August 25, 2006, the United States District Court entered final judgment in favor of Anchen based on its prior August 1, 2006 order granting Anchen's Motion for Summary Judgment of Non-Infringement. A copy of the court's final decision can be found at **Exhibit 1**

As stated in our August 21, 2006 Minor Amendment – Final Request for Approval, Anchen has adequately addressed all outstanding deficiencies and there are no other changes made to the application.

One archival and one review copy of this amendment is included. In accordance with 21 CFR 314.96(b), one (1) field copy of the application will be forwarded to the Los Angeles District Office. Anchen Pharmaceuticals, Inc. certifies that the Field Copy is a true copy of the technical sections contained in the archival and review copies of this ANDA.

We believe that this amendment adequately addresses all the requirements for final approval. Should any additional information be required, please contact me at (949) 837-6178 ext. 127 or by fax at (949) 837-6120.

Sincerely,

M. Choy

Margaret L. Choy, M.S.
Vice President, Regulatory Affairs

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Anchen ANCHEN PHARMACEUTICALS, INC.

Archival Copy

September 18, 2006

ORIG AMENDMENT

Telephone Amendment

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 77-284
Bupropion Hydrochloride Extended-Release (ER) Tablets USP (XL)
150 mg and 300 mg

Dear Mr. Buehler:

Anchen Pharmaceuticals, Inc. (Anchen) is submitting this Telephone Amendment in response to comments provided by the Agency via facsimile on September 13, 2006 (see attached). For convenience of review, your comments are provided in bold face type, followed by our responses.

A. Deficiencies:

1. (b) (4)

2.

Following this page, 2 pages withheld in full-(b)(4) CCI/TS (CMC deficiencies)

5 Goodyear. Irvine, CA 92618. (949)837-6178. Fax (949)837-6120

4. (b) (4)

One archival and one review copy of this amendment is included. In accordance with 21 CFR 314.96(b), one (1) field copy of the application will be forwarded to the Los Angeles District Office. Anchen Pharmaceuticals, Inc. certifies that the Field Copy is a true copy of the technical sections contained in the archival and review copies of this ANDA.

We believe that this response adequately addresses OGD's comments. Should any additional information be required, please contact me at (949) 837-6178 ext. 127 or by fax at (949) 837-6120.

Sincerely,

M. Choy

Margaret L. Choy, M.S.
Vice President, Regulatory Affairs

Anchen **ANCHEN PHARMACEUTICALS, INC.**

Archival Copy

October 2, 2006

ORIG AMENDMENT
N/Am

Telephone Amendment

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 77-284
Bupropion Hydrochloride Extended-Release (ER) Tablets USP (XL)
150 mg and 300 mg

Dear Mr. Buehler:

Anchen Pharmaceuticals, Inc. (Anchen) is submitting this Telephone Amendment in response to comments provided by the Agency via facsimile on September 29, 2006 (see attached). For convenience of review, your comments are provided in bold face type, followed by our responses.

A. Deficiencies:

1. (b) (4)

2. (b) (4)

(b) (4)

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3. (b) (4)

One archival and one review copy of this amendment is included. In accordance with 21 CFR 314.96(b), one (1) field copy of the application will be forwarded to the Los Angeles District Office. Anchen Pharmaceuticals, Inc. certifies that the Field Copy is a true copy of the technical sections contained in the archival and review copies of this ANDA.

We believe that this response adequately addresses OGD's comments. Should any additional information be required, please contact me at (949) 837-6178 ext. 127 or by fax at (949) 837-6120.

Sincerely,

M. Choy

Margaret L. Choy, M.S.
Vice President, Regulatory Affairs

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 15, 2006

FROM: Bing Wu, Ph.D.

TO: Naiqi Ya, Ph.D.
Team Leader

CC: Florence Fang, Division Director
Richard Adams, Deputy Director RCA 10/31/06

SUBJECT: For the file of ANDA 77-284 - Response to the Keller and Heckman LLP's letter dated August 27, 2006, regarding the (b) (4) formulation in Anchen's Drug product Bupropion Hydrochloride Extended Release Tablets (XL) USP

Introduction:

Keller and Heckman LLP, on behalf of their client Biovail Corporation, the manufacturer of the RLD, submitted a correspondence dated August 27, 2006 to OGD Director Gary Buehler. A product quality issue was raised in the letter resulting from (b) (4) (b) (4) in Anchen's drug product Bupropion Hydrochloride Extended Release Tablets (XL) USP. Anchen has responded to the formulation issue in an amendment dated September 18, 2006, in response to the Agency deficiency letter. The formulation issue, concerns raised in the Keller and Heckman letter, and Anchen's response have been reviewed as part of the ANDA review. This memo summarizes the chemistry assessment of the formulation issue based on both the information and data provided in the Keller and Heckman letter and Anchen's response.

The 8/27/06 letter from Keller and Heckman LLP:

(b) (4)

(b) (4)

[redacted]

Anchen's response in the 9/18/06 amendment:

(b) (4)

[redacted]

Following this page, 2 pages withheld in full-(b)(4) CCI/TS

Conclusion:

Anchen's drug product formulation differs from that of the RLD and may represent a unique formulation for the delayed and extended release drug product. Based on the information and data submitted in the ANDA 77-284, it is clear that (b) (4) Anchen's drug product formulation does not have any adverse effect on the quality and performance of the drug product.

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]

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[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.

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
12/13/2006 07:40:13 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 11:53:11 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 11:58:54 AM
BIOPHARMACEUTICS

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-284 Applicant Anchen Pharmaceuticals, Inc.
Drug Bupropion Hydrochloride Extended Release (ER) Tablets USP (XL) Strength(s) 150 mg and 300 mg

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: | **DRAFT Package** | **FINAL Package**

1. **Martin Shimer** — Date 10/17/06 — Date _____
Chief, Reg. Support Branch — Initials MHS — Initials _____
Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☐
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = _____ NDA# _____
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked _____
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☒ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐ Study Submitted ☐
Has case been settled: Yes ☒ No ☐ Date settled:
Is applicant eligible for 180 day Yes, for both strengths
Generic Drugs Exclusivity for each strength: Yes ☒ No ☐
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Ap
Comments: Anchen submitted PIV certs to both '341 and '327 and in turn was sued on both patents. Claims related to '327 patent were dismissed with prejudice on 2/3/2006. Final judgement in favor of Anchen for non-infringement on the '341 patent was entered 8/24/2006. Anchen was the first applicant to provide PIV certifications to the listed patents and therefore is eligible for 180 day exclusivity for each strength. MMA 30 month forfeiture of exclusivity would not occur until 3/21/2007. Eligible for Full Approval

2. Project Manager, Thomas Hinchliffe Team 10 — Date 12/14/2006 — Date 10/30/06
Review Support Branch — Initials TOH — Initials TOH

Original Rec'd date September 21, 2004 — EER Status Pending ☐ Acceptable ☒ OAI ☐
Date Acceptable for Filing September 21, 2004 — Date of EER Status 10/12/2006
Patent Certification (type) IV — Date of Office Bio Review 8/29/2006
Date Patent/Exclus.expires Oct 30, 2018 — Date of Labeling Approv. Sum 9/14/2006
Citizens' Petition/Legal Case Yes ☒ No ☐ — Labeling Acceptable Email Rec'd Yes ☒ No ☒
(If YES, attach email from PM to CP coord) — Labeling Acceptable Email filed Yes ☒ No ☒
First Generic Yes ☒ No ☐ — Date of Sterility Assur. App. N/A
Priority Approval Yes ☒ No ☐ — Methods Val. Samples Pending Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise) — MV Commitment Rcd. from Firm Yes ☒ No ☐
Acceptable Bio reviews tabbed Yes ☒ No ☐ — Modified-release dosage form: Yes ☒ No ☐
Bio Review Filed in DFS: Yes ☐ No ☐ — Interim Dissol. Specs in AP Ltr: Yes ☒
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☒ Date 11/14/2005
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer: — Labeling Team Leader:
Date 10/20/06 — Date 10/20/2006
Name/Initials MDillahunt/md — Name/Initials LGolson/lg

Comments:

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ — Date 10/30/06
OGD Regulatory Counsel, Post-MMA Language Included ☐ — Initials DTR

Comments:See Revised Letter

5. Div. Dir./Deputy Dir.
Chemistry Div. II

Date10/31/06
InitialsRCA for FF

Comments:See Memo: Bing Wu to Naiqi Ya: "Response to Keller and Heckman LLP's letter of August 27, 2006……..", October 15, 2006. Memo concluded that although Anchen's drug product formulation differs from RLD (b) (4) …difference has no adverse effect upon quality and performance of drug product.

6. Frank Holcombe **First Generics Only**
Assoc. Dir. For Chemistry
Comments: (First generic drug review)

Date
Initials_____

7. Vacant
Deputy Dir., DLPS

Date_____
Initials_____

8. Peter Rickman
Director, DLPS

Date12/14/06
InitialsWPR

Para.IV Patent Cert: Yes☒ No☐;Pending Legal Action: Yes ☐No ☒;Petition: Yes☒ No☐
Comments:Anchen made PIVs to the '341 patent and the '327 patent. Claims related to the '327 patent were dismissed 2/3/06; Final judgement in favor of Anchen for non-infringement of the '341 patent was entered on the 8/24/06. Anchen was first to file PIVs on both patents. Eligible for 180 day exclusivity. Bio acceptable 8/24/06 (fasting & fed studies 150 mg) no DSI needed; Labeling acceptable 9/14/06; EER accetable 10/12/06. okay for full approval.

OR

8. Robert L. West
Deputy Director, OGD

Date _____
Initials _____

Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Press Release Acceptable ☐
Comments:

9. Gary Buehler
Director, OGD

Date _____
Initials _____

Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Thomas Hinchliffe Team 10
Review Support Branch

Date_____
Initials _____

_____Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
2:55Time notified of approval by phone 3:00Time approval letter faxed
FDA Notification:
12/14Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
12/14Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

REVIEWER: **FINAL ACTION**

Tom and Lisa:

Please place a copy of Barbara's memo in the approval packages for the Anchen and Impax Bupropion HCl Extended-Release Tablets (Once-A-Day).

Thank you,

Bob

From: Parise, Cecelia M
Sent: Friday, October 13, 2006 8:18 AM
To: West, Robert L
Subject: FW: For Bupropion HCl ER tablet CP, memo about how OGD will evaluate in vitro dose-dumping study

Bob could you have someone file this memo in the affected ANDA's?

Thanks,

Cec

From: Parise, Cecelia M
Sent: Friday, October 13, 2006 8:16 AM
To: Lee, LaiMing
Subject: FW: For Bupropion HCl ER tablet CP, memo about how OGD will evaluate in vitro dose-dumping study

LaiMing,

Barbara did a general memo not one specific to Impax.

Cec

From: Davit, Barbara M
Sent: Monday, September 11, 2006 4:47 PM
To: Parise, Cecelia M; Kim, Nam
Cc: Conner, Dale P
Subject: For Bupropion HCl ER tablet CP, memo about how OGD will evaluate in vitro dose-dumping study

Hello:

Here is our memo to the file.

Barbara

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 11, 2006

FROM: Barbara M. Davit, J.D., Ph.D.
Deputy Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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

SUBJECT: In vitro study to compare potential for dose-dumping in the presence of ethanol between Wellbutrin XL® and potential generic Bupropion Extended-Release Tablets

TO: 2005P-0498
OGD Controlled Document #051564
ANDA 77284
ANDA 77285
ANDA 77415
ANDA 77455
ANDA 77475

Introduction: In a Citizen Petition, Docket No. 2005P-0498, the petitioner asks the FDA to assess any generic bupropion hydrochloride (HCl) extended-release (ER) tablet formulation for the impact of alcohol consumption on dose release. A working group comprised of CDER scientists (CDER working group) from the Office of Generic Drugs (OGD), Office of Drug Evaluation II (ODEII), Office of New Drug Quality Assessment (ONDQA), and Office of Testing and Research (OTR) developed an in vitro test to evaluate the potential for dose-dumping in the presence of alcohol (in vitro dose-dumping test). Subsequently, OGD asked all applicants who submitted ANDAs for generic bupropion HCl ER tablets to use the test to compare the generic product with Wellbutrin XL®. This memo describes the in vitro dose-dumping test and clarifies how in vitro test results will be evaluated by the OGD.

Background: The Wellbutrin XL® label states that, in postmarketing experience, there have been rare reports of adverse neuropsychiatric events in patients who were drinking alcohol during treatment with bupropion. The label also cautions that the consumption of alcohol during treatment with Wellbutrin XL® should be avoided. To ensure that any potential for bupropion dose-dumping in the presence of alcohol would be comparable for a generic bupropion ER tablet and Wellbutrin XL®, the CDER working group developed an in vitro dose-dumping test. The test evaluates the effect of increasing ethanol content on bupropion release from the dosage form.

Description of the in vitro dose dumping test: FDA's regulatory method for evaluating Wellbutrin XL® dissolution performance (for stability and quality controls testing) uses the following conditions: (1) 900 mL of 0.1 N hydrochloric acid (HCl) media; (2) the USP Apparatus I (basket) at a rotation of 75 rpm: (3) a temperature of 37°C. For the in vitro dose dumping test, increasing amounts of ethanol are added to the 0.1 N

HCl medium. The same dissolution conditions are used as for the regulatory method. The dissolution performance of the generic (test) product and Wellbutrin XL® are compared at the various ethanol concentrations. Differing amounts of ethanol are added to the 0.1 N HCl media on a volume/volume (v/v) basis to give the following percentages:

- % ethanol (no ethanol added)
- 5% ethanol
- 20% ethanol
- 40% ethanol

Twelve (12) units of the test product and 12 units of Wellbutrin XL® are tested separately in 900 mL volumes of each medium. Samples of the media are taken once every 15 minutes until 2 hours is reached. The percent of labeled amount of bupropion dissolved in the medium (% dissolved) is calculated for each sample. Dissolution data are expressed as % dissolved.

Data analysis: The OGD compares the % dissolved at 2 hours in 0.1 N HCl with no ethanol to the % dissolved at 2 hours in 40% ethanol/60% 0.1 N HCl (v/v) for the test product. If the % dissolved is comparable for no ethanol versus 40% ethanol, the test product is considered robust and no further comparisons are needed. If, however, the % dissolved from the test product increases as the amount of ethanol in the media increases, then the OGD compares % dissolved data at 2 hours in 40% ethanol for the test product and Wellbutrin XL®. If for both products, the % dissolved at 2 hours in 40% ethanol is comparable, then the OGD concludes that the risk of dose-dumping from the generic product is the same as for Wellbutrin XL®.

OGD requests to generic applicants: OGD asked all applicants who submitted ANDAs for generic bupropion HCl ER tablet formulations to conduct the in vitro dose-dumping study. OGD also asked applicants to submit: standard operating procedures (SOPs) for the dissolution testing, individual dissolution data, mean values, standard deviations, and plots of the % dissolved data.

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/s/

Thomas Hinchliffe
12/14/2006 03:41:33 PM