CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 77-285

Name: Bupropion Hydrochloride Extended-release Tablets (XL), 300 mg (Once-A-Day)

Sponsor: Actavis South Atlantic LLC

Approval Date: August 15, 2008

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APPLICATION NUMBER:

ANDA 77-285

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APPLICATION NUMBER:

ANDA 77-285

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-285

Actavis South Atlantic LLC
Attention: Monique Weitz
Senior Director, Project and Site Management
13800 NW 2nd Street, Suite 190
Sunrise, FL 33325

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated September 23, 2004, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg and 300 mg (Once-A-Day).

Reference is made to your amendments dated June 14, July 8, December 7, and December 21, 2005; December 7, 2007; and March 19, March 20, March 27, April 1, May 19, June 9, June 16, June 23, June 26, and July 25, 2008.

We have completed the review of this ANDA, and based upon the information you have presented to date, we have concluded that adequate information has been presented to demonstrate that your Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg and 300 mg (Once-A-Day), are safe and effective for use as recommended in the submitted labeling. However, final approval of your Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg (Once-A-Day), is blocked at this time by another ANDA applicant's eligibility for 180-day generic drug exclusivity as noted in further detail below. **Therefore, final approval is granted for your Bupropion Hydrochloride Extended-release Tablets (XL), 300 mg (Once-A-Day).** Please note that your Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg (Once-A-Day), is **tentatively approved**, and will be eligible for final approval upon the expiration of the other applicant's 180-day generic drug exclusivity for the 150 mg strength.

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 periods of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent Nos. 6,096,341 (the '341 patent) and 6,143,327 (the '327 patent) are both scheduled to expire on October 30, 2018.

Your ANDA contains paragraph IV certifications to each of these patents under section 505(j)(2)(A)(vii)(IV) of the Act stating that these patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg and 300 mg (Once-A-Day), under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action was brought against Actavis South Atlantic LLC (Actavis) for infringement of one or more of these patents that were the subjects of the paragraph IV certifications. You have notified the agency that Actavis 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 Actavis in the United States District Court for the Southern District of Florida, Miami Division [Biovail Laboratories International SRL v. Abrika, LLLP; Abrika Pharmaceuticals, Inc.; and Abrika Pharmaceuticals, LLLP, Civil Action No. 04-61704-CIV-Altonaga/Bandstra]. You have informed the agency that on July 31, 2007, this litigation was dismissed with prejudice.

I. Approval of Bupropion Hydrochloride Extended-release Tablets (XL), 300 mg (Once-A-Day)

The Division of Bioequivalence has determined your Bupropion Hydrochloride Extended-release Tablets (XL), 300 mg (Once-A-Day), to be bioequivalent, and therefore, therapeutically equivalent to the listed drug, Wellbutrin XL Extended-release Tablets, 300 mg (Once-A-Day), of GlaxoSmithKline. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

Stage I: Acid Stage

Medium:	0.1 N HCl
Volume:	750 ml
Apparatus:	USP Paddle
Rotation Speed:	50 RPM
Specification:	[redacted] (Q) of the labeled amount of bupropion in the dosage form is dissolved in 120 minutes.

b(4)

Stage II: Buffer Stage

Medium:	pH 6.8 Sodium Phosphate Buffer, 0.05 M
Volume:	1000 ml (250 mL of 0.20 M tribasic sodium phosphate added to the acid stage media, adjust pH if necessary)
Apparatus:	USP Paddle
Rotation Speed:	50 RPM
Specification:	3 hours: [redacted] 8 hours: [redacted] 16 hours: [redacted]

b(4)

In addition, you have committed to conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL of 0.1 N HCl using apparatus I (basket) at 75 rpm, with and without alcohol:

Test 1: 12 units of the drug products analyzed according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units of the drug products analyzed by substituting 5% (v/v) of test medium with Alcohol USP, with data collected every 15 minutes for a total of 2 hours.

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

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

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

We note that if FDA requires a Risk Evaluation & Mitigation Strategy for a listed drug, an ANDA citing that listed drug also will be required to have a REMS, See 505-1(i).

Postmarketing requirements for this ANDA for Bupropion Hydrochloride Extended-release Tablets (XL), 300 mg (Once-A-Day) are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of your Bupropion Hydrochloride Extended-release Tablets (XL), 300 mg (Once-A-Day).

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 directly to:

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

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

II. Tentative Approval of Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg (Once-A-Day

Our decision to tentatively approve your Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg (Once-A-Day), is based upon information currently available to the agency (i.e., data in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This decision is subject to change on the basis of new information that may come to our attention.

We are unable to grant final approval to your Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg (Once-A-Day), at this time because an ANDA submitted by Anchen Pharmaceuticals Inc. (Anchen) providing for Bupropion Hydrochloride Extended-release Tablets (XL) 150 mg (Once-A-Day) and containing paragraph IV certifications to the patents listed in the "Orange Book" was submitted prior to the submission of your ANDA. Upon approval on December 14, 2006, Anchen became eligible for 180-day generic drug marketing exclusivity. Accordingly, your Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg (Once-A-Day), will be eligible for final approval beginning on November 26, 2008. This represents the date that is 180 days after May 30, 2008, which, the agency was notified, is the date the of the first commercial marketing of the 150 mg strength under Anchen's ANDA.

To reactivate this ANDA to provide for final approval of your Bupropion Hydrochloride Extended-release Tablets (XL) 150 mg (Once-A-Day), you must submit a "Supplemental Application 150 MG FINAL APPROVAL REQUEST - Expedited Review Requested". This prior-approval supplemental application should be submitted approximately 90 to 180 days prior to the date you believe that your Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg (Once-A-Day), will be eligible for final approval. The supplement should include a detailed explanation of why and when you believe final approval should be granted. Please include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate to support approval of this strength. This supplemental application should be submitted even if no additional changes have been made to the application since the date of this approval/tentative approval action. Significant changes, as well as an update of the status of the manufacturing and testing facilities' compliance with

cGMPs are subject to agency review before final approval of the supplemental application will be granted. We request that you categorize the changes as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt.

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

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

Please note that under section 505 of the Act, your Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg (Once-A-Day), may not be marketed without final agency approval. The introduction or delivery for introduction into interstate commerce of your Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg (Once-A-Day), before the final approval date is prohibited under section 301 of the Act. Also, until the agency issues the final approval letter, your Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg (Once-A-Day) will not be deemed approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book."

For further information on the status of this application, or prior to submitting additional amendments, please contact Thomas Hinchliffe, Project Manager, at 240-276-8536.

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
8/15/2008 11:03:38 AM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-285

LABELING

actavis

Prescribing Information

BuPROPion Hydrochloride Extended-Release Tablets (XL)

Rev. 06/08

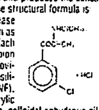
F.P.O.

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents and young adults in short-term studies of 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, adolescent or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and 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 use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

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 $C_{13}H_{18}ClNO•HCl$. 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 300-mg, off-white extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: copovidone, hydroxypropyl cellulose (NF), colloidal silicon dioxide (NF), magnesium stearate (NF), polyvinyl alcohol, macrogol (NF), talc, methacrylic acid copolymer, titanium dioxide, triethyl citrate, colloidal anhydrous silica, sodium bicarbonate, sodium lauryl sulfate, povidone, purified water, and hydrochloric acid (NF).

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 isozyme involved in the formation of hydroxybupropion, while cytochrome P450 isozymes 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) isozyme. 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 isozyme (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 1 1/2-fold for hydroxybupropion and about 2 1/2-fold for threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold, respectively, in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Renal: There is limited information on the pharmacokinetics of bupropion in patients with renal impairment. An inter-study comparison between normal subjects and patients with 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-blind phase was defined as the investigator's judgment that drug treatment was needed for worsening depressive symptoms. Patients receiving continued bupropion treatment experienced significantly lower relapse rates over the subsequent 44 weeks compared to those receiving placebo.

Although there are no independent trials demonstrating the antidepressant effectiveness of Bupropion Hydrochloride Extended-Release Tablets (XL), studies have demonstrated similar bioavailability of Bupropion Hydrochloride Extended-Release Tablets (XL) to both the immediate-release formulation and to the sustained-release formulation of bupropion under steady-state conditions, i.e., Bupropion Hydrochloride Extended-Release Tablets (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 TRIALS).

A major depressive episode (DSM-IV) implies the presence of 1) depressed mood or 2) loss of interest or pleasure; in addition, at least 5 of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt, or suicidal ideation.

The efficacy of bupropion in maintaining an antidepressant response for up to 44 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial with the sustained-release formulation of bupropion (see CLINICAL TRIALS). Nevertheless, the physician who elects to use Bupropion Hydrochloride Extended-Release Tablets (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® (bupropion hydrochloride) Sustained-Release Tablets; WELLBUTRIN® (bupropion hydrochloride), the immediate-release formulation; WELLBUTRIN SR® (bupropion hydrochloride), the 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. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated
Increases Compared to Placebo	
<18	14 additional cases
18-24	5 additional cases
Decreases Compared to Placebo	
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and 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.

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 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.

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®, 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), the sustained-release formulation, or WELLBUTRIN® (bupropion hydrochloride), the immediate-release formulation.

Seizures: Bupropion is associated with a dose-related risk of seizures. The risk of seizures is also related to patient factors, clinical situations, and concomitant medications, which must be considered in selection of patients for therapy with Bupropion Hydrochloride Extended-Release Tablets (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 (WELLBUTRIN SR®), the incidence of seizure is approximately 0.1% (1/1,000).**

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

  Additional data accumulated for the immediate-release formulation of bupropion suggested that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day. The 600 mg dose is twice the usual adult dose and one and one-third the maximum recommended daily dose (450 mg) of Bupropion Hydrochloride Extended-Release Tablets (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 WELLBUTRIN SR®, the sustained-release formulation of bupropion, experienced agitation, anxiety, and insomnia as shown in Table 2.

Table 2. Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials of WELLBUTRIN SR® for Major Depressive Disorder

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

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

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

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

Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in bipolar disorder patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Bupropion Hydrochloride Extended-Release Tablets (XL) are expected to pose similar risks.

Altered Appetite and Weight: In placebo-controlled studies of major depressive disorder using WELLBUTRIN SR®, the sustained-release formulation of bupropion, patients experienced weight gain or weight loss as shown in Table 3.

Table 3. Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials of WELLBUTRIN SR® for Major Depressive Disorder

Weight Change	WELLBUTRIN SR® 300 mg/day (n = 339)	WELLBUTRIN SR® 400 mg/day (n = 112)	Placebo (n = 347)
Gained > 5 lbs	3%	2%	4%
Lost > 5 lbs	14%	19%	6%

In studies conducted with the immediate-release formulation of bupropion, 35% of patients receiving tricyclic antidepressants gained weight, compared to 9% of patients treated with the immediate-release formulation of bupropion. If weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight-reducing potential of Bupropion Hydrochloride Extended-Release Tablets (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 postmarketing 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 preexisting hypertension.

Data from a comparative study of the sustained-release formulation of bupropion (ZYBAN® Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of sustained-release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS, and placebo, respectively. The majority of these patients had evidence of preexisting hypertension. Three patients (1.2%) treated with the combination of ZYBAN® and NTS and 1 patient (0.4%) treated with NTS had study medication discontinued due to hypertension compared to none of the patients treated with ZYBAN® or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

There is no clinical experience establishing the safety of Bupropion Hydrochloride Extended-Release Tablets (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 patient Medication Guide about "Antidepressant Medicines,

Medication Guide

BuPROPion Hydrochloride Extended-Release Tablets (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 both sections of this Medication Guide. The first section is about the risk of suicidal thoughts and actions with antidepressant medicines; the second section is entitled "What other important information should I know about Bupropion Hydrochloride Extended-Release Tablets (XL)?"

Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions

This section of the Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
   - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
   - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

Bupropion Hydrochloride Extended-Release Tablets (XL) have not been studied in children under the age of 18 and are not approved for use in children and teenagers.

What other important information should I 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 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 WELLBUTRIN® Tablets or WELLBUTRIN SR® 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. If you can use Bupropion Hydrochloride Extended-Release Tablets (XL) while you are pregnant, talk to your doctor about how you can be on the Bupropion Pregnancy Registry.
  - **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.

(continued on other side)

- 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 nonprescription 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).

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 many Bupropion Hydrochloride Extended-Release Tablets (XL) can increase your chance of having a seizure.
- If you take too many Bupropion Hydrochloride Extended-Release Tablets (XL), or overdose, call your local emergency room or poison control center right away.
- **Do not take any other medicines while using Bupropion Hydrochloride Extended-Release Tablets (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) are 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) are 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) affect 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 taking 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 or you can visit www.actavis.us or call toll-free 1-800-432-6534.

What are the ingredients in Bupropion Hydrochloride Extended-Release Tablets (XL)?

Active ingredient: bupropion hydrochloride.

Inactive ingredients: copovidone, hydroxypropyl cellulose (NF), colloidal silicon dioxide (NF), magnesium stearate (NF), polyvinyl alcohol, macrogol (NF), talc, methacrylic acid copolymer, titanium dioxide, triethyl citrate, colloidal anhydrous silica, sodium bicarbonate, sodium lauryl sulfate, povidone, purified water, and hydrochloric acid (NF).

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Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions" and other important information about using Bupropion Hydrochloride Extended-Release Tablets (XL) 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 Guide is provided by the authorized dispenser.

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 look 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) 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 hydrochloride (such as WELLBUTRIN SR®, the sustained-release formulation, and WELLBUTRIN®, the immediate-release formulation).

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.

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 congenital malformations overall, or cardiovascular malformations specifically, following first trimester bupropion exposure compared to exposure to all other antidepressants in the first trimester, or bupropion outside of the first trimester. The results of this study have not been corroborated. Bupropion Hydrochloride Extended-Release Tablets (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 WELLBUTRIN SR® Tablets, the sustained-release formulation of bupropion.

Adverse Events Leading to Discontinuation of Treatment With WELLBUTRIN® or WELLBUTRIN SR®: In placebo-controlled clinical trials, 9% and 11% of patients treated with 300 and 400 mg/day, respectively, of the sustained-release formulation of bupropion and 4% of patients treated with placebo discontinued treatment due to adverse events. The specific adverse events in these trials that led to discontinuation in at least 1% of patients treated with either 300 mg/day or 400 mg/day of WELLBUTRIN SR®, the sustained-release formulation of bupropion, and at a rate at least twice the placebo rate are listed in Table 4.

Table 4. Treatment Discontinuations Due to Adverse Events in Placebo-Controlled Trials for Major Depressive Disorder

Adverse Event Term	WELLBUTRIN SR® 300 mg/day (n = 376)	WELLBUTRIN SR® 400 mg/day (n = 114)	Placebo (n = 385)
Rash	2.4%	0.9%	0.0%
Nausea	0.8%	1.8%	0.3%
Agitation	0.3%	1.8%	0.3%
Migraine	0.0%	1.8%	0.3%

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

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated With WELLBUTRIN® or WELLBUTRIN SR®: Table 5 enumerates treatment-emergent adverse events that occurred among patients treated with 300 and 400 mg/day of the sustained-release formulation of bupropion and with placebo in controlled trials. Events that occurred in either the 300- or 400-mg/day group at an incidence of 1% or more and were more frequent than in the placebo group are included. Reported adverse events were classified using a COSTART-based Dictionary.

Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

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

Table 5. Treatment-Emergent Adverse Events in Placebo-Controlled Trials* for Major Depressive Disorder

Body System/ Adverse Event	WELLBUTRIN SR® 300 mg/day (n = 376)	WELLBUTRIN SR® 400 mg/day (n = 114)	Placebo (n = 385)
Body (General)			
Headache	26%	25%	23%
Infection	8%	9%	6%
Abdominal pain	3%	9%	2%
Asthenia	2%	4%	2%
Chest pain	3%	4%	1%
Pain	2%	3%	2%
Fever	1%	2%	—
Cardiovascular			
Palpitation	2%	6%	2%
Flushing	1%	4%	—
Migraine	1%	4%	1%
Hot flashes	1%	3%	1%
Digestive			
Dry mouth	17%	24%	7%
Nausea	13%	18%	8%
Constipation	10%	5%	7%
Diarrhea	5%	7%	6%
Anorexia	5%	3%	2%
Vomiting	4%	2%	2%
Dysphagia	0%	2%	0%
Musculoskeletal			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	0%	2%	0%
Twitch	1%	2%	—
Nervous system			
Insomnia	11%	16%	6%
Dizziness	7%	11%	5%
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Tremor	6%	3%	1%
Nervousness	5%	3%	3%
Somnolence	2%	3%	2%
Irritability	3%	2%	2%
Memory decreased	—	3%	1%
Paresthesia	1%	2%	1%
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%	—
Blurred vision or diplopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	—	2%	0%
Vaginal hemorrhage[†]	0%	2%	—
Urinary tract infection	1%	0%	—

* Adverse events that occurred in at least 1% of patients treated with either 300 or 400 mg/day of the sustained-release formulation of bupropion, but equally or more frequently in the placebo group, were: abnormal dreams, accidental injury, acne, appetite increased, back pain, bronchitis, dysmenorrhea, dyspepsia, flatulence, flu syndrome, hypertension, neck pain, respiratory disorder, rhinitis, and tooth disorder.

† Incidence based on the number of female patients.

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

Additional events to those listed in Table 5 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 5 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 WELLBUTRIN SR®: Anorexia, dry mouth, rash, sweating, tinnitus, and tremor.

400 mg/day of WELLBUTRIN SR®: Abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary frequency.

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

Adverse events for which frequencies are provided below occurred in clinical trials with the sustained-release formulation of bupropion. The frequencies represent the proportion of patients who experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled studies for depression (n = 987) or smoking cessation (n = 1,013), or patients who experienced an adverse event requiring discontinuation of treatment in an open-label surveillance study with the sustained-release formulation of bupropion (n = 3,100). All treatment-emergent adverse events are included except those listed in Tables 2 through 8, 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 WELLBUTRIN® Tablets or from WELLBUTRIN SR® Sustained-Release Tablets: When switching patients from WELLBUTRIN® Tablets to Bupropion Hydrochloride Extended-Release Tablets (XL), or from WELLBUTRIN SR® 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 WELLBUTRIN® 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® 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 (XL), 300 mg of bupropion hydrochloride, are off-white, oval, tablets debossed into the surface with "142" in bottles of 30 tablets (NDC 67767-142-30) and 90 tablets (NDC 67767-142-90).

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

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Manufactured by: VPS Corporation
Cranbury, New Jersey 08512

actavis

Distributed by: Actavis South Atlantic LLC
Sunrise, FL 33325
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Medication Guide
BuPROPion Hydrochloride Extended-Release Tablets (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 both sections of this Medication Guide. The first section is about the risk of suicidal thoughts and actions with antidepressant medicines; the second section is entitled "What other important information should I know about Bupropion Hydrochloride Extended-Release Tablets (XL)?"

Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions

This section of the Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
   - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
   - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

Bupropion Hydrochloride Extended-Release Tablets (XL) have not been studied in children under the age of 18 and are not approved for use in children and teenagers.

What other important information should I 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 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 WELLBUTRIN® Tablets or WELLBUTRIN SR® 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. If you can use Bupropion Hydrchloride Extended-Release Tablets (XL) while you are pregnant, talk to your doctor about how you can be on the Bupropion Pregnancy Registry.
  - **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 nonprescription 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).

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 many Bupropion Hydrochloride Extended-Release Tablets (XL) can increase your chance of having a seizure.
- If you take too many Bupropion Hydrochloride Extended-Release Tablets (XL), or overdose, call your local emergency room or poison control center right away.
- **Do not take any other medicines while using Bupropion Hydrochloride Extended-Release Tablets (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) are 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) are 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) affect 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 taking 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 or you can visit www.actavis.us or call toll-free 1-800-432-8534.

What are the ingredients in Bupropion Hydrochloride Extended-Release Tablets (XL)?

Active ingredient: bupropion hydrochloride.

Inactive ingredients: copovidone, hydroxypropyl cellulose (NF), colloidal silicon dioxide (NF), magnesium stearate (NF), polyvinyl alcohol, macrogol (NF), talc, methacrylic acid copolymer, titanium dioxide, triethyl citrate, colloidal anhydrous silica, sodium bicarbonate, sodium lauryl sulfate, povidone, purified water, and hydrochloric acid (NF).

Rx Only

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

Manufactured by: VPS Corporation, Cranbury, New Jersey 08512

actavis

Distributed by: Actavis South Atlantic LLC, Sunrise, FL 33325

Rev. 06/08

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-285

LABELING REVIEWS

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

ANDA Number: **77-285**

Date of Submissions: **June 16, 23 and 26, 2008**

Applicant's Name: **Actavis South Atlantic LLC**

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No, electronic

*** **Only the 300 mg strength is eligible for full approval*****

1. CONTAINER- 30s and 90s

   Satisfactory in FPL as of the June 16, 2008 submission.

2. INSERT/MEDICATION GUIDE

   Satisfactory in FPL as of the June 26, 2008 submission.
   Satisfactory in SPL as of the June 26, 2008 submission.

3. MEDICATION GUIDE

   Satisfactory in FPL as of the June 26, 2008 submission.

Revisions needed post approval:

INSERT/MEDICATION GUIDE
DESCRIPTION - delete "NF" associated with the inactive ingredients.
PRECAUTIONS, Information for Patients, first paragraph, last sentence, revise to read" The complete text of the Medication Guide is reprinted at the end of this document."

MEDICATION GUIDE- delete the perforated line that separates the Medication Guide since you are providing the Medication Guide separately.

In accordance with the requirements for a toll-free number for the reporting of adverse events, include the following text at the end of the What are the possible side effects of bupropion XL subsection:

"Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800- FDA 1088".

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

Code	Reference	Expiration	Labeling Impact
I-497	Prevention of seasonal major depressive episodes in patients with seasonal affective disorder	June 12, 2009	Carved out

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Wellbutrin XL Tablets
NDA Number: 21-515
NDA Drug Name: Wellbutrin XLTablets
NDA Firm: GlaxoSmithKline
Date of Approval of ANDA Insert and supplement #: S-020; August 2, 2007
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug

FOR THE RECORD:
1. MODEL LABELING
This review was based on the labeling for Wellbutrin XL® (GlaxoSmithKline; Approved 8-02-07) NDA 21-515/S-020.

2. DESCRIPTION
The inactive ingredients are listed accurately in the DESCRIPTION section.
(Vol. 1.12 Page 4376, 4451, & 4502)

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
VPS Corporation
Cedar Brook Corporate Center
3 Cedar Brook Drive N., Suite 3
Cranbury, New Jersey 08512
(Vol. 1.12. Page 4567).

4. 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. 1.13 page 4957 & Vol. 2.2 page 655-658)

5. 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

Code	Reference	Expiration	Labeling Impact
I-497	Prevention of seasonal major depressive episodes in patients with seasonal affective disorder	June 12, 2009	Carved out

6. Summary of Container/Closure system:

Packaging Size		150 mg	300 mg
Bottle of 30s	Container	[redacted]	bottle
	Closure		[redacted]
Bottle of 90s	Container		bottle
	Closure		[redacted]

b(4)

[Vol. 1.13 page 4904 & Vol. 2.2 page 642]

7. Per memo from Kim Dettelbach, [redacted] b(5)

8. Storage/dispensing recommendations:
RLD - Store at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) [see USP Controlled Room Temperature].
ANDA - "Store at 20º-25ºC (68º-77ºF); excursions permitted to 15-30ºC (59-86ºF) [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 90s.

10. **Anchen still holds 180 day exclusivity on the 150 mg strength and has not yet gone to market, so Actavis is eligible for Tentative Approval on the 150 mg strength and Full Approval on the 300 mg. Actavis has carved out reference to the 150 mg strength from their insert.**

11. Medication Guides
Actavis will provide Medication Guides in tear-off pads of 12 which will be included in each shipper of 12 bottles for both 30 and 90 count.

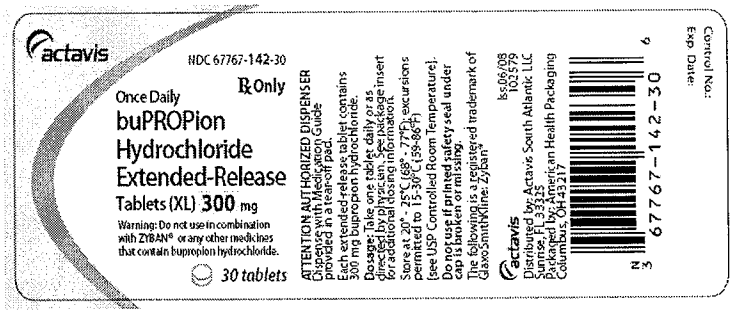
Date of Review: **July 3, 2008** **Date of Submissions: June 16, 23, and 26, 2008**

Primary Reviewer: _____ Michelle Dillahunt _____ Date:

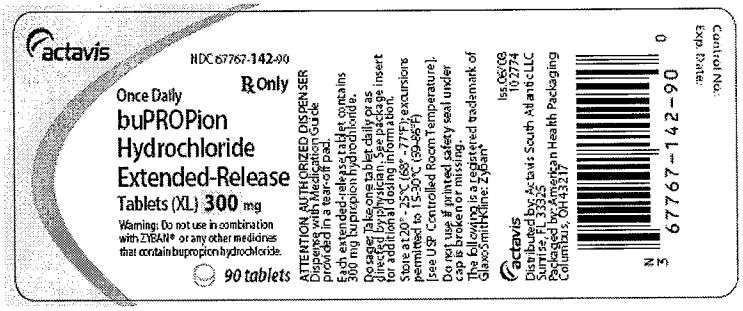
Team Leader: _____ Lillie Golson _____ Date:

cc: ANDA 77-285
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
Review
V:\FIRMSAM\ACTAVIS South Atlantic LLC\LTRS&REV\77285AP1.labeling.doc

Bupropion Hydrochloride Extended-Release Tablets (XL) 300 mg, 30 tablets



Bupropion Hydrochloride Extended-Release Tablets (XL) 300 mg, 90 tablets



actavis

Prescribing Information

BuPROPion Hydrochloride Extended-Release Tablets (XL)

Rev. 06/08

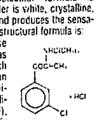
F.P.O.

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents and young adults in short-term studies of 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, adolescent or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and 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 use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

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 $C_{13}H_{18}ClNO•HCl$. 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 300-mg, off-white extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: copovidone, hydroxypropyl cellulose (NF), colloidal silicon dioxide (NF), magnesium stearate (NF), polyvinyl alcohol, macrogol (NF), talc, methacrylic acid copolymer, titanium dioxide, triethyl citrate, colloidal anhydrous silica, sodium bicarbonate, sodium lauryl sulfate, povidone, purified water, and hydrochloric acid (NF).

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 1 1/2-fold for hydroxybupropion and about 2 1/2-fold for threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold, respectively, in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Renal: There is limited information on the pharmacokinetics of bupropion in patients with renal impairment. An inter-study comparison between normal subjects and patients with 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-blind phase was defined as the investigator's judgment that drug treatment was needed for worsening depressive symptoms. Patients receiving continued bupropion treatment experienced significantly lower relapse rates over the subsequent 44 weeks compared to those receiving placebo.

Although there are no independent trials demonstrating the antidepressant effectiveness of Bupropion Hydrochloride Extended-Release Tablets (XL), studies have demonstrated similar bioavailability of Bupropion Hydrochloride Extended-Release Tablets (XL) to both the immediate-release formulation and to the sustained-release formulation of bupropion under steady-state conditions, i.e., Bupropion Hydrochloride Extended-Release Tablets (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 TRIALS).

A major depressive episode (DSM-IV) implies the presence of 1) depressed mood or 2) loss of interest or pleasure; in addition, at least 5 of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt, or suicidal ideation.

The efficacy of bupropion in maintaining an antidepressant response for up to 44 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial with the sustained-release formulation of bupropion (see CLINICAL TRIALS). Nevertheless, the physician who elects to use Bupropion Hydrochloride Extended-Release Tablets (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® (bupropion hydrochloride) Sustained-Release Tablets; WELLBUTRIN® (bupropion hydrochloride) the immediate-release formulation; WELLBUTRIN SR® (bupropion hydrochloride) the 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. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated
Increases Compared to Placebo	
<18	14 additional cases
18-24	5 additional cases
Decreases Compared to Placebo	
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and 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.

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 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.

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®, 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), the sustained-release formulation, or WELLBUTRIN® (bupropion hydrochloride), the immediate-release formulation.

Seizures: Bupropion is associated with a dose-related risk of seizures. The risk of seizures is also related to patient factors, clinical situations, and concomitant medications, which must be considered in selection of patients for therapy with Bupropion Hydrochloride Extended-Release Tablets (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 (WELLBUTRIN SR®), the incidence of seizure is approximately 0.1% (1/1,000).**

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

  Additional data accumulated for the immediate-release formulation of bupropion suggested that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day. The 600 mg dose is twice the usual adult dose and one and one-third the maximum recommended daily dose (450 mg) of Bupropion Hydrochloride Extended-Release Tablets (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 WELLBUTRIN SR®, the sustained-release formulation of bupropion, experienced agitation, anxiety, and insomnia as shown in Table 2.

Table 2. Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials of WELLBUTRIN SR® for Major Depressive Disorder

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

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

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

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

Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in bipolar disorder patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Bupropion Hydrochloride Extended-Release Tablets (XL) are expected to pose similar risks.

Altered Appetite and Weight: In placebo-controlled studies of major depressive disorder using WELLBUTRIN SR®, the sustained-release formulation of bupropion, patients experienced weight gain or weight loss as shown in Table 3.

Table 3. Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials of WELLBUTRIN SR® for Major Depressive Disorder

Weight Change	WELLBUTRIN SR® 300 mg/day (n = 339)	WELLBUTRIN SR® 400 mg/day (n = 112)	Placebo (n = 347)
Gained > 5 lbs	3%	2%	4%
Lost > 5 lbs	14%	19%	6%

In studies conducted with the immediate-release formulation of bupropion, 35% of patients receiving tricyclic antidepressants gained weight, compared to 9% of patients treated with the immediate-release formulation of bupropion. If weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight-reducing potential of Bupropion Hydrochloride Extended-Release Tablets (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 postmarketing 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 preexisting hypertension.

Data from a comparative study of the sustained-release formulation of bupropion (ZYBAN® Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of sustained-release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS, and placebo, respectively. The majority of these patients had evidence of preexisting hypertension. Three patients (1.2%) treated with the combination of ZYBAN® and NTS and 1 patient (0.4%) treated with NTS had study medication discontinued due to hypertension compared to none of the patients treated with ZYBAN® or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

There is no clinical experience establishing the safety of Bupropion Hydrochloride Extended-Release Tablets (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 patient Medication Guide about "Antidepressant Medicines,

Medication Guide
BuPROPion Hydrochloride Extended-Release Tablets (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 both sections of this Medication Guide. The first section is about the risk of suicidal thoughts and actions with antidepressant medicines; the second section is entitled "What other important information should I know about Bupropion Hydrochloride Extended-Release Tablets (XL)?"

Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions

This section of the Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
   - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
   - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

Bupropion Hydrochloride Extended-Release Tablets (XL) have not been studied in children under the age of 18 and are not approved for use in children and teenagers.

What other important information should I 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 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 WELLBUTRIN® Tablets or WELLBUTRIN SR® 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. If you can use Bupropion Hydrchloride Extended-Release Tablets (XL) while you are pregnant, talk to your doctor about how you can be on the Bupropion Pregnancy Registry.
  - **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.**

(continued on other side)

- 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 nonprescription 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).

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 many Bupropion Hydrochloride Extended-Release Tablets (XL) can increase your chance of having a seizure.
- If you take too many Bupropion Hydrochloride Extended-Release Tablets (XL), or overdose, call your local emergency room or poison control center right away.
- **Do not take any other medicines while using Bupropion Hydrochloride Extended-Release Tablets (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) are 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) are 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) affect 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 taking 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 or you can visit www.actavis.us or call toll-free 1-800-432-6534.

What are the ingredients in Bupropion Hydrochloride Extended-Release Tablets (XL)?

Active ingredient: bupropion hydrochloride.

Inactive ingredients: copovidone, hydroxypropyl cellulose (NF), colloidal silicon dioxide (NF), magnesium stearate (NF), polyvinyl alcohol, macrogol (NF), talc, methacrylic acid copolymer, titanium dioxide, triethyl citrate, colloidal anhydrous silica, sodium bicarbonate, sodium lauryl sulfate, povidone, purified water, and hydrochloric acid (NF).

The following are registered trademarks of their respective manufacturers: NARDIL®/Warner Lambert Company; WELLBUTRIN®, WELLBUTRIN SR®, ZYBAN® and PARNATE®/GlaxoSmithKline; MARPLAN®/Oxford Pharmaceutical Services, Inc.

Rx Only

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actavis

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Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions" and other important information about using Bupropion Hydrochloride Extended-Release Tablets (XL) 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 Guide is provided by the authorized dispenser.

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 look 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) 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 hydrochloride (such as WELLBUTRIN SR®, the sustained-release formulation, and WELLBUTRIN®, the immediate-release formulation).

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.

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 congenital malformations overall, or cardiovascular malformations specifically, following first trimester bupropion exposure compared to exposure to all other antidepressants in the first trimester, or bupropion outside of the first trimester. The results of this study have not been corroborated. Bupropion Hydrochloride Extended-Release Tablets (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 WELLBUTRIN SR® Tablets, the sustained-release formulation of bupropion.

Adverse Events Leading to Discontinuation of Treatment With WELLBUTRIN® or WELLBUTRIN SR®: In placebo-controlled clinical trials, 9% and 11% of patients treated with 300 and 400 mg/day, respectively, of the sustained-release formulation of bupropion and 4% of patients treated with placebo discontinued treatment due to adverse events. The specific adverse events in these trials that led to discontinuation in at least 1% of patients treated with either 300 mg/day or 400 mg/day of WELLBUTRIN SR®, the sustained-release formulation of bupropion, and at a rate at least twice the placebo rate are listed in Table 4.

Table 4. Treatment Discontinuations Due to Adverse Events in Placebo-Controlled Trials for Major Depressive Disorder

Adverse Event Term	WELLBUTRIN SR® 300 mg/day (n = 376)	WELLBUTRIN SR® 400 mg/day (n = 114)	Placebo (n = 385)
Rash	2.4%	0.9%	0.0%
Nausea	0.8%	1.8%	0.3%
Agitation	0.3%	1.8%	0.3%
Migraine	0.0%	1.8%	0.3%

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

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated With WELLBUTRIN® or WELLBUTRIN SR®: Table 5 enumerates treatment-emergent adverse events that occurred among patients treated with 300 and 400 mg/day of the sustained-release formulation of bupropion and with placebo in controlled trials. Events that occurred in either the 300- or 400-mg/day group at an incidence of 1% or more and were more frequent than in the placebo group are included. Reported adverse events were classified using a COSTART-based Dictionary.

Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

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

Table 5. Treatment-Emergent Adverse Events in Placebo-Controlled Trials* for Major Depressive Disorder

Body System/ Adverse Event	WELLBUTRIN SR® 300 mg/day (n = 376)	WELLBUTRIN SR® 400 mg/day (n = 114)	Placebo (n = 385)
Body (General)			
Headache	26%	25%	23%
Infection	8%	9%	6%
Abdominal pain	3%	9%	2%
Asthenia	2%	4%	2%
Chest pain	3%	4%	1%
Pain	2%	3%	2%
Fever	1%	2%	—
Cardiovascular			
Palpitation	2%	6%	2%
Flushing	1%	4%	—
Migraine	1%	4%	1%
Hot flashes	1%	3%	1%
Digestive			
Dry mouth	17%	24%	7%
Nausea	13%	18%	8%
Constipation	10%	5%	7%
Diarrhea	5%	7%	6%
Anorexia	5%	3%	2%
Vomiting	4%	2%	2%
Dysphagia	0%	2%	0%
Musculoskeletal			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	0%	2%	0%
Twitch	1%	2%	—
Nervous system			
Insomnia	11%	16%	6%
Dizziness	7%	11%	5%
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Tremor	6%	3%	1%
Nervousness	5%	3%	3%
Somnolence	2%	3%	2%
Irritability	3%	2%	2%
Memory decreased	—	3%	1%
Paresthesia	1%	2%	1%
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%	—
Blurred vision or diplopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	—	2%	0%
Vaginal hemorrhage†	0%	2%	—
Urinary tract infection	1%	0%	—

* Adverse events that occurred in at least 1% of patients treated with either 300 or 400 mg/day of the sustained-release formulation of bupropion, but equally or more frequently in the placebo group, were: abnormal dreams, accidental injury, acne, appetite increased, back pain, bronchitis, dysmenorrhea, dyspepsia, flatulence, flu syndrome, hypertension, neck pain, respiratory disorder, rhinitis, and tooth disorder.

† Incidence based on the number of female patients.

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

Additional events to those listed in Table 5 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 5 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 WELLBUTRIN SR®: Anorexia, dry mouth, rash, sweating, tinnitus, and tremor.

400 mg/day of WELLBUTRIN SR®: Abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary frequency.

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

Adverse events for which frequencies are provided below occurred in clinical trials with the sustained-release formulation of bupropion. The frequencies represent the proportion of patients who experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled studies for depression (n = 987) or smoking cessation (n = 1,013), or patients who experienced an adverse event requiring discontinuation of treatment in an open-label surveillance study with the sustained-release formulation of bupropion (n = 3,100). All treatment-emergent adverse events are included except those listed in Tables 2 through 8, 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 WELLBUTRIN® Tablets or from WELLBUTRIN SR® Sustained-Release Tablets: When switching patients from WELLBUTRIN® Tablets to Bupropion Hydrochloride Extended-Release Tablets (XL), or from WELLBUTRIN SR® 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 WELLBUTRIN® 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® 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 (XL), 300 mg of bupropion hydrochloride, are off-white, oval, tablets debossed into the surface with '142' in bottles of 30 tablets (NDC 67767-142-30) and 90 tablets (NDC 67767-142-90).

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

The following are registered trademarks of GlaxoSmithKline: WELLBUTRIN®, WELLBUTRIN SR® and ZYBAN®.

Manufactured by: VPS Corporation
Cranbury, New Jersey 08512

actavis

Distributed by: Actavis South Atlantic LLC
Sunrise, FL 33325
Rev. 06/08

Medication Guide
BuPROPion Hydrochloride Extended-Release Tablets (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 both sections of this Medication Guide. The first section is about the risk of suicidal thoughts and actions with antidepressant medicines; the second section is entitled "What other important information should I know about Bupropion Hydrochloride Extended-Release Tablets (XL)?"

Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions

This section of the Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
   - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
   - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

Bupropion Hydrochloride Extended-Release Tablets (XL) have not been studied in children under the age of 18 and are not approved for use in children and teenagers.

What other important information should I 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 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 WELLBUTRIN® Tablets or WELLBUTRIN SR® 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. If you can use Bupropion Hydrchloride Extended-Release Tablets (XL) while you are pregnant, talk to your doctor about how you can be on the Bupropion Pregnancy Registry.
  - **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 nonprescription 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).

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 many Bupropion Hydrochloride Extended-Release Tablets (XL) can increase your chance of having a seizure.
- If you take too many Bupropion Hydrochloride Extended-Release Tablets (XL), or overdose, call your local emergency room or poison control center right away.
- **Do not take any other medicines while using Bupropion Hydrochloride Extended-Release Tablets (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) are 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) are 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) affect 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 taking 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 or you can visit www.actavis.us or call toll-free 1-800-432-8534.

What are the ingredients in Bupropion Hydrochloride Extended-Release Tablets (XL)?

Active ingredient: bupropion hydrochloride.

Inactive ingredients: copovidone, hydroxypropyl cellulose (NF), colloidal silicon dioxide (NF), magnesium stearate (NF), polyvinyl alcohol, macrogol (NF), talc, methacrylic acid copolymer, titanium dioxide, triethyl citrate, colloidal anhydrous silica, sodium bicarbonate, sodium lauryl sulfate, povidone, purified water, and hydrochloric acid (NF).

The following are registered trademarks of their respective manufacturers: NARDIL®/Warner Lambert Company; WELLBUTRIN®, WELLBUTRIN SR®, ZYBAN® and PARNATE®/GlaxoSmithKline; MARPLAN®/Oxford Pharmaceutical Services, Inc.

Rx Only

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

Manufactured by: VPS Corporation, Cranbury, New Jersey 08512

actavis

Distributed by: Actavis South Atlantic LLC, Sunrise, FL 33325

Rev. 06/08

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

/s/

Michelle Dillahunt
7/10/2008 03:24:24 PM
LABELING REVIEWER

Lillie Golson
7/11/2008 01:15:27 PM
LABELING REVIEWER

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

ANDA Number: **77-285**

Date of Submissions: **April 1 and May 19, 2008**

Applicant's Name: **Actavis South Atlantic LLC**

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

Labeling Deficiencies:

1. GENERAL - Please ensure that the proprietary symbol "®" is used with the brand name products throughout your labeling.

2. CONTAINER

   Please include a statement as to how the Medication Guide is being distributed. (Refer to 21 CFR 208.24 (d)).

3. INSERT

   a. CONTRAINDICATIONS

   Second paragraph, delete "

   b. WARNINGS

   (i) Delete the sixth paragraph, '

   (ii) Screening for Bipolar Disorder, second paragraph, delete '

   c. PRECAUTIONS

   Clinical Worsening and Suicide Risk, second paragraph, delete '

   d. HOW SUPPLIED

   Delete reference to

4. MEDICATION GUIDE

   a. Your medication guide attached to the insert does not appear to be 10 font. Please revise. See 21 CFR 208.20.

   b. Include a statement in your submission, describing how Medication Guides will be distributed for each package size.

   c. Who should not take Bupropion Hydrochloride Extended-Release Tablets (XL)?, second bullet, delete "

b(4)

b(4)

d. What are the ingredients in Bupropion Hydrochlorde Extended-Release Tablets (XL)?, second paragraph, delete [redacted] b(4)

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

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://service.govdelivery.com/service/subscribe.html?code=USFDA_17

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

{See appended electronic signature page}

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

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/s/

Lillie Golson
6/12/2008 05:37:14 PM
Lillie Golson for Wm. Peter Rickman

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

ANDA Number: **77-285**

Date of Submissions: **April 1 and May 19, 2008**

Applicant's Name: **Actavis South Atlantic LLC**

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

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   a. CONTRAINDICATIONS

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   b. WARNINGS

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   c. PRECAUTIONS

   Clinical Worsening and Suicide Risk, second paragraph, delete "

   d. HOW SUPPLIED

   Delete reference to '

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   b. Include a statement in your submission, describing how Medication Guides will be distributed for each package size.

   c. Who should not take Bupropion Hydrochloride Extended-Release Tablets (XL)?, second bullet, delete '

b(4)

b(4)

d. What are the ingredients in Bupropion Hydrochlordie Extended-Release Tablets (XL)?, second paragraph, delete b(4)

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

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

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Wellbutrin XL® (Glaxo Wellcome; Approved 8-02-07) NDA 21-515/S-020.

2. DESCRIPTION

The inactive ingredients are listed accurately in the DESCRIPTION section.

(Vol. 1.12 Page 4376, 4451, & 4502)

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

VPS Corporation
Cedar Brook Corporate Center
3 Cedar Brook Drive N., Suite 3
Cranbury, New Jersey 08512

(Vol. 1.12. Page 4567).

4. 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. 1.13 page 4957 & Vol. 2.2 page 655-658)

5. 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.

6. Summary of Container/Closure system:

Packaging Size		150 mg	300 mg
Bottle of 30s	Container	[redacted]	bottle
	Closure		
Bottle of 90s	Container		bottle
	Closure		

b(4)

[Vol. 1.13 page 4904 & Vol. 2.2 page 642]

b(5)

7. Per memo from Kim Dettelbach, [redacted]

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); excursions permitted to 15-30°C (59-86°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 90s.

10. Anchen still holds 180 day exclusivity on the 150 mg strength and has not yet gone to market, so Actavis is eligible for Tentative Approval on the 150 mg strength and Full Approval on the 300 mg.

Date of Review: June 3, 2008 Date of Submission: April1 and May 18, 2008

Primary Reviewer: _____ _____
Michelle Dillahunt Date:

Team Leader: _____ _____
Lillie Golson Date

cc:

ANDA: 77-285
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
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Review

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

/s/

Michelle Dillahunt
6/10/2008 08:25:03 AM
LABELING REVIEWER

Lillie Golson
6/11/2008 05:07:00 PM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING #2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-285

Date of Submission: September 28, 2005

Applicant's Name: Abrika Pharmaceuticals, LLP

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

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Labeling Deficiencies:

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

- Satisfactory in final print as of September 28, 2005 submission.

\\Cdsesub1\n77285\N_000\2005-09-28\Proposed.pdf

PHYSICIAN INSERT

- Add the following paragraph under the WARNINGS section after the 4th paragraph:

  "Adults with MDD or co-morbid depression in the ..... either increases or decreases.

  In addition, patient 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 suicidial thoughts or suicide attempts, and should receive careful monitoring during treatment. [American Psychiatric Association Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviorts, 2003] [Brown, 2000]"

Please revise your labeling as described above and submit electronically 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

1. MODEL LABELING

This review was based on the labeling for Wellbutrin XL (Glaxo Wellcome; Approved 2/28/06) NDA 21-515/S-012.

2. DESCRIPTION

The inactive ingredients are listed accurately in the DESCRIPTION section.

(Vol. 1.12 Page 4376, 4451, & 4502)

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

VPS Corporation
Cedar Brook Corporate Center
3 Cedar Brook Drive N., Suite 3
Cranbury, New Jersey 08512

(Vol. 1.12. Page 4567).

4. 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. 1.13 page 4957 & Vol. 2.2 page 655-658)

5. 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.

6. Summary of Container/Closure system:

Packaging Size		150 mg	300 mg
Bottle of 30s	Container		bottle
	Closure		
Bottle of 100s	Container		bottle
	Closure		

b(4)
b(4)
b(4)

[Vol. 1.13 page 4904 & Vol. 2.2 page 642]

7. Per memo from Kim Dettelbach [redacted] b(5)

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 25°C (77°F); excursions permitted to 15-30°C (59-86°F)

I recommended the following:

"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 [redacted] b(4)

Date of Review: June 2, 2006 Date of Submission: September 28, 2005

Primary Reviewer: [signature] 6-7-06
Melaine Shin Date:

Team Leader: [signature] 6/7/06
Lillie Golson Date

cc:

ANDA: 77-285
DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)

Review

File Path:V:\FIRMSAM\ABRIKA\LTRS&REV\77285 NA2.labeling.doc
FINAL: June 2, 2006

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

ANDA Number:	77-285
Date of Submission:	July 8, 2005
EDR Path:	\\Cdsesub1\n77285\N_000\2005-07-08
Applicant's Name:	Abrika Pharmaceuticals, LLP
Established Name:	Bupropion Hydrochloride Extended-release Tablets USP, (XL) 150 mg and 300 mg
Proposed 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? Yes, E-submission (PI only) & Paper

CONTAINER LABELS – 30s for 150 mg & 300 mg

Satisfactory in final print as of July 8, 2005 submission (Vol. 7.1)

PROFESSIONAL PACKAGE INSERT

Satisfactory in final print as of July 8, 2005 submission

\\Cdsesub1\n77285\N_000\2005-07-08\Outsert.pdf

REVISIONS NEEDED POST-APPROVAL: None

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. MODEL LABELING

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

2. DESCRIPTION

The inactive ingredients are listed accurately in the DESCRIPTION section.

(Vol. 1.12 Page 4376, 4451, & 4502)

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

VPS Corporation
Cedar Brook Corporate Center
3 Cedar Brook Drive N., Suite 3 b(4)
Cranbury, New Jersey 08512

(Vol. 1.12. Page 4567).

4. 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. 1.13 page 4957 & Vol. 2.2 page 655-658)

5. 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.

6. Summary of Container/Closure system:

** b(4)

Packaging Size		150 mg	300 mg
Bottle of 30s	Container	[redacted]	[redacted] bottle b(4)
	Closure	[redacted]	[redacted] b(4)

[Vol. 1.13 page 4904 & Vol. 2.2 page 642]

7. Per memo from Kim Dettelbach, [redacted] b(5)

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 30s.

Date of Review: August 26, 2005 Date of Submission: July 8, 2005

Primary Reviewer: Melaine Shin 8-31-05 Date:

Team Leader: Lillie Golson 8/31/05 Date

cc:
ANDA: 77-285
DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)

File Path:V:\FIRMSAM\ABRIKA\LTRS&REV\77285 AP .LABELING.doc

FINAL: August 31, 2005

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

ANDA Number: **77-285**

Date of Submission: **September 23, 2004 (Original Submission)**
October 1, 2004 (Addition of 300 mg strength)
October 25, 2004 (Telephone Amendment)

Applicant's Name: Abrika Pharmaceuticals, LLP

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.

- Please 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

  XXX Tablets Rx only

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

- Put "ATTENTION: Dispense with Medication Guide" on the side display panel if it's not possible to put it on the principal display panel due to space limitation.

- Revise the storage temperature recommendation as follow:

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

- See comment under **GENERAL**

PHYSICIAN INSERT

- See comment under GENERAL
- Update your insert labeling based on the attached approved labeling for the reference listed drug, Wellbutrin XL. Please note that all antidepressants are now required to be dispensed with a medication guide, and we need you to submit your proposal for dissemination of the medication guide for review.

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

7. Per memo from Kim Dettelbach, [redacted] b(5)

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 25°C (77°F); excursions permitted to 15-30°C (59-86°F)

   I recommended the following:

   "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 [redacted] b(4)

Date of Review: June 1, 2005

Date of Submission: **September 23, 2004**
October 1, 2004
October 25, 2004

Primary Reviewer: [signature] Melaine Shin — Date: 6-6-05

Team Leader: [signature] Lillie Golson — Date: 6/6/05

cc:

ANDA: 77-285
DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)
V:Firmsam\ABRIKA\Ltr&Rev\77285NA1.Labeling Review

DRAFT: June 1, 2005
FINAL: June 6, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-285

CHEMISTRY REVIEWS

ANDA 77-285

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

Actavis South Atlantic LLC
(formerly Abrika Pharmaceuticals, LLLP)

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 77-285

2. REVIEW #: 4

3. REVIEW DATE: 23-MAY-2008; 07-JUL-2008

4. REVIEWER: Bing Wu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	September 29, 2004
Major Amendment	October 1, 2004
Telephone Amendment	October 25, 2004
Chemistry Review #1	March 7, 2005
Minor Amendment	April 14, 2005
Chemistry Review #2	September 20, 2005
Telephone Amendment	September 28, 2005
Chemistry Review #2b	October 5, 2005
Telephone Amendment	February 15, 2006
Chemistry Review #2c	February 17, 2006
Telephone Amendment	March 14, 2006
Chemistry Review #2d (Not approval)	April 19, 2006
Major Amendment	April 27, 2007
Chemistry Review #3 (Not approval)	September 14, 2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Major Amendment	**December 7, 2007**
Gratuitous Amendment	**March 27, 2008**
Telephone Amendment	**June 9, 2008**
Telephone Amendment	**July 16, 2008**
Telephone Amendment	**July 22, 2008**
Telephone Amendment	**July 25, 2008**

7. NAME & ADDRESS OF APPLICANT:

Name:	Actavis South Atlantic LLC (formerly Abrika Pharmaceuticals LLLP)
Address:	13800 N.W. 2nd Street Suite 190 Sunrise, Florida 33325
Representative:	Monique Weitz
Telephone:	(954) 315-6502
Fax:	(954) 315-6550

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 Abrika's drug product. A revised Paragraph IV patent certification is provided on pp. 7-8 of the 10/25/04 Amendment.

An exclusivity statement is provided on p. 19 (v1.1). 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

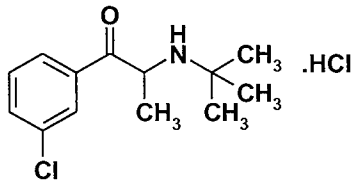
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____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
					Adequate	9/14/07	

b(4)

b(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	5/2/08	Per OC
Methods Validation	N/A		
Labeling	Acceptable	7/3/08	Michelle Dillahunt
Bioequivalence	Acceptable	4/3/08	Nam Chun
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 Amendment

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 77-285

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 off-white extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the following inactive ingredients: copovidone, hydroxypropyl cellulose, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol, talc, methacrylic acid copolymer, triethyl citrate, colloidal anhydrous silica, sodium bicarbonate, sodium lauryl sulfate, and povidone. Bupropion HCl ER Tablets, 150 mg and 300 mg, are supplied in bottles of 30 tablets and — tablets. b(4)

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

Bupropion HCl ER Tablets are indicated for the treatment of major depression disorder.

C. Basis for Approvability or Not-Approval Recommendation

Approval is recommended. All CMC issues identified in the previous chemistry reviews have been satisfactorily addressed.

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of trade secret and/or

confidential commercial

information from

Chemistry Review #4

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
8/13/2008 10:33:30 AM
CHEMIST

Naiqi Ya
8/21/2008 09:58:44 AM
CHEMIST

Thomas Hinchliffe
8/21/2008 02:23:31 PM
CSO

ANDA 77-285

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

Abrika Pharmaceuticals, LLLP

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 77-285

2. REVIEW #: 3

3. REVIEW DATE: 14-SEP-07

4. REVIEWER: Bing Wu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	September 29, 2004
Major Amendment	October 1, 2004
Telephone Amendment	October 25, 2004
Chemistry Review #1	March 7, 2005
Minor Amendment	April 14, 2005
Chemistry Review #2	September 20, 2005
Telephone Amendment	September 28, 2005
Chemistry Review #2b	October 5, 2005
Telephone Amendment	February 15, 2006
Chemistry Review #2c	February 17, 2006
Telephone Amendment	March 14, 2006
Chemistry Review #2d	April 19, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Major Amendment	**April 27, 2007**

7. NAME & ADDRESS OF APPLICANT:

Name:	Abrika Pharmaceuticals LLLP
Address:	13800 N.W. 2nd Street Suite 190 Sunrise, Florida 33325
Representative:	Monique Weitz
Telephone:	(954) 315-6600
Fax:	(954) 315-6601

Chemistry Review Data Sheet

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 Abrika's drug product. A revised Paragraph IV patent certification is provided on pp. 7-8 of the 10/25/04 Amendment.

   An exclusivity statement is provided on p. 19 (v1.1). 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):

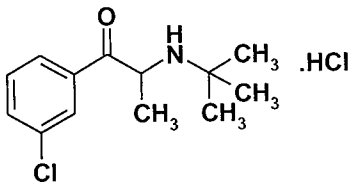
    _____ SPOTS product – Form Completed

    __X__ Not a SPOTS product

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

    Buproprion Hydrochloride

Chemistry Review Data Sheet



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
					Adequate	9/14/07	

b(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	Pending		Per OC
Methods Validation	N/A		
Labeling	Not acceptable	6/2/06	Melaine Shin
Bioequivalence	Incomplete	6/29/07	Ethan M. Stier
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 77-285

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable is recommended. – The firm needs to address the minor deficiencies identified in this chemistry review #3.

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 off-white extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the following inactive ingredients: copovidone, hydroxypropyl cellulose, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol, talc, methacrylic acid copolymer, triethyl citrate, colloidal anhydrous silica, sodium bicarbonate, sodium lauryl sulfate, and povidone. Bupropion HCl ER Tablets, 150 mg and 300 mg, are supplied in bottles of 30 tablets and — tablets. b(4)

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

Bupropion HCl ER Tablets are indicated for the treatment of major depression disorder.

C. Basis for Approvability or Not-Approval Recommendation

Not approval is recommended for the ANDA 77-285 due to the minor deficiencies in the raw material testing, container/closure testing, and in-process testing (See Section 36).

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of trade secret and/or

confidential commercial

information from

Chemistry Review #3

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
10/31/2007 03:53:34 PM
CHEMIST

Thomas Hinchliffe
11/1/2007 12:16:01 PM
CSO

Naiqi Ya
11/1/2007 01:30:02 PM
CHEMIST

ANDA 77-285

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

Abrika Pharmaceuticals, LLLP

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 77-285

2. REVIEW #: 2d

3. REVIEW DATE: 19-APR-2005

4. REVIEWER: Bing Wu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	September 29, 2004
Major Amendment	October 1, 2004
Telephone Amendment	October 25, 2004
Minor Amendment	April 14, 2005
Telephone Amendment	September 28, 2005
Telephone Amendment	February 15, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Telephone Amendment	March 14, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Abrika Pharmaceuticals LLLP
Address:	13800 N.W. 2nd Street Suite 190 Sunrise, Florida 33325
Representative:	Monique Weitz
Telephone:	(954) 315-6600
Fax:	(954) 315-6601

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

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

Chemistry Review Data Sheet

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 Abrika's drug product. A revised Paragraph IV patent certification is provided on pp. 7-8 of the 10/25/04 Amendment.

An exclusivity statement is provided on p. 19 (v1.1). 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

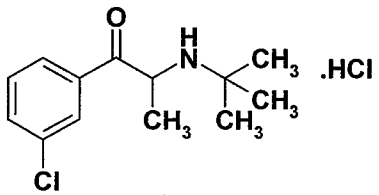
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

___X___ Not a SPOTS product

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

Buproprion 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
					Adequate	10/24/05	

b(4)

b(4)

b(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	3/14/05	Per OC
Methods Validation	N/A		
Labeling	Acceptable	8/31/05	Melaine Shin
Bioequivalence	Acceptable	12/23/05	Ethan M. Stier
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 Amendment

The Chemistry Review for ANDA 77-285

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable 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 off-white extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the following inactive ingredients: copovidone, hydroxypropyl cellulose, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol, talc, methacrylic acid copolymer, triethyl citrate, colloidal anhydrous silica, sodium bicarbonate, sodium lauryl sulfate, and povidone. Bupropion HCl ER Tablets, 150 mg and 300 mg, are supplied in bottles of 30 tablets and —tablets. b(4)

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

Bupropion HCl ER Tablets are indicated for the treatment of major depression disorder.

C. Basis for Approvability or Not-Approval Recommendation

Not approval is recommended for the ANDA 77-285 due to the major deficiencies in dissolution failures.

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of trade secret and/or

confidential commercial

information from

Chemistry Review #2

cc: ANDA 77-285
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/BWu/4/19/06 4/24/06

HFD-640/NYa/4/21/06 4/24/06

HFD-617/THinchliffe/4/21/06 4/24/06

F/T by:rad4/24/06

V:\FIRMSAM\ABRIKA\LTRS&REV\77285Rev2d.doc

TYPE OF LETTER: NOT APPROVABLE – MAJOR AMENDMENT

ANDA 77-285

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

Abrika Pharmaceuticals, LLLP

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 77-285

2. REVIEW #: 2c

3. REVIEW DATE: 17-FEB-2005

4. REVIEWER: Bing Wu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	September 29, 2004
Major Amendment	October 1, 2004
Telephone Amendment	October 25, 2004
Minor Amendment	April 14, 2005
Telephone Amendment	September 28, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Telephone Amendment	Feb 15, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Abrika Pharmaceuticals LLLP
Address:	13800 N.W. 2nd Street Suite 190 Sunrise, Florida 33325
Representative:	Monique Weitz
Telephone:	(954) 315-6600
Fax:	(954) 315-6601

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 Abrika's drug product. A revised Paragraph IV patent certification is provided on pp. 7-8 of the 10/25/04 Amendment.

An exclusivity statement is provided on p. 19 (v1.1). 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

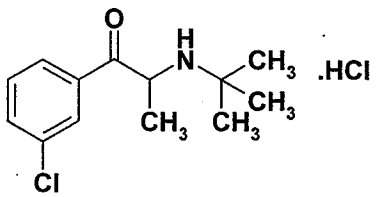
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

__X__ Not a SPOTS product

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

Buproprion 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
[redacted]					Adequate	10/24/05	

b(4)

b(4)

b(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	3/14/05	Per OC
Methods Validation	N/A		
Labeling	Acceptable	8/31/05	Melaine Shin
Bioequivalence	Acceptable	12/23/05	Ethan M. Stier
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 Amendment

The Chemistry Review for ANDA 77-285

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable 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 off-white extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the following inactive ingredients: copovidone, hydroxypropyl cellulose, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol, talc, methacrylic acid copolymer, triethyl citrate, colloidal anhydrous silica, sodium bicarbonate, sodium lauryl sulfate, and povidone. Bupropion HCl ER Tablets, 150 mg and 300 mg, are supplied in bottles of 30 tablets and — tablets. b(4)

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

Bupropion HCl ER Tablets are indicated for the treatment of major depression disorder.

C. Basis for Approvability or Not-Approval Recommendation

Not-approval is recommended for the ANDA 77-285 for the following deficiency:

- The firm needs to address the out-of-specification dissolution data.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Endorsements (Draft and Final with Dates)

HFD-640/BWu/2/17/06 2/24/06
HFD-640/NYa/ 2/24/2006
HFD-617/Thinchliffe 2/24/06

C. CC Block

ANDA 77-285
DIV FILE
Field Cop

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of trade secret and/or

confidential commercial

information from

Chemistry Review #2c

cc: ANDA 77-285
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/BWu/2/17/06,2/22/06 2/24/06

HFD-640/NYa/2/22/06 2/24/2006

HFD-617/THinchliffe/2/23/06 2/24/06

F/T by:rad2/23/06

V:\FIRMSAM\ABRIKA\LTRS&REV\77285Rev2c.doc

TYPE OF LETTER: NOT APPROVABLE – MINOR AMENDMENT

ANDA 77-285

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

Abrika Pharmaceuticals, LLLP

Bing Wu, Ph.D.

Division of Chemistry II
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-285

2. REVIEW #: 1

3. REVIEW DATE: 07-MAR-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 29, 2004
Major Amendment	October 1, 2004
Telephone amendment	October 25, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Abrika Pharmaceuticals LLLP
Address:	13800 N.W. 2nd Street Suite 190 Sunrise, Florida 33325
Representative:	Monique Weitz
Telephone:	(954) 315-6600
Fax:	(954) 315-6601

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 Abrika's drug product. A revised Paragraph IV patent certification is provided on pp. 7-8 of the 10/25/04 Amendment.

An exclusivity statement is provided on p. 19 (v1.1). 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

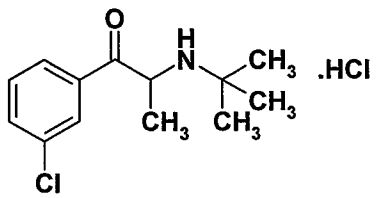
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Buproprion 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
					Adequate	12/29/04	

b(4)

b(4)

b(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	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 77-285

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 off-white extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the following inactive ingredients: copovidone, hydroxypropyl cellulose, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol, talc, methacrylic acid copolymer, triethyl citrate, colloidal anhydrous silica, sodium bicarbonate, sodium lauryl sulfate, and povidone. Bupropion HCl ER Tablets, 150 mg and 300 mg, are supplied in bottles of 30 tablets and ——ablets. b(4)

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

Bupropion HCl ER Tablets are indicated for the treatment of major depression disorder.

C. Basis for Approvability or Not-Approval Recommendation

Not-approval is recommended for the ANDA 77-285 for the following deficiencies:

- The drug substance specifications for Total Unidentified Impurities and Residual Solvent——————need to be revised.
- Comments on the inactive ingredients——————, and—— ——should be addressed. b(4)
- Acceptance criteria for the ——————should be provided. b(4)
- Test protocol for the in-process blend uniformity test was not provided, and the acceptance criteria for ——tablet weigh gain and ——————tablet weight gain need to be justified. b(4)

- The drug product release and stability specifications for ID need to be revised.
- Comments regarding the [redacted] method for Residual Solvents in the drug substance and the HPLC method for the Related Substances in the drug product need to be addressed. b(4)
- The storage statement for the drug product should be revised and the name and address of the contract drug product manufacturer should be provided.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Endorsements (Draft and Final with Dates)

HFD-640/BWu/3/7/05,3/11/05 3/14/05
HFD-640/SRosencrance/DSkanchy for 3/14/05 3/15/05
HFD-617/Thinchliffe/3/14/05 3/15/05

C. CC Block

ANDA 77-285
DIV FILE
Field Cop

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confidential commercial

information from

Chemistry Review #1

cc: ANDA 77-285
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/BWu/3/7/05 3/14/05

HFD-640/SRosecrance/DSkanchy for 3/14/05 3/15/05

HFD-617/THinchliffe/3/14/05 3/15/05

F/T by: rad3/14/05

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TYPE OF LETTER: NOT APPROVABLE – MINOR AMENDMENT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-285

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	77-285
Drug Product Name	Bupropion Extended Release Tablets
Strength	150 mg and 300mg
Applicant Name	Actavis South Atlantic LLC
Submission Date	March 20, 2008
Reviewer	Nam Chun, Pharm.D.

EXECUTIVE SUMMARY

This is a review of the dissolution specification acknowledgement from the firm.

The firm has accepted the FDA post-approval commitment to conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium as specified by our correspondence dated July2, 2007. The firm commits to provide the data within 6 months after approval.

The application is complete.

COMMENTS:

None

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

From a bioequivalence point of view, the firm has met the requirements for *in-vivo* bioequivalence and *in-vitro* dissolution testing and the application is approvable.
The firm has accepted the FDA post-approval commitment to conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium as specified by our correspondence dated July 2, 2007. The firm commits to provide the data within 6 months after approval.

I. Completed Assignment for 77285 ID: 5160

Reviewer: Chun, Nam **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
5160	3/20/2008	Dissolution Data	Dissolution Acknowledgement	1	0
				Bean Total:	0

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

/s/

Nam J Chun
4/3/2008 02:58:27 PM
BIOPHARMACEUTICS

Lizzie Sanchez
4/3/2008 04:46:26 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW- ADDENDUM

ANDA No.	77-285
Drug Product Name	Bupropion XL Tablets
Strength	150 mg and 300 mg
Applicant Name	Abrika
Address	13800 NW 2nd St. Suite 190 Sunrise, Florida 33325
Submission Date(s)	09-23-04
Amendment Date(s)	06-14-05, 12-07-05, 12-21-05
Reviewer	**Ethan M. Stier, R.Ph., Ph.D.**
First Generic	**No**
DSI	No Inspection Necessary

Addendum to a Review

I. Executive Summary

This is an addendum to the review of ANDA #77-285. Due to concern that certain extended-release products may release drug rapidly when ingested with alcohol ("dose dumping")[1], the Agency currently requests that the firm conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium. The testing conditions for the additional testing are described in the Deficiency Comments section.

The application has previously been found **acceptable** with other bioequivalence requirement aspects[2].

II. Deficiency Comments

Due to concern of dose dumping for the drug product, the Agency currently requests that the firm conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium (see email in attachment), as follows:

Testing Conditions: 900 mL of 0.1 N HCl using apparatus I (basket) at 75 rpm, with and without alcohol:

Test 1: 12 units of the drug products analyzed according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units of the drug products analyzed by substituting 5% (v/v) of test medium with Alcohol USP, with data collected every 15 minutes for a total of 2 hours.

---

[1] FDA News (2005). FDA asks Purdue Pharma to withdraw Palladone® for safety reasons (July 12, 2005), http://www.fda.gov/bbs/topics/news/2005/NEW0105.html.

[2] DBE review , dated September 23, 2004 (V:\firmsam\abrika\ltrs&rev\77285A1205)

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

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

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

III. Recommendations

The *in vitro* dissolution testing conducted by Abrika on its Bupropion Hydrochloride Extended Release Tablets, 150 mg and 300 mg, is **incomplete** for the reasons cited in the Deficiency Comments above.

The firm is requested to conduct additional dissolution testing as described in the Deficiency Comments above.

IV. Attachments

From: Sayeed, Vilayat A
Sent: Thursday, June 22, 2006 9:16 AM
To: Conner, Dale P; Davit, Barbara M; Haidar, Sam H; Yu, Lawrence; Parise, Cecelia M; Nerurkar, Shriniwas G
Cc: Buehler, Gary J
Subject: Protocol to assess alcohol impact - ANDA Bupropion ER (Wellbutrin XL)

Dear All

Here is revised plan based on the in-put.

Please provide multi-point dissolution data using the following conditions:

(900 mL, 0.1 N HCl, apparatus 1, 75 rpm) with and without the alcohol. .

The products (test and reference) must be tested accordingly and data must be provided on individual unit, means, range and %CV on both strengths.

12 units tested according to the proposed method with data collected every 15 minutes for a total of 2 hours.

12 units analyzed by substituting 5% of test medium with alcohol and data collection every 15 minutes for a total of 2 hours.

12 units analyzed by substituting 20% of test medium with alcohol and data collection every 15 minutes for a total of 2 hours.

12 units analyzed by substituting 40% of test medium with alcohol and data collection every 15 minutes for a total of 2 hours.

Any thoughts Thanks

Vilayat

BIOEQUIVALENCE DEFICIENCY

ANDA: 77-285 APPLICANT: Abrika, Inc.

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

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

Due to concern that some extended-release drug products may release drug quickly ("dose dumping") if ingested with alcoholic beverages, the Agency currently requests that you conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL of 0.1 N HCl using apparatus I (basket) at 75 rpm, with and without alcohol:

Test 1: 12 units of the drug products analyzed according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units of the drug products analyzed by substituting 5% (v/v) of test medium with Alcohol USP, with data collected every 15 minutes for a total of 2 hours.

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

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

Please submit standard operating procedures (SOPs) for the dissolution testing above, individual dissolution data, mean values, standard deviations, coefficient of variation (CV%), and plots of the percent dissolved data.

We ask that these studies be performed as post-approval commitments, and completed within 6 months of approval.

Please acknowledge your agreement to perform the aforementioned dissolution studies.

Sincerely yours,

{See appended electronic signature page}

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

CC:77-285

ANDA 77-285

1.	**Addendum**	Strength(s):	150 mg and 300 mg
	(OTH)	Outcome:	IC & WC (Addendum for Additional Dissolution Request)
	Submission Date(s)	**09-23-04, 06-14-05, 12-07-05, and 12-21-05**	

BIOEQUIVALENCE OUTCOME DECISIONS:	AC – Acceptable IC – Incomplete UN – Unacceptable WC – Without Credit

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

/s/

Ethan Stier
6/27/2007 09:37:14 AM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
6/27/2007 09:47:45 AM
BIOPHARMACEUTICS

Barbara Davit
6/28/2007 03:07:04 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-285
Drug Product Name	Bupropion XL Tablets
Strength	150 mg and 300 mg
Applicant Name	Abrika
Address	13800 NW 2nd St. Suite 190 Sunrise, Florida 33325
Submission Date(s)	09-23-04
Amendment Date(s)	10-01-04
Reviewer	**Ethan M. Stier, Ph.D.**
First Generic	**No**
File Location	**V:\firmsam\abrika\ltrs&rev\77285N0904**

I. Executive Summary

This application references Wellbutrin® XL Tablets and includes one fasting and fed BE study. The fasting study is a single-dose two-way crossover study using a total of 26 healthy male volunteers given a dose of 1 X 150 mg. The results (point estimate, 90% CI) of the fasting BE study for bupropion are LAUC∞ 0.95, 83.72-107.09, LAUCT 0.95, 83.71-107.89, and LCmax of 0.91, 80.25-104.53.

The non-fasting study is a single-dose two-way crossover study using a total of 28 healthy male volunteers given a dose of 1 X 150 mg. The results (point estimate, 90% CI) of the non-fasting BE study for bupropion are LAUC∞ 1.02, 98.66-106.04, LAUCT 1.02, 98.66-106.18, and LCmax of 1.04, 93.38-116.14.

The bioequivalence studies are incomplete. The firm needs to provide additional information regarding potency and content uniformity for the products.

The firm has requested a waiver of *in vivo* BE study requirements for the 300 mg XL tablet. The formulation of the bupropion 300 mg XL tablet is proportionally similar to the 150 mg XL tablet which underwent bioequivalence testing. However, the dissolution testing is incomplete. The firm must provide additional information.

A waiver of *in vivo* bioequivalence study requirements for the 300 mg XL tablet of the test product will be granted upon receipt of a satisfactory response to the deficiencies.

The application is incomplete.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Bupropion XL Tablets
Reference Product	Wellbutrin XL®
RLD Manufacturer	SmithKline Beecham (as listed Orange Book)
NDA No.	21-515
RLD Approval Date	08-28-03
Indication	To treat depression.

B. PK/PD Information

Bioavailability	The absolute bioavailability has not been determined since there is not an I.V. formulation available for bupropion. Studies have shown that the 300 mg XL tablet has similar bioavailability to 3X100 mg immediate release tablets under steady-state conditions.
Food Effect	Food does not affect the Tmax
Tmax	5 hours
Metabolism	Bupropion is extensively metabolized. There are three active metabolites: hydroxybupropion, threohydroxybupropion, and erythrohydroxybupropion. The relative potencies of the metabolites relative to the parent compound are 50%, 20%, and 20%, respectively. CYP2B6 is the principal isoenzyme involved in the formation of hydroxybupropion.
Excretion	87% to 10% of the drug was recovered in the urine and feces, respectively
Half-life	Bupropion: 21 hours after steady dosing Hydroxybupropion: 20 hours Threohydroxybupropion: 33 hours Erythrohydroxybupropion: 37 hours
Relevant OGD or DBE History	The dissolution portion of this application has been previously reviewed by DBE (see: V:\firmsam\abrika\ltrs&rev\77285D0904) The dissolution testing method and specification have not been determined for this product. They will be determined after the firm responds to the deficiency related to dissolution testing. There is one other ANDA submission for this test product (77-284/Anchen). The most recent control document (04-344 to the firm Anchen on 05-18-04) made the following recommendations: 1. Bioequivalence of the 150 mg XL tablet of the test and reference products should be based on an in vivo bioequivalence study conducted under fasting and fed conditions. 2. The 150 mg tablet is the RLD for this test product and should be used for bioequivalence studies due to safety concerns regarding the 300 mg tablet.

3. The sponsor may submit a request for a waiver of in vivo bioequivalence study requirements for the 300 mg XL tablet of the test product if this product (i) has compositional proportionality to the 150 mg XL tablet tested in the bioequivalence study, and (ii) exhibits a dissolution profile similar to the 150 mg XL tablet.

4. Wellbutrin XL tablets are a USP product. Comparative dissolution of the test and reference products should be conducted following the procedure given in the USP XXVIII and the test products should meet the USP specifications.

Agency Guidance None
Drug Specific Issues (if any) None

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	-
In vitro dissolution	Yes	2
Waiver requests	Yes	1
BCS Waivers	No	-
Vasoconstrictor Studies	No	-
Clinical Endpoints	No	-
Failed Studies	No	-
Amendments	No	-
CTD Tables	Yes	8

D. Pre-Study Bioanalytical Method Validation (provided by firm as CTD table)

	Volume Page (Bioanalytical Report)
Analyte	***Bupropion** (Page000733) ***Hydroxybupropion** (Page 000733)
Internal standard (IS)	*Threohydroxybupropion-d_9 (Page 000733)
Method description	Liquid-liquid extraction (Page 000594)
Limit of quantitation (ng/mL)	**Bupropion**: 1.00 (Pages 000614 & 001989) **Hydroxybupropion**: 1.00 (Pages 000614 & 001990)
Average recovery of drug (%)	**Bupropion**: 64.33, 71.11, 79.10 (Pages 001826 & 001982) **Hydroxybupropion**: 52.59, 58.67, 68.01 (Pages 001826 & 001983)
Average recovery of IS (%)	70.82 (Pages 001826 & 001984)
Standard curve concentrations (ng/mL)	**Bupropion**: CS1: 1.00, CS2: 2.00, CS3: 40.00, CS4: 80.00, CS5: 160.00, CS6: 240.00, CS7: 320.00, CS8: 400.00 (Page 001974) **Hydroxybupropion**: CS1: 1.00, CS2: 1.99, CS3: 39.88, CS4: 79.76, CS5: 159.52, CS6: 239.28, CS7: 319.04, CS8: 398.80 (Page 001975)
QC concentrations (ng/mL)	**Bupropion**: QC1: 3.00, QC2: 119.86, QC3: 279.66 (Pages 001825 & 001978) **Hydroxybupropion**: QC1: 2.99, QC2: 119.66, QC3:279.22 (Pages 001825 & 001979)
QC Intraday precision range (%)	**Bupropion**: LLQC: 2.94, QC1: 1.97, QC2: 2.52, QC3: 0.73, ULQC: 1.20 (Pages 001825 & 001980) **Hydroxybupropion**: LLQC: 3.84, QC1: 1.98, QC2: 4.28, QC3: 2.35, ULQC: 1.87 (Pages 001825 & 001981)
QC Intraday accuracy range (%)	**Bupropion**: LLQC: 104.17, QC1: 101.11, QC2: 98.75, QC3: 101.01, ULQC: 102.36 (Pages 001825 & 001980) **Hydroxybupropion**: LLQC: 97.83, QC1: 102.40, QC2: 96.90, QC3: 99.47, ULQC: 100.38 (Pages 001825 & 001981)
QC Interday precision range (%)	**Bupropion**: QC1: 7.20, QC2: 2.51, QC3: 3.36 (Pages 001825 & 001978) **Hydroxybupropion**: QC1: 9.86, QC2: 3.76, QC3: 3.40 (Pages 001825 & 001979)
QC Interday accuracy range (%)	**Bupropion**: QC1: 95.03, QC2: 99.00, QC3: 100.11 (Pages 001825 & 001978) **Hydroxybupropion**: QC1: 95.94, QC2: 102.37, QC3: 101.25 (Pages 001825 & 001979)
Bench-top stability (hrs)	**Bupropion**: 2 hours at room temperature and 10 hours at 4°C (Pages 001822, 001945, and 001949) **Hydroxybupropion**: 24 hours at room temperature and 24 hours at 4°C (Pages 001822, 001946, and 001949)
Stock stability (days)	**Bupropion**: 48 days at –20°C (Pages 001823 & 001958)

	77 days at –80°C (Pages 001823 & 001962) **Hydroxybupropion**: 48 days at –20°C (Pages 001823 & 001959) 77 days at –80°C (Pages 001823 & 001963) **IS**:48 days at –20°C (Pages 001824 & 001966) 77 days at –80°C (Pages 001824 &001967)
Processed stability (hrs)	**Bupropion**: 91 hours at room temperature (Pages 001828 and 001998) **Hydroxybupropion**: 91 hours at room temperature (Pages 001828 and 001998)
Freeze-thaw stability (cycles)	**Bupropion**: 4 at –20°C and 4 at –80°C (Pages 001821, 001822 and 001937, 001941) **Hydroxybupropion**: 4 at –20°C and 4 at –80°C (Pages 001821, 001822 and 001938, 001942)
Long-term storage stability (days)	**Bupropion**: 616 days at –80°C (Pages 001824 and 001968) **Hydroxybupropion**: 616 days at –80°C (Pages 001824 and 001969)
Dilution integrity	**Bupropion**: QC3: CV(%) 1.03, Nominal (%) 97.18 DQC: CV (%) 1.98, Nominal (%) 97.06 (Pages 001827 and 001991) **Hydroxybupropion**: QC3: CV(%) 3.27, Nominal (%) 97.67 DQC: CV (%) 3.75, Nominal (%) 97.09 (Pages 001827 and 001992)
Selectivity	**Bupropion**: No significant interferences were observed in 9 out of 10 matrix. (Pages 001826 and 001985) **Hydroxybupropion**: No significant interferences were observed in 9 out of 10 matrix. (Pages 001826 and 00185)

Note: The firm provided the pre-study bioanalytical method validation data for the parent and metabolite in a single table.

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	41040
Study Design	Single-dose, two-way crossover, fasted
No. of subjects enrolled	28
No. of subjects completing	28
No. of subjects analyzed	26 (Note: the protocol states that data from the first 26 subjects to complete the study will be analyzed. Therefore, although all subjects completed the study only 26 were analyzed).
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Males: 28 Females: 0
Test product	Bupropion XL tablet
Reference product	Wellbutrin XL Tablet
Strength tested	150 mg
Dose	1X150 mg

The following CTD tables were provided by the firm.

Bupropion Hydrochloride Extended-Release Tablets 150 mg and 300 mg
ANDA 77-285
Section VI. BA/BE

Abrika Pharmaceuticals LLLP
Bioequivalency Amendment

Table 1 A. Summary of Bioavailability Studies for Bupropion

Study Ref. No.	Study Objective	Study Design	Treatment: (Dose, Dosage, Form, Route)	Subjects (No. M/F) Type, Age and Weight: mean (range)	Mean Parameters (SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng-h/mL)	AUC_{0-inf} (ng-h/mL)	$T_{1/2}$ (h)	K_{el} (h^{-1})	
41040	A Randomized, Single-Dose, Two-Way Crossover Relative Bioavailability Study of Bupropion XL Tablet Formulations in Fasted, Normal, Healthy Subjects	Randomized, single-dose, 2-way crossover	Bupropion HCl (1 x 150 mg) extended-release tablet p.o. Lot/Batch No.: CF4C7020015	28 completing (28 males/0 females) Healthy subjects Age (years) = 31.5 (18-45) Weight (kg) = 84.5 (65.9-104.5) Data set for statistical analysis = 26	80.57 (24.71)	6.33 (3.83) 5.25 (1.50)*	843.72 (232.21)	878.13 (254.54)	17.20 (5.53)	0.0434 (0.0122)	Volume 2 Page 002334
			Wellbutrin XL® (1 x 150 mg) tablet p.o. Lot/Batch No.: 0420048F		89.63 (37.84)	4.96 (0.75) 5.00 (0.50)*	873.92 (263.41)	915.94 (267.75)	18.35 (5.84)	0.0413 (0.0116)	
41041	A Randomized, Single-Dose, Two-Way Crossover Relative Bioavailability Study of Bupropion XL Tablet Formulations in Normal, Healthy Men Following a Standard Meal	Randomized, single-dose, 2-way crossover	Bupropion HCl (1 x 150 mg) extended-release tablet p.o. Lot/Batch No.: CF4C7020015	28 completing (28 males/0 females) Healthy subjects Age (years) = 34.2 (19-48) Weight (kg) = 80.9 (61.8-101.0) Data set for statistical analysis = 26	96.67 (44.20)	9.88 (4.07) 9.00 (5.53)*	1026.55 (285.74)	1066.53 (286.18)	18.75 (4.09)	0.0380 (0.0089)	Volume 3 Page 002355
			Wellbutrin XL® (1 x 150 mg) tablet p.o. Lot/Batch No.: 0420048F		88.51 (19.72)	6.45 (2.22) 6.50 (2.00)*	967.23 (259.57)	1037.64 (268.89)	17.90 (3.40)	0.0420 (0.0083)	

* Median (interquartile range)

A. Bupropion, (1 x 150 mg)
Geometric Means, Ratio of Means and 90% Confidence Intervals

Project 40140, Fasted Bioequivalence Study

Parameters		Test (A)	Reference (B)	Ratio A/B	90%C.I.
AUC_{0-t}	(ng·h/mL)	799.32	841.10	95.03%	83.71% to 107.89%
$AUC_{0-\infty}$	(ng·h/mL)	834.45	881.28	94.69%	83.72% to 107.09%
C_{max}	(ng/mL)	76.80	83.85	91.59%	80.25% to 104.53%

Table 8 A. Reanalysis of Study Samples for Bupropion, Fasted

Study No.40140 A Randomized Single-Dose, Two-Way Crossover Relative Bioavailability Study of Bupropion XL Tablet Formulations in Fasted Normal, Healthy Subjects								
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]	0	0	0.0	0.0	0	0	0.0	0.0
Analytical reason	5	2	0.44	0.17	5	2	0.44	0.17
Unacceptable internal standard response	5	2	0.44	0.17	5	2	0.44	0.17
Total	5	2	0.44	0.17	5	2	0.44	0.17

[1] If no reports were performed for pharmacokinetic reasons, insert "0.0" throughout table
T :Bupropion 150 mg Lot no. CF4CY038I1O
R :Bupropion (Wellbutrin XL) 150 mg Lot no. 04CD469

2. Single-dose Non-fasting Bioequivalence Study

Study Summary, Non-fasting Bioequivalence Study	
Study No.	41041
Study Design	Single-dose, two-way crossover, non-fasting
No. of subjects enrolled	30
No. of subjects completing	28
No. of subjects analyzed	26
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Males: 28 Females: 0
Test product	Bupropion XL tablet
Reference product	Wellbutrin XL Tablet
Strength tested	150 mg
Dose	1X150 mg

The following CTD tables were provided by the firm.

Bupropion Hydrochloride Extended-Release Tablets 150 mg and 300 mg **Abrika Pharmaceuticals LLLP**
ANDA 77-285 **Bioequivalency Amendment**
Section VI. BA/BE

Table 1 A. Summary of Bioavailability Studies for Bupropion

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage, Form, Route)	Subjects (No. M/F) Type, Age and Weight: mean (range)	Mean Parameters (SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng-h/mL)	$AUC_{0-\infty}$ (ng-h/mL)	$T_{1/2}$ (h)	K_{el} (h^{-1})	
41640	A Randomized, Single-Dose, Two-Way Crossover Relative Bioavailability Study of Bupropion XL Tablet Formulations in Fasted, Normal, Healthy Subjects	Randomized, single-dose, 2-way crossover	Bupropion HCl (1 x 150 mg) extended-release tablet p.o. Lot/Batch No.: CP4CY003N16	28 completing (28 males/0 females) Healthy subjects Age (years) = 31.5 (18-45) Weight (kg) = 84.5 (65.9-104.5) Data set for statistical analysis = 26	80.57 (24.71)	6.33 (3.83) 5.25 (1.50)*	843.72 (252.21)	878.15 (254.54)	17.20 (5.55)	0.0434 (0.0122)	Volume 2 Page 000334
			Wellbutrin XL® (1 x 150 mg) tablet p.o. Lot/Batch No.: 0420459*		89.63 (37.84)	4.96 (0.75) 5.00 (0.56)*	875.92 (263.41)	915.94 (267.75)	18.35 (5.84)	0.0411 (0.0116)	
41641	A Randomized, Single-Dose, Two-Way Crossover Relative Bioavailability Study of Bupropion XL Tablet Formulations in Normal, Healthy Men Following a Standard Meal	Randomized, single-dose, 2-way crossover	Bupropion HCl (1 x 150 mg) extended-release tablet p.o. Lot/Batch No.: CP4CY003N16	28 completing (28 males/0 females) Healthy subjects Age (years) = 34.2 (19-48) Weight (kg) = 80.9 (61.8-105.0) Data set for statistical analysis = 28	96.87 (44.20)	9.86 (4.07) 9.00 (5.50)*	1026.55 (282.74)	1066.53 (286.18)	18.75 (4.08)	0.0390 (0.0089)	Volume 7 Page 002355
			Wellbutrin XL® (1 x 150 mg) tablet p.o. Lot/Batch No.: 0420459*		88.21 (19.72)	6.45 (2.22) 6.50 (2.05)*	927.27 (232.37)	1037.64 (248.69)	17.99 (3.45)	0.0420 (0.0085)	

* Median (interquartile range)

C. Bupropion (1X150 mg)
Geometric means, Ratio of Means and 90% Confidence Intervals
Project 41041, Fed bioequivalence Study

Parameters	Test (A)	Reference (B)	Ratio A/B	90% C.I.
AUC_{0-t}	992.13	969.33	102.35	98.66-106.18
$AUC_{0-\infty}$	1032.08	1009.02	102.29	98.66-106.04
C_{max}	89.81	86.24	104.14	93.38-116.14

Note: The firm's table had a typographical error for the Reference AUC_{0-t} value. Therefore, the firm's submitted table was not used. All other values for the submitted tables are correct. Also, the firm correctly reported the value in the statistical analysis section in the ANDA.

Table 8 C. Reanalysis of Study Samples for Bupropion, Fed

Study No. 40141 A Randomized Single-Dose Two-Way Crossover Relative Bioavailability Study of Bupropion XL Tablet Formulations in Normal Healthy Men Following a Standard Meal.								
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]	0	0	0.0	0.0	0	0	0.0	0.0
Analytical repeat	2	5	0.16	0.41	2	5	0.16	0.41
Unacceptable internal standard response	1	5	0.08	0.41	1	5	0.08	0.41
Incomplete analysis	1	0	0.08	0.0	1	0	0.08	0.0
Total	2	5	0.16	0.41	2	5	0.16	0.41

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table
[2] Bupropion 150 mg Lot no. CP4CV0SN1G
[3] Bupropion (Wellbutrin XL) 150 mg Lot no. 04C0469

F. Formulation

Location in appendix	
Are inactive ingredients within IIG limits?	**Yes**
If no, list ingredients outside of limits	**N.A.**
If a tablet, is the product scored?	**No**
If yes, which strengths are scored?	**N.A.**
Is scoring of RLD the same as test?	**RLD tablets are not scored**
Is the formulation acceptable?	**Yes**
If not acceptable, why?	**N.A.**

G. In Vitro Dissolution

Firm's Method	
Medium	"pH Switch" – 0.1 N HCl followed by pH 6.8 buffer
Volume (mL)	Acid Stage: 750 mL of 0.1 N HCl Buffer Stage: 1000 mL of Sodium Phosphate Buffer (0.05 M), pH 6.8
USP Apparatus type	II
Rotation (rpm)	50
Firm's Proposed Specification	2 hrs: [redacted] 3 hrs: b(4) 8 hrs: 16 hrs: [redacted]
FDA-recommended method (source)	There are three methods listed in the USP 28 for this test product. Based on in vitro dissolution testing, the firm developed an alternate method.
F2 metric calculated?	A F2 of 56.7 was calculated for comparison of the 150 mg test product to the 300 mg test product in the pH switch buffer.
If no, reason why F2 not calculated	N.A.
Is method acceptable?	No
If not then why?	The firm did not provide a SOP for their proposed dissolution testing method.

H. Waiver Request(s)

Strengths for which waivers are requested	300 mg XL tablet
Regulation cited	21 CFR 320.22 (d) (2)
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	No
Waivers granted?	No
If not then why?	Due to deficiencies.

I. Deficiency Comments

1. The firm did not provide a SOP describing their proposed dissolution testing method.

2. The firm did not provide the potency of the RLD formulation.

3. The firm did not provide the content uniformity of the test product.

4. The firm did not provide the time periods (dates of analysis) for plasma sample analysis for the fasting and non-fasting bioequivalence studies.

J. Recommendations

1. The *in vivo* bioequivalence study conducted under fasting conditions by Abrika comparing its 150 mg bupropion XL tablet, to the reference product Wellbutrin XL® 150 mg tablet (GSK) is incomplete due to deficiencies #2-4.

2. The *in vivo* bioequivalence study conducted under non-fasting conditions by Abrika comparing its 150 mg bupropion XL tablet, to the reference product Wellbutrin XL® 150 mg tablet (GSK) is incomplete due to deficiencies #2-4.

3. The dissolution testing conducted by Abrika on its bupropion XL tablets, 150 mg and 300 mg is incomplete due to deficiency #1. Recommendations for the dissolution testing method and specification will be determined after the deficiency has been addressed.

4. The formulation of Abrika's 300 mg bupropion XL tablet is proportional to the 150 mg bupropion XL tablet, which underwent *in vivo* bioequivalence testing. A waiver of a bioequivalence requirement for the 300 mg bupropion XL tablet will granted after the deficiencies have been addressed.

The application is incomplete.

Ethan M Stier 11/30/05

Ethan M. Stier, Ph.D. Team II

Gur Jai Pal Singh 11-30-05

Gur Jai Pal Singh, Ph.D. Team II

Barbara M David 11/30/05

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

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	40140
Study Title	*A randomized, single-dose, two-way crossover relative bioavailability study of Bupropion XL tablet formulations in fasted, normal, healthy Subjects*
Clinical Site	SFBC FT. Myers, Inc. 3745 Broadway, Suite 100 Ft. Myers, FL 33901 USA
Principal Investigator	Antonio R. Pizzaro, M.D.
Dosing Dates	Period I: 6/26/04 Period II: 7/10/04
Analytical Site	[redacted] b(4)
Analytical Director	[redacted] b(4)
Analysis Dates	Not Provided
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	47 days

Treatment ID	A	B
Test or Reference	**Test**	**Reference**
Product Name	Bupropion XL Tablet	Wellbutrin XL Tablet
Manufacturer	Abrika	SmithKlineBeecham
Batch/Lot No.	CF4CY03N10	04C049P
Manufacture Date	06/04	N.A.
Expiration Date	N.A.	7/05
Strength	150 mg	150 mg
Dosage Form	Tablet	Tablet
Batch Size	———	———
Production Batch Size	The firm reported that the production batch size will be the same as the biobatch.	N.A.
Potency (%)	98.1	Not provided (N.P.)
Content Uniformity (mean, %CV)	N.P.	N.A.
Formulation	See Appendix Section B	
Dose Administered	1X150 mg	1X150 mg
Route of Administration	oral	

b(4)

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme (subjects analyzed)	AB:1,2,5,6,8,9,10,16,17,18,21,25,26,27 BA: 3,4,7,12,13,14,15, 19,20, 22,23,24
Blood Sampling Times (h)	Pre-dose, 1.5, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, 16, 20, 24, 36, 48, 72, and 96
Blood Volume Collected/Sample	7 mL
Blood Sample Processing/Storage	Centrifuged and stored at -30°C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table I
Length of Fasting	At least 10 hours
Length of Confinement	Subjects were confined from at least 20 hours prior to administration till the 24 hour sample is collected
Safety Monitoring	Vital signs were monitored

Comments on Study Design:
The firm did not provide the potency of the RLD product, content uniformity of the test product, dates of sample analysis.

b) Clinical Results

Table 1 Demographics of Study Subjects

Bupropion Hydrochloride Extended-Release Tablets 150 mg and 300 mg
ANDA 77-285
Section VI. BA/BE

Abrika Pharmaceuticals LI
Bioequivalency Amendmen

Table 6 A. Demographic Profile of Subjects Completing the Bioequivalence Studies, Fasted

Project No. 40140				
		Randomization		
Category		A/B	B/A	Total
Age (years)	Mean ± SD	31.4 ± 9.0	31.7 ± 8.6	31.5 ± 8.6
	Range	19 - 45	18 - 44	18 - 45
	Median	30.5	32.5	30.5
	N	14	14	28
Age Groups	<18	0 (0.0%)	0 (0.0%)	0 (0.0%)
	18-40	11 (78.6%)	11 (78.6%)	22 (78.6%)
	41-64	3 (21.4%)	3 (21.4%)	6 (21.4%)
	65-75	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>75	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gender	Female	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Male	14 (100.0%)	14 (100.0%)	28 (100.0%)
Race	Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
	African American	1 (7.1%)	0 (0.0%)	1 (3.6%)
	Caucasian	2 (14.3%)	0 (0.0%)	2 (7.1%)
	Hispanic	11 (78.6%)	14 (100.0%)	25 (89.3%)
Height (cm)	Mean ± SD	179.6 ± 6.6	177.0 ± 5.7	178.3 ± 6.2
	Range	167.64 - 188.0	170.2 - 188.0	167.6 - 188.0
	Median	180.3	175.3	177.8
	N	14	14	28
Weight (kg)	Mean ± SD	86.7 ± 12.0	82.4 ± 9.2	84.5 ± 10.7
	Range	65.9 - 104.5	69.1 - 104.1	65.9 - 104.5
	Median	87.3	81.6	84.5
	N	14	14	28
BMI (kg/m^2)	Mean ± SD	26.8 ± 2.7	26.3 ± 2.4	26.5 ± 2.5
	Range	21.5 - 29.8	22.4 - 30.0	21.5 - 30.0
	Median	27.3	26.1	26.3
	N	14	14	28

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
None			

Table 3 Study Adverse Events

Table 7. Incidence of Adverse Events in Individual Studies

System Class	40140		40141	
COSTART	A	B	A	B
Inj&P				
Ecchymosis				1
Pain			1	
Inv				
Tachycardia		1		
Hypertens		1		
Nerv				
Headache			4	3
Somnolence	1	2		
Skin				
Petechiae	1			
Rash		1		
TOTAL	2	5	5	4

Note: 41040 is the fasting study; 41041 is the non-fasting study.

Table 4 Protocol Deviations

Type	Test (Total #)	Ref (Total #)	Pre-Dose (Total #)	Post-Dose (Total #)
Subject lied down during restricted time	2	-	-	-
Sampling Time Deviation (The absolute time of deviation ranged from 2.1 to 7.3 % for sampling times of 3-96 hours. If a sampling time deviated more than 2% from the actual time the actual sampling time was used to calculate pharmacokinetic parameters.	6	9	-	-
Subject arrived late to the clinic	-	-	2	-
Subject 11 drank coca cola 25 minutes prior to dosing. Subject's data was not analyzed.	-	-	1	-
Plasma sample was centrifuged within 1-19 minutes of scheduled time	15	1	-	-

Comments on Adverse Events/Protocol Deviations:

The number of adverse events in the test product treated group was lower than those observed in the RLD treated group. The reported adverse events did not influence the outcome of the study.

One protocol deviation (subject 11 drank coke prior to dosing) led to the subject not being analyzed.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Bupropion			
QC Conc. (ng/mL)	3.0	120.1	280.22	60.05
Inter day Precision (%CV)	4.32	3.62	4.16	11.36
Inter day Accuracy (%)	105.44	105.78	105.3	105.24

Cal. Standards Conc. (ng/mL)	1.0	2.01	40.12	80.24	160.48	240.72	320.96	401.2
Inter day Precision (%CV)	2.48	3.79	2.35	2.79	2.5	2.36	2.21	2.62
Inter day Accuracy (%)	99.7	100.75	102.17	99.32	98.12	99.23	100.4	100.45

Linearity Range (range of R^2 values)	0.9992-0.9997

Comments on Study Assay Quality Control:
Acceptable

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

Comments on Chromatograms:
Acceptable

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

SOP No.	Date of SOP	SOP Title
ANI 156.08	07-01-03	Sample Reassays and Reporting of Final Concentrations

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	There were no repeats classified as PK.
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N.A.

Summary/Conclusions, Study Assays:
Acceptable

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters

Bupropion

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
$AUC_{0-\infty}$	ng·hr/mL	878.13	28.99	915.94	29.23	0.96
AUC_{0-t}	ng·hr/mL	843.72	29.89	875.92	30.07	0.96
CMAX	ng/mL	80.37	30.75	89.63	42.22	0.90
KE	$hour^{-1}$	0.04	28.09	0.04	28.26	1.06
LAUCI	ng·hr/mL	839.46	0.04	882.04	0.03	0.95
LAUCT	ng·hr/mL	804.37	0.04	841.81	0.03	0.96
LCMAX	ng/mL	76.97	0.39	83.80	0.43	0.92
THALF	hour	17.39	31.80	18.35	31.83	0.95
TMAX	hour	6.33	60.51	4.96	15.06	1.28

Hydroxybupropion

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
$AUC_{0-\infty}$	ng·hr/mL	9503.17	41.11	10322.33	35.58	0.92
AUC_{0-t}	ng·hr/mL	8769.06	40.63	9485.81	35.49	0.92
CMAX	ng/mL	203.50	35.13	213.24	36.17	0.95
KE	$hour^{-1}$	0.03	16.21	0.03	15.26	1.04
LAUCI	ng·hr/mL	8708.78	0.01	9686.30	0.00	0.90
LAUCT	ng·hr/mL	8062.98	0.01	8920.34	0.00	0.90
LCMAX	ng/mL	192.74	0.17	201.34	0.17	0.96
THALF	hour	23.40	17.29	24.33	16.76	0.96
TMAX	hour	15.77	33.14	13.15	39.65	1.20

Table 9 Geometric Means and 90% Confidence Intervals

Bupropion

PARAMETER	TEST	REFERENCE	RATIO T/R	90 % CI	
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
$AUC_{0-\infty}$	874.48	916.57	0.95	82.92	107.90
AUC_{0-t}	840.10	876.64	0.96	82.89	108.77
CMAX	80.30	90.04	0.89	73.69	104.68
LAUCI	834.45	881.28	0.95	83.72	107.09
LAUCT	799.32	841.10	0.95	83.71	107.89
LCMAX	76.80	83.85	0.92	80.25	104.53

Table 10 Additional Study Information

Bupropion

Root mean square error, $LAUC_{0-t}$	0.2666
Root mean square error, $LAUC_{\infty}$	0.2586
Root mean square error, LC_{max}	0.2777
K_{el} and AUC_{∞} determined for how many subjects?	26
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}	N.A.
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic and Statistical Analysis:
Metabolite (hydroxybupropion) plasma concentrations were comparable for the test and reference products

Analysis of the parent and metabolite data is acceptable

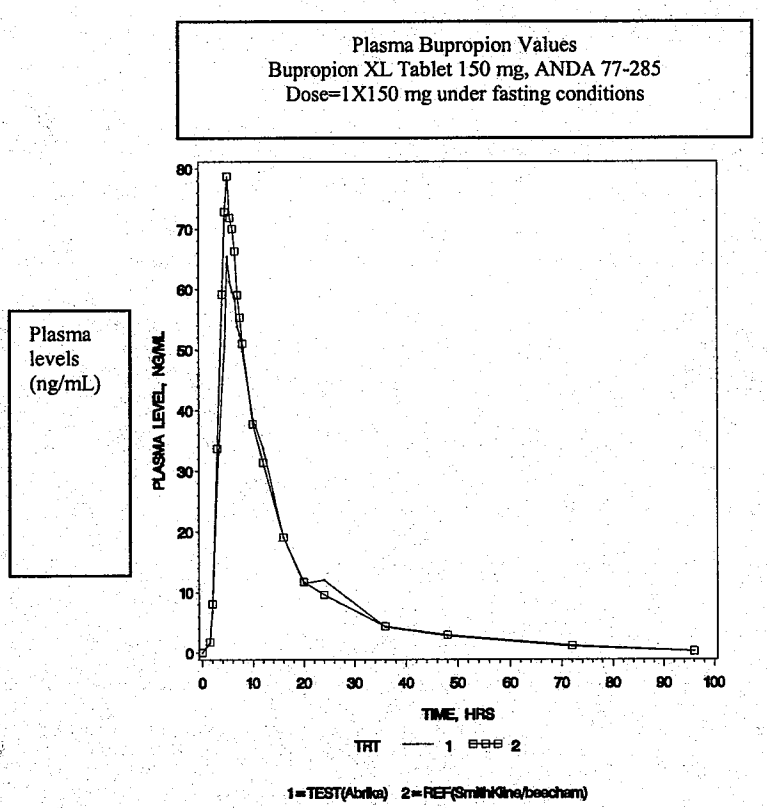
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:
Incomplete

Table 11 Mean Plasma Concentrations of Bupropion, Single-Dose Fasting Bioequivalence Study

Time (h)	Test (n=26)		Reference (n=26)		T/R
	Mean Conc. (ng/mL)	%CV	Mean Conc. (ng/mL)	%CV	
0	0.00	.	0.00	.	.
1.5	1.57	296.43	1.76	207.76	0.89
2	6.77	200.43	8.07	137.78	0.84
3	28.20	99.93	33.70	93.94	0.84
4	44.40	86.10	59.16	52.87	0.75
4.5	50.70	70.88	72.85	52.65	0.70
5	65.48	40.54	78.73	51.71	0.83
5.5	61.26	38.68	71.92	44.88	0.85
6	59.57	40.56	70.06	41.16	0.85
6.5	58.77	43.88	66.32	34.57	0.89
7	53.86	44.04	59.07	32.99	0.91
7.5	52.56	44.37	55.35	31.78	0.95
8	49.75	39.68	51.06	30.84	0.97
10	38.66	41.84	37.79	28.80	1.02
12	33.87	42.33	31.41	34.61	1.08
16	19.06	41.69	19.08	33.85	1.00
20	11.46	34.03	11.73	34.99	0.98
24	12.07	134.39	9.59	37.15	1.26
36	4.24	35.28	4.37	37.75	0.97
48	2.75	40.08	2.95	38.42	0.93
72	1.05	75.67	1.15	72.20	0.91
96	0.23	212.04	0.21	240.39	1.08

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Figure 1 Bupropion Levels for Fasting Study



2. Single-dose Fed Bioequivalence Study

a) Study Design

Study Information	
Study Number	40141
Study Title	A Randomized, Single-Dose, Two-Way Crossover Relative Bioavailability Study of Bupropion XL Tablet Formulations in Normal, Healthy Men Following a Standard Meal
Clinical Site	SFBC FT. Myers, Inc. 3745 Broadway, Suite 100 Ft. Myers, FL 33901 USA
Principal Investigator	Antonio R. Pizzaro, M.D.
Dosing Dates	Period I: 07-10-04 Period II: 07-24-04
Analytical Site	[redacted] b(4)
Analytical Director	[redacted] b(4)
Analysis Dates	Not Provided
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	49 days

Treatment ID	A	B
Test or Reference	**Test**	**Reference**
Product Name	Bupropion XL Tablet	Wellbutrin XL Tablet
Manufacturer	Abrika	SmithKlineBeecham
Batch No.	CF4CY03N10	04C049P
Manufacture Date	06/04	N.A.
Expiration Date	N.A.	7/05
Strength	150 mg	150 mg
Dosage Form	Tablet	Tablet
Batch Size (tablets)	[redacted]	[redacted]
Production Batch Size (tablets)	The firm reported that the production batch size will be the same as the biobatch.	N.A.
Potency	98.1	Not provided (N.P.)
Content Uniformity (AVG/RSD)	N.P.	N.A.
Formulation	See Appendix Section B	
Dose Administered	1X150 mg	1X150 mg
Route of Administration	oral	

b(4)

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB: 3,7,8,9,10,14,15,17,19,20,21,27,30 BA: 1,2,4,5,6,11,13,16,18,22,23,24,25,26,29
Blood Sampling Times (h)	Pre-dose, 1.5, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 16, 20, 24, 36, 48, 72, and 96
Blood Volume Collected/Sample	7 mL
Blood Sample Processing/Storage	Centrifuged and stored at -70°C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 13
Length of Fasting before Meal	Subjects fasted for at least 10 hours prior to consuming the high-fat meal.
Length of Confinement	Same as fasting study
Safety Monitoring	Same as fasting study
Standard FDA Meal Used?	Yes

Comments on Study Design:
The firm did not provide the potency of the RLD product, content uniformity of the test product, dates of sample analysis.

b) Clinical Results

Table 12 Demographics of Study Subjects

Table 6 B. Demographic Profile of Subjects Completing the Bioequivalence Studies, Fed

Project No. 40141				
		Randomization		
Category		A/B	B/A	Total
Age (years)	Mean ± SD	34.5 ± 6.1	33.8 ± 10.1	34.2 ± 8.2
	Range	21 - 42	19 - 48	19 - 48
	Median	34	31	34
	N	15	15	30
Age Groups	<18	0 (0.0%)	0 (0.0%)	0 (0.0%)
	18-40	12 (80.0%)	10 (66.7%)	22 (73.3%)
	41-64	3 (20.0%)	5 (33.3%)	8 (26.7%)
	65-75	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>75	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gender	Female	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Male	15 (100.0%)	15 (100.0%)	30 (100.0%)
Race	Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
	African American	1 (6.7%)	1 (6.7%)	2 (6.7%)
	Caucasian	6 (40.0%)	4 (26.7%)	10 (33.3%)
	Hispanic	8 (53.3%)	10 (66.7%)	18 (60.0%)
Height (cm)	Mean ± SD	174.5 ± 6.2	174.1 ± 6.7	174.3 ± 6.3
	Range	167.64 - 188.0	162.6 - 188.0	162.6 - 188.0
	Median	175.3	174.0	174.6
	N	15	15	30
Weight (kg)	Mean ± SD	82.5 ± 9.3	79.2 ± 10.4	80.9 ± 9.8
	Range	65.5 - 100.0	61.8 - 98.2	61.8 - 100.0
	Median	83.6	81.8	82.3
	N	15	15	30
BMI (kg/m^2)	Mean ± SD	27.1 ± 2.5	26.1 ± 3.1	26.6 ± 2.8
	Range	23.3 - 30.5	19.8 - 32.2	19.8 - 32.2
	Median	27.0	25.9	26.6
	N	15	15	30

- 000002 -

Table 13 Dropout Information

Subject No	Reason	Period	Replaced?
12	Subject was leaving the area	I	No
28	Withdrew due to Adverse Events (painful blood draw)	I	No

Table 14 Study Adverse Events

Table 7. Incidence of Adverse Events in Individual Studies

System Class	40140		40141	
COSTART	A	B	A	B
Inj&P				
Ecchymosis				1
Pain			1	
Inv				
Tachycardia		1		
Hypertens		1		
Nerv				
Headache			4	3
Somnolence	1	2		
Skin				
Petechiae	1			
Rash		1		
TOTAL	2	5	5	4

Note: 41040 is the fasting study; 41041 is the non-fasting study.

Table 15 Protocol Deviations

Type	Total # (Test)	Total # (Ref.)	Total# (pre-study)
Due to insufficient documentation it can not be confirmed that subjects did not smoke more than 25 cigarettes per day	15	15	-
Due to insufficient documentation it can not be confirmed that subjects did not drink water while in the restroom	15	15	-
Subject was screened for another study and transferred to this study	-	-	1
Blood Sample not Obtained	-	3	-
Subject exceeded upper limit of BMI	-	-	3
Sample analysis not repeated for 17 h timepoint for hydroxybupropion	27	-	-
Sampling Time Deviation (due to documentation error the sample value for the 7 hour, period 2 timepoint for subject 9 was not reported. The timepoint was not the Cmax for the subject.)	-	9	-

Comments on Adverse Events/Protocol Deviations: The number of adverse events in the test product treated group was greater than those observed in the RLD treated group. The adverse events and protocol deviations did not influence the outcome of the study.

Bioanalytical Results

Table 16 Assay Quality Control – Within Study

	Bupropion			
QC Conc. (ng/mL)	3.0	120.1	280.22	60.05
Inter day Precision (%CV)	3.6	3.62	3.55	3.86
Inter day Accuracy (%)	103.54	105.78	106.63	104.77

Cal. Standards Conc. (ng/mL)	1.0	2.01	40.12	80.24	160.48	240.72	320.96	401.2
Inter day Precision (%CV)	3.64	4.6	3.71	2.77	2.64	3.02	3.03	2.56
Inter day Accuracy (%)	99.6	100.85	101.65	99.14	98.65	99.15	100.16	100.82

Linearity Range (range of R^2 values)	0.9988-0.9997

Comments on Study Assay Quality Control: Acceptable

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

Comments on Chromatograms: Acceptable

Table 17 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
ANI 156.08	07-01-03	Sample Reassays and Reporting of Final Concentrations

Table 18 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	There were no repeats classified as PK.
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N.A.

Summary/Conclusions, Study Assays:
Acceptable

c) Pharmacokinetic Results

Table 19 Arithmetic Mean Pharmacokinetic Parameters

Bupropion

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
$AUC_{0-\infty}$	ng·hr/mL	1066.53	26.83	1037.64	23.91	1.03
AUC_{0-t}	ng·hr/mL	1026.55	27.35	997.27	24.00	1.03
CMAX	ng/mL	96.87	45.63	88.21	22.36	1.10
KE	$hour^{-1}$	0.04	25.36	0.04	20.71	0.98
LAUCI	ng·hr/mL	1033.60	0.02	1010.15	0.02	1.02
LAUCT	ng·hr/mL	993.53	0.03	970.60	0.02	1.02
LCMAX	ng/mL	90.08	0.40	86.04	0.27	1.05
THALF	hour	18.75	21.83	17.99	18.91	1.04
TMAX	hour	9.88	41.24	6.45	34.39	1.53

Hydroxybupropion

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
$AUC_{0-\infty}$	ng·hr/mL	14005.62	44.83	12771.84	41.10	1.10
AUC_{0-t}	ng·hr/mL	12385.31	39.61	11411.71	35.94	1.09
CMAX	ng/mL	284.75	36.69	256.37	36.41	1.11
KE	$hour^{-1}$	0.03	23.70	0.03	19.60	1.02
LAUCI	ng·hr/mL	12867.77	0.00	11932.70	0.00	1.08
LAUCT	ng·hr/mL	11534.30	0.00	10775.61	0.00	1.07
LCMAX	ng/mL	267.65	0.13	241.60	0.14	1.11
THALF	hour	26.15	25.85	26.20	23.93	1.00
TMAX	hour	16.50	31.58	15.14	30.75	1.09

Table 20 Geometric Means and 90% Confidence Intervals

Bupropion

PARAMETER	TEST	REFERENCE	RATIO T/R	90 % CI	
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
$AUC_{0-\infty}$	1064.26	1035.89	1.03	98.90	106.58
AUC_{0-t}	1024.41	995.37	1.03	98.96	106.88
CMAX	96.38	88.39	1.09	95.16	122.92
LAUCI	1032.08	1009.02	1.02	98.66	106.04
LAUCT	992.13	969.33	1.02	98.66	106.18
LCMAX	89.81	86.24	1.04	93.38	116.14

Table 21 Additional Study Information

Bupropion

Root mean square error, LAUC0-t	0.0803
Root mean square error, LAUC∞	0.0789
Root mean square error, LCmax	0.2386
Kel and AUC∞ determined for how many subjects?	28
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:
Metabolite (hydroxybupropion) plasma concentrations were comparable for the test and reference products

Analysis of the parent and metabolite data is acceptable

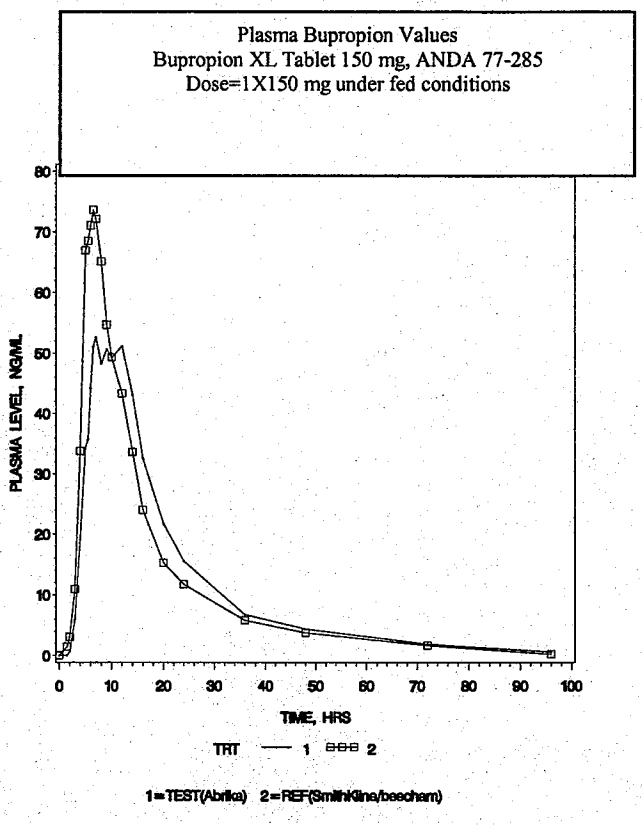
Summary/Conclusions, Single-Dose Fed Bioequivalence Study: Incomplete

Table 22 Mean Plasma Bupropion Concentrations, Single-Dose Fed Bioequivalence Study

Time (h)	Test (n=28)		Reference (n=28)		T/R
	Mean Conc. (ng/mL)	%CV	Mean Conc. (ng/mL)	%CV	
0	0.00	.	0.00	.	.
1.5	0.00	.	1.47	507.08	0.00
2	0.57	176.69	3.04	349.09	0.19
3	5.96	270.90	10.93	133.72	0.55
4	19.14	241.64	33.74	70.60	0.57
5	34.38	152.47	66.96	33.46	0.51
5.5	35.70	130.21	68.51	32.77	0.52
6	44.20	100.88	71.08	35.18	0.62
6.5	51.02	79.84	73.64	32.03	0.69
7	52.64	78.07	72.13	33.69	0.73
8	48.24	69.30	65.09	35.21	0.74
9	50.67	72.32	54.69	31.45	0.93
10	49.24	57.72	49.28	30.67	1.00
12	51.15	48.27	43.30	35.38	1.18
14	43.07	50.08	33.61	38.33	1.28
16	32.48	45.33	23.98	35.22	1.35
20	21.72	61.68	15.26	24.58	1.42
24	15.57	59.76	11.74	23.05	1.33
36	6.77	37.86	5.81	34.69	1.17
48	4.36	35.71	3.71	33.76	1.17
72	1.88	55.67	1.65	46.99	1.14
96	0.57	125.60	0.24	225.27	2.36

Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Figure 2 Bupropion Levels for Fed Study



B. Formulation Data

Bupropion Hydrochloride Extended-Release Tablets 150 mg and 300 mg
ANDA 77-285
Section VI. BA/BE

Abrika Pharmaceuticals LLLP
Bioequivalency Amendment

Table 5. Formulation Data

Ingredients	Amount (mg) / Tablet		Amount (%) Tablet	
	150 mg	300 mg	150 mg	300 mg
Core				
[redacted]	150.00	300.00	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

b(4)

Note: [redacted] Thus, minimal dissolution is observed for the test product in acidic media. The CTD table provided by the firm is listed above. b(4)

C. Dissolution Data (The firm provided the following CTD tables)

Bupropion Hydrochloride Extended-Release Tablets 150 mg and 300 mg
ANDA 77-285
Section VI. BA/BE

Abrika Pharmaceuticals LLLP
Bioequivalency Amendment

Table 4 A: Summary Dissolution Test Results for USP App. 1 (Baskets) at 75 RPM in DI Water

Study Ref. No.	Product ID/Batch No.	Dosage Form	Condition	No. of Dosage Units	Collection Times Mean % Dissolved (Range)					Study Report Location
					2 hrs	4 hrs	8 hrs	12 hrs	16 hrs	
Dissolution Study Report # AS015 (150 mg) Report # AS017 (300 mg)	Wellbutrin XL # 04C049P	150 mg Tablets	USP App. 1 75 rpm DI Water Volume: 900 mL Temp.: 37 °C	12	1 (1 - 1)	7 (3 - 10)	30 (24 - 34)	51 (40 - 58)	70 (57 - 78)	ANDA Vol. 11 004388
	Bupropion HCl ER # CP4CT03N1DA	150 mg Tablets		12	6 (4 - 9)	25 (24 - 33)	66 (63 - 70)	87 (80 - 89)	92 (90 - 94)	ANDA Vol. 11 004388
	Wellbutrin XL # 04H021P	300 mg Tablets		12	1 (1 - 3)	7 (2 - 12)	25 (22 - 28)	42 (37 - 48)	57 (51 - 65)	19960/56 Amend Vol 1 490058
	Bupropion HCl ER # CP4CT03Q1BA	300 mg Tablets		12	4 (2 - 7)	18 (15 - 23)	46 (43 - 50)	67 (60 - 70)	80 (78 - 83)	19960/56 Amend Vol 1 490058

Table 4 B: Summary Dissolution Test Results for USP App. 1 (Baskets) at 75 RPM in 0.1 N HCl

Study Ref. No.	Product ID/Batch No.	Dosage Form	Condition	No. of Dosage Units	Collection Times Mean % Dissolved (Range)					Study Report Location
					2 hrs	4 hrs	8 hrs	12 hrs	16 hrs	
Dissolution Study Report # AS015 (150 mg) Report # AS017 (300 mg)	Wellbutrin XL # 04C049P	150 mg Tablets	USP App. 1 75 rpm 0.1 N HCl Volume: 900 mL Temp.: 37 °C	6	2 (2 - 3)	28 (24 - 34)	79 (74 - 86)	95 (93 - 98)	97 (95 – 100)	ANDA Vol. 11 004387
	Bupropion HCl ER # CP4CT03N10A	150 mg Tablets		6	1 (0 - 2)	0 (0 - 0)	0 (0 - 1)	0 (0 - 2)	1 (0 - 4)	ANDA Vol. 11 004387
	Wellbutrin XL # 04H021P	300 mg Tablets		6	3 (2 - 3)	28 (22 - 31)	89 (87 - 73)	97 (85 - 92)	93 (89 - 95)	19960/56 Amend Vol 1 490058
	Bupropion HCl ER # CP4CT03Q1BA	300 mg Tablets		6	0 (0 - 0)	0 (0 - 0)	1 (0 - 3)	4 (0 - 10)	13 (3 - 47)	19960/56 Amend Vol 1 490058

E. SAS Output

Statistical Analysis	Program file	Output file
Single dose fasting study Bupropion	 fastbupprog	 fastbupoutput
Single dose fed study Bupropion	 fedbupprog	 fedbupoutput

F. Additional Attachments

None

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-285 APPLICANT: Abrika

DRUG PRODUCT: Bupropion XL Tablet
150 mg and 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:

The following pieces of information were not found in the submitted application, and they are requested for completeness of our review of your application:

a) the potency of the RLD batch

b) the content uniformity of the test product

c) the dates of analysis (e.g. starting and ending dates) for plasma samples

d) a detailed SOP describing your proposed in vitro dissolution method

Sincerely yours,

Barbara M Davit

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

CC: ANDA 77-285
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/E. Stier E Stier 11/30/05
HFD-655/ Gur-Jai Pal Singh CMSS 11-30-05
HFD-617/ K. Suh
HFD-650/Dale Conner BZD 11/30/05

V:\firmsam\abrika\ltrs&rev\77285N0904.doc
Printed in final on 11/30/05

BIOEQUIVALENCY - DEFICIENCIES Submission Date: 09/23/04

1. **FASTING STUDY** (STF) **Strength: 150 mg**
Clinical: SFBC FT. Myers, Inc.
3745 Broadway, Suite 100
Ft. Myers, FL 33901
USA Clinical Unit **Outcome: IC**

Analytical: [redacted] b(4)

2. **FOOD STUDY** (STF) **Strength: 150 mg**
Clinical: SFBC FT. Myers, Inc.
3745 Broadway, Suite 100
Ft. Myers, FL 33901
USA Clinical Unit **Outcome: IC**

Analytical: [redacted] b(4)

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

Outcome Decisions: IC
AC - Acceptable ***UN*** - Unacceptable ***WC*** – Without Charge
IC - Incomplete

WinBio Comments

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	77-285
Drug Product Name	Bupropion HCl ER Tablets
Strength	150 mg and 300 mg
Applicant Name	Abrika
Submission Date(s)	09-23-04
First Generic	Yes
Reviewer	Ethan M. Stier, Ph. D.
File Location	**V:\firmsam\abrika\ltrs&rev\77285D0904 .doc**
Clinical Site	b(4)
	SFBC Ft. Myers, Inc. 3745 Broadway, Suite 100 Ft. Myers, FL 33901 USA

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 four dissolution media (water, 0.1 N HCl, pH 4.5 buffer, and pH 6.8 buffer) using USP apparatus I (Basket) and one dissolution medium (0.1 N HCl to pH 6.8 Buffer (In Situ)) using apparatus II (Paddle).

The firm will be asked to conduct additional dissolution testing using the USP method.

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: [redacted] b(4)
	4 hour: [redacted]
	8 hours: [redacted]

***Source of Method:** USP

Table 1. Summary of In Vitro Dissolution Data in Water

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range) 60 min	240 min	480 min	720 min	960 min	Study Report Location
Not Provided (N.P.)	04C049P/ GlaxoSmithKline	150 mg E.R. Tab	Dissolution: **Apparatus 1 (USP)** Speed of Rotation: 75 rpm Medium: Water at 37°C	12	1 (1-1)	7 (3-10)	30 (24-34)	51 (40-58)	70 (57-78)	V 1.11 p. 4366
N.P.	CF4CY03N10A/ Abrika	150 mg E.R. Tab		12	6 (4-9)	29 (24-33)	66 (61-70)	87 (83-89)	92 (90-94)	b(4)
N.P.	04B021P / GlaxoSmithKline	300 mg E.R. Tab		12	1 (1-3)	7 (2-12)	25 (22-28)	42 (37-48)	57 (51-65)	V 2.1 p. 258
N.P.	CF4CY03Q18A/ Abrika	300 mg E.R. Tab		12	4 (2-7)	18 (15-23)	46 (43-50)	67 (63-70)	80 (78-83)	

Table 2. 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	Mean %Dissolved (Range) Collection Times					Study Report Location
					60 min	240 min	480 min	720 min	960 min	
Not Provided (N.P.)	04C049P/ GlaxoSmithKline	150 mg E.R. Tab	Dissolution: **Apparatus 1 (USP)** Speed of Rotation: 75 rpm 0.1 N HCl at 37°C	12	2 (2-3)	28 (24-34)	79 (74-86)	95 (93-98)	97 (96-100)	V 1.11 p. 4367
N.P.	CF4CY03N10A/ Abrika	150 mg E.R. Tab		12	1 (0-2)	0 (0-0)	0 (0-1)	1 (0-2)	1 (0-4)	
N.P.	04B021P / GlaxoSmithKline	300 mg E.R. Tab		12	3 (2-3)	28 (22-31)	69 (67-73)	89 (85-92)	93 (89-95)	V 2.1 p. 259-260
N.P.	CF4CY03Q18A/ Abrika	300 mg E.R. Tab		12	0 (0-0)	0 (0-0)	1 (0-3)	4 (0-16)	13 (3-47)	

Table 3. Summary of In Vitro Dissolution Data in pH 4.5 buffer

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Mean %Dissolved (Range) Collection Times					Study Report Location
					60 min	240 min	480 min	720 min	960 min	
Not Provided (N.P.)	04C049P/ GlaxoSmithKline	150 mg E.R. Tab	Dissolution: **Apparatus 1 (USP)** Speed of Rotation: 75 rpm Medium: pH 4.5 buffer at 37°C	12	1 (0-2)	5 (2-8)	27 (24-31)	48 (42-56)	67 (59-74)	V 1.11 p. 4368
N.P.	CF4CY03N10A/ Abrika	150 mg E.R. Tab		12	1 (1-2)	12 (6-16)	47 (39-52)	73 (67-79)	88 (85-92)	
N.P.	04B021P / GlaxoSmithKline	300 mg E.R. Tab		12	1 (0-2)	8 (4-12)	31 (25-35)	52 (44-57)	69 (60-74)	V 2.1 p. 261
N.P.	CF4CY03Q18A/ Abrika	300 mg E.R. Tab		12	1 (0-1)	2 (2-8)	19 (12-23)	45 (36-68)	63 (49-87)	

Table 4a. 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
					120 min	240 min	320 min	720 min	960 min	
Not Provided (N.P.)	04C049P/ GlaxoSmithKline	150 mg E.R. Tab	Dissolution: Apparatus 1 (USP) Speed of Rotation: 75 rpm Medium: pH 6.8 buffer at 37°C	12	39 (36-42)	67 (64-70)	89 (87-91)	93 (91-96)	95 (93-97)	V 1.11 p. 4369
N.P.	CF4CY03N10A/ Abrika	150 mg E.R. Tab		12	37 (34-39)	57 (53-59)	76 (73-77)	79 (77-80)	79 (78-81)	
N.P.	04B021P / GlaxoSmithKline	300 mg E.R. Tab		12	38 (35-40)	63 (60-65)	87 (84-89)	94 (92-96)	97 (94-99)	V 2.1 p. 262-63
N.P.	CF4CY03Q18A/ Abrika	300 mg E.R. Tab		12	32 (30-34)	49 (48-52)	69 (68-71)	76 (76-78)	77 (76-79)	

Table 4b. 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
					120 min	240 min	320 min	720 min	960 min	
Not Provided (N.P.)	04C049P/ GlaxoSmithKline	150 mg E.R. Tab	Dissolution: Apparatus 1 (USP) Speed of Rotation: 100 rpm Medium: pH 6.8 buffer at 37°C	12	40 (37-42)	59 (57-61)	78 (75-79)	80 (78-82)	81 (78-82)	V 1.11 p. 4370
N.P.	CF4CY03N10A/ Abrika	150 mg E.R. Tab		12	41 (38-42)	69 (66-71)	90 (88-92)	94 (92-86)	96 (94-98)	
N.P.	04B021P / GlaxoSmithKline	300 mg E.R. Tab		12	40 (38-41)	64 (62-67)	89 (87-93)	95 (93-99)	97 (95-101)	V 2.1 p. 264
N.P.	CF4CY03Q18A/ Abrika	300 mg E.R. Tab		12	33 (31-35)	50 (48-53)	70 (68-72)	77 (76-79)	78 (76-80)	

Table 5. Summary of In Vitro Dissolution Data in In-Situ pH Switch

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Mean %Dissolved (Range) Collection Times						Study Report Location
					120 min	180 min	300 min	480 min	720 min	960 min	
Not Provided (N.P.)	04C049P/ GlaxoSmithKline	150 mg E.R. Tab	Dissolution: **Apparatus II (USP)** Speed of Rotation: 50 rpm Medium: In-Situ pH Switch at 37°C	12	2 (2-3)	29 (25-33)	61 (57-61)	87 (57-67)	94 (78-82)	97 (78-82)	V 1.11 p. 4370
N.P.	CF4CY03N10A/ Abrika	150 mg E.R. Tab		12	1 (1-2)	19 (16-20)	46 (41-49)	72 (69-75)	84 (82-85)	84 (82-86)	
N.P.	04B021P / GlaxoSmithKline	300 mg E.R. Tab		12	3 (2-5)	31 (28-34)	56 (54-59)	79 (74-82)	94 (91-97)	98 (95-101)	V 2.1 p. 265-66
N.P.	CF4CY03Q18A/ Abrika	300 mg E.R. Tab		12	0 (0-0)	15 (12-22)	38 (33-47)	62 (53-68)	79 (73-83)	81 (77-84)	

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 Abrika 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 be informed of the above recommendations and comment #2.

Ethan M. Stier 5/25/05

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

Barbara M Davit 5/25/05

Gur-Jai Pal Singh, Ph.D.
Team II
Division of Bioequivalence
Office of Generic Drugs

Dale P. Conner 5/25/05

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

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-285 APPLICANT: Abrika

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:

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:	37ºC
Apparatus:	Apparatus II (paddles)
Rotation:	50 rpm
Specification:	[redacted] in 1 hour [redacted] in 4 hours [redacted] in 8 hours

b(4)

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: 77-285

CC: ANDA 77-285
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ E. Stier

V:\FIRMSAM\Abrika\LTRS&REV\77285A0904.doc
Printed in final on 05/25/2005

Endorsements: (Final with Dates)
HFD-655/ E. Stier 5/25/05
HFD-655/ GJP Singh 5/25/05
HFD-617/ K. Suh
HFD-650/ D. Conner 5/25/05

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-285

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

1. Paragraph IV Patent Certification

PARAGRAPH IV CERTIFICATION

I, Abrika Pharmaceuticals LLLP, certify that, to the best of its knowledge, U.S. Patent No. 6,096,341 and U.S. Patent No. 6,143,327, both due to expire on October 30, 2018, will not be infringed by the manufacture, use, or sale of Abrika Pharmaceuticals LLLP's Bupropion Hydrochloride Extended-Release Tablets USP, 150 mg and 300 mg, for which the abbreviated new drug application (ANDA) number 77-285 was submitted, or in the alternative, that U.S. Patent No. 6,096,341 and/or U.S. Patent No. 6,143,327 are invalid and/or unenforceable.

As required by Section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)) and 21 C.F.R.§§ 314.94 and 314.95, Abrika Pharmaceuticals LLLP hereby states that this ANDA is sufficiently complete to permit substantive review.

Furthermore, on November 12, 2004 and November 16, 2004, in accordance with 21 C.F. R. §§314.95(a) and (b), Abrika Pharmaceuticals LLLP sent a "Patent Certification Under 21 U.S.C. §355 and Notice of Certification of Invalidity or Noninfringement of a Patent Under 21 U.S.C. §355" (hereinafter "the Notice") to GLAXOSIMITHKLINE, as NDA holder for Wellbutrin XL 150 mg and 300 mg, respectively, and Biovail Laboratories, Inc., as owner of record of the above-referenced patents, via United States registered mail, return receipt requested. The Notice meets the content requirements under 21 C.F.R. §314.95(c). A copy is attached in Section III, Patent Certification. In addition, copies of the United States Postal Service receipts of mailing are also attached in Section III, Patent Certification.

ABRIKA PHARMACEUTICALS LLLP

By: _____
James S. New
Chief Executive Officer, Abrika Pharmaceuticals
November 17, 2004

Patent Certification Under 21 U.S.C. § 355 and Notice of Certification of Invalidity or Noninfringement of a Patent Under 21 U.S.C. § 355

I. Abrika Pharmaceuticals LLLP (Abrika), having a place of business at 13800 N.W. 2nd Street, Suite 190, Sunrise, Florida 33325 hereby certifies to the following persons that it has filed an Abbreviated New Drug Application (ANDA) under 21 U.S.C. § 355(j)(2)(B)(ii) (also referred to as Section 505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act) in order to obtain approval to engage in the commercial manufacture, use, or sale of Bupropion Hydrochloride Extended-Release Tablets USP, 300 mg that are bioequivalent to Wellbutrin XL® 300 mg tablets:

1. Holder of New Drug Application for Wellbutrin XL®, 300 mg:

GLAXOSMITHKLINE
5 Moore Drive
Research Triangle Park, NC 27709

2. On information and belief the owner of U.S. Letters Patent Nos. 6,096,341 and 6,143,327 is:

BIOVAIL LABORATORIES INC.
Building No. 2, Chelston Park
Collymore Rock, St. Michael
Barbados, West Indies

II. The United States Food and Drug Administration has received an ANDA from Abrika which contains the required bioequivalence data showing that the Abrika Bupropion Hydrochloride Extended-Release Tablets USP, 300 mg, is bioequivalent to Wellbutrin XL® Tablets 300 mg.

III. The Abrika Abbreviated New Drug Application Number is ANDA 77-285.

IV. The established name for the proposed drug product is Bupropion Hydrochloride Extended-Release Tablets USP, 300 mg.

V. The active ingredient for the proposed drug product is bupropion hydrochloride; the dosage form is an oral tablet that will be sold in 300 mg strength.

VI. The following patents (the "listed patents") which have been listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") are known to Abrika and will not be infringed by the making, using, or selling of the Abrika Bupropion Hydrochloride Extended-Release Tablet USP product (Abrika proposed product):

U.S. Patent No.	Expiration Date
6,096,341	October 30, 2018.
6,143,327	October 30, 2018.

VII. The ANDA indicates that Abrika intends to engage in the commercial manufacture, use, or sale of the proposed product before the expiration dates of U.S. Patent Nos. 6,096,341 and 6,143,327.

VIII. The above U.S. patents, which have been listed in the Orange Book, will not be infringed by the Abrika proposed product for the detailed factual and legal reasons set forth below or, in the alternative, would be invalid and/or unenforceable against the Abrika proposed product.

A. Noninfringement of U.S. Patent No. 6,096,341

All of the claims of the '341 patent require a delayed release tablet including bupropion hydrochloride and exhibiting a dissolution profile such that "after 1hour, from 0 up to 30% of the bupropion hydrochloride is released, after 4 hours, from 10 to 60% of the bupropion hydrochloride is released, after 6 hours, from 20 to 70% of the bupropion hydrochloride is released, after 8 hours, more than 40% of the bupropion hydrochloride is released." The table below compares these claimed dissolution rates with the dissolution rates of the Abrika proposed product, tested under the same conditions -- 0.1N HCl, USP Apparatus I at 75 RPM. These dissolution testing conditions are specified in the Examples of the '341 patent and were relied upon by the patentee during prosecution of the '341 patent:

TABLE I. Dissolution Profile Comparison: '341 Patent Formulation v. Abrika Proposed Product

Time	% Released in 0.1N HCl, USP Apparatus I @ 75 RPM **Claims of the '341 Patent**	% Released in 0.1N HCl, USP Apparatus I @ 75 RPM **Abrika Proposed Product**
1hr	0-30	—
4 hrs	10-60	—
6 hrs	20-70	—
8 hrs	>40	—

b(4)

b(4)

The claims of the '341 patent, themselves, do not specify any dissolution testing conditions. However, a proper claim interpretation limits the claims of the '341 patent not just to the claimed dissolution profile, but to the claimed dissolution profile *as obtained using the same dissolution testing conditions used by the patentee*. In situations where the results of a test or assay are claimed, but the actual test conditions are not, courts have limited the claims to those test results as performed under the same testing conditions; this is especially true where, like here, the results may vary greatly depending upon the test conditions. See Genentech v. Wellcome Found., 29 F.3d 1555 (Fed. Cir.

1994); J.T. Eaton & Co. v. Atlantic Paste & Glue Co., 106 F.3d 1563, 1565 (Fed. Cir. 1997).

In the '341 patent, the patentee emphasized these dissolution testing conditions, and their importance to the claims, during prosecution. In response to a 35 U.S.C. §102(a) rejection, the Applicant argued that "Claim 1 requires a specific dissolution profile," that the prior art was "silent on the dissolution medium and conditions that are used," and the prior art's failure "to teach the dissolution medium and conditions that are used" rendered "its disclosure deficient." '341 Patent File History, Paper No. 6, page 6. The Applicant then directed the examiner to its own dissolution medium and conditions, stating "***[t]he dissolution medium and conditions that are used in the invention is***, on the contrary, ***disclosed in example 1, page 8. (It corresponds to gastric juice.)***" Id. Thus, the claimed release profile should be interpreted as being derived from using the same conditions as described in Example 1 of Applicant's specification., *i.e.*, in 1000 ml of 0.1N HCl at 75 rpm using USP Apparatus I. See '341 Patent, Col. 5, Lines 10-13.

For these reasons, it is clear that the Abrika proposed product fails to meet, or even come close to, the claimed dissolution at 4 hours, 6 hours, and 8 hours and therefore cannot infringe any claim of the '341 patent either literally or under the doctrine of equivalents.

B. Noninfringement of U.S. Patent No. 6,143,327

All of the claims of the '327 patent require the claimed tablets exhibit a dissolution profile such that "after 2 hours, from 0 up to 30% of the bupropion hydrochloride is released, after 4 hours, from 3 to 22% of the bupropion hydrochloride is released, after 6 hours, from 15 to 38% of the bupropion hydrochloride is released, after 8 hours, more than 40% of the bupropion hydrochloride is released." The table below compares the claimed dissolution rates with the dissolution rates of the Abrika proposed product, tested under the same conditions -- 0.1N HCl, USP Apparatus I at 75 RPM. These dissolution testing conditions are specified in the Examples of the '327 patent and were relied upon by the patentee during prosecution of the '327 patent:

TABLE II. Dissolution Profile Comparison: '327 patent formulation v. Abrika Proposed Product

Time	% Released in 0.1N HCl, USP Apparatus I @ 75 RPM **Claims of the '341 Patent**	% Released in 0.1N HCl, USP Apparatus I @ 75 RPM **Abrika Proposed Product**
1hr	0-30	[redacted] b(4)
4 hrs	3-22	[redacted]
6 hrs	15-38	[redacted]
8 hrs	>40	[redacted] b(4)

Again, the claims of the '327 patent do not specify the dissolution testing conditions. Just as in the '341 patent, proper claim interpretation should include the limitation of the actual dissolution testing conditions used to obtain the claimed dissolution profile. See Genentech v. Wellcome Found., 29 F.3d 1555, 1561 (Fed. Cir. 1994); J.T. Eaton & Co. v. Atlantic Paste & Glue Co., 106 F.3d 1563, 1565 (Fed. Cir. 1997); discussed *supra*.

"When multiple patents derive from the same initial application, the prosecution history regarding a claim limitation in any patent that has issued applies with equal force to subsequently issued patents that contain the same claim limitation." Biovail Corp. Int'l. v. Andrx Pharmaceuticals, Inc., 239 F.3d 1297, 1301 (Fed. Cir. 2001), quoting Elkay Mfg. Co. v. Ebco Mfg. Co., 192 F.3d 973, 980 (Fed. Cir. 1999). Thus, statements made by the patentee of the '327 patent during prosecution of its parent, *i.e.*, the '341 patent, regarding the dissolution profiles apply "with equal force" to the claims of the '327 patent. As noted above, during prosecution of the '341 patent, the Applicant emphasized the importance of, not only the dissolution profile, but the dissolution medium and conditions, in distinguishing its claimed invention. The Applicant in arguing that the testing conditions need to be disclosed and read into the claimed dissolution profile unequivocally stated to the examiner that the dissolution medium and conditions are as disclosed in example 1, page 8. See '341 Patent File History, Paper No. 6.

For these reasons, it is clear that the Abrika proposed product fails to meet, or even come close to, the claimed dissolution at 4 hours, 6 hours, and 8 hours, and therefore cannot infringe any claim of the '327 patent either literally or under the doctrine of equivalents.

For the above reasons, the Abrika proposed product will not infringe the listed patents.

The information provided herein is supplied for the purpose of complying with the above-referenced statutes and regulations, and neither Abrika nor its attorneys waive any attorney-client privilege or attorney work product immunity concerning the subject matter of this communication.

In accordance with 21 U.S.C. § 355(j)(2)(B)(i), it is hereby certified that on November 16, 2004 a copy of this notice has been sent by United States registered mail, return receipt requested, to Biovail Laboratories as owner of U.S. Patent Nos. 6,096,341 and 6,143,327 as required by 21 U.S.C. § 355(j)(2)(B)(i)(I), and to GlaxoSmithKline as the holder of the approved application for Welbutrin XL® as required by 21 U.S.C. § 355(j)(2)(B)(i)(II), in envelopes addressed to:

GLAXOSMITHKLINE
5 Moore Drive
Research Triangle Park, NC 27709

BIOVAIL LABORATORIES INC.
Building No. 2, Chelston Park
Collymore Rock, St. Michael
Barbados, West Indies

By: _____
Dr. James New
Chief Executive Officer
Abrika Pharmaceuticals LLLP
13800 N.W. 2nd Street, Suite 190
Sunrise, Florida 33325

ABRIKA
PHARMACEUTICALS

NAI
Notice sent to GSK + Biovail for PIV cert to 1341 + 1377 for 150mg + 300mg Strength
N/XP
11/29/04

November 17, 2004

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

Re: Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg
ANDA 77-285
PATENT AMENDMENT

Mr. Margand:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg, which was submitted to the Agency on September 23, 2004 and October 1, 2004, respectively. We are enclosing the amended "Paragraph IV Certification", which applies to both the 150 mg and the 300 mg dosage form.

The enclosed "Paragraph IV Certification" has been amended, in accordance with 21 C.F.R. §314.95(b), to include a statement certifying that notice was provided on November 12, 2004 (for the 150 mg) and November 16, 2004 (for the 300 mg) to Biovail Laboratories Inc., as owner of the listed patents, and Glaxosmithkline, as NDA holder of Wellbutrin XL, 150 mg and 300 mg. For your convenience, and further to a conversation with Mr. Martin Shimer and Ian Margand of your office, the amended paragraph IV certification for Bupropion Hydrochloride Extended-Release Tablets USP, 150 mg **and** 300mg, is now being timely submitted together.

In accordance with 21 C.F.R. §314.95(e), once received, proof of receipt of the Notices, by Glaxosmithkline and Biovail Laboratories, Inc., will be provided.

If anything further is required at this time, please contact us.

Sincerely,

James S. New
Chief Executive Officer
Abrika Pharmaceuticals

13800 N.W. 2nd St • Suite 190 • Sunrise, Florida 33325 • Phone: 954-315-6600 • Fax: 954-315-6601

ABRIKA PHARMACEUTICALS

PARAGRAPH IV CERTIFICATION

I, Abrika Pharmaceuticals, LLLP, certify that, to the best of its knowledge, U.S. Patent No. 6,096,341 and U.S. Patent No. 6,143,327, both due to expire on October 30, 2018, will not be infringed by the manufacture, use, or sale of Abrika Pharmaceuticals, LLLP's Bupropion HCl Extended-release Tablets, 300 mg. for which this abbreviated new drug application (ANDA) is submitted, or in the alternative, that U.S. Patent No. 6,096,341 and/or U.S. Patent No. 6,143,327 are invalid and/or unenforceable.

As required by Section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)) and 21 C.F.R.§§ 314.94 and 314.95, Abrika Pharmaceuticals, LLLP hereby states that this ANDA is sufficiently complete to permit substantive review and that Abrika Pharmaceuticals, LLLP will give notice as required by 21 U.S.C. 355(j) and 21 CFR § 314.95 to GLAXOSIMITHKLINE, the NDA holder for Wellbutrin XL 300 mg., and to Biovail Laboratories, Inc., the owner of the above-referenced patents.

The notices will be sent by registered or certified mail, return receipt requested, and meet the requirements of 21 CFR§ 314.95(a, c).

Concurrently with sending the notices to GLAXOSMITHKLINE and Biovail Laboratories, Inc., Abrika Pharmaceuticals, LLLP will, as required by 21 CFR § 314.95(b), amend its ANDA to include a certification that the notice has been provided to each person identified under 21 CFR § 314.95(a), and that the notices met the content requirements specified in 21 CFR § 314.95(c).

ABRIKA PHARMACEUTICALS, LLLP

By: _____
James S. New
Chief Executive Officer

000008

Sampling times: 1, 2, 4, 6 and 8 hours and until at [redacted] of the labeled content is dissolved. b(4)

For modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. F2 values should be estimated within and between test and reference products. The specifications for your product will be determined after the data submitted in your ANDA is reviewed.

5. Please provide a table that identifies every missing sample in the study. Also, for every reassayed sample, please provide a table identifying the reason(s) for reassay, as well as the original and reassayed values of the sample. Please identify which value was selected for the PK analysis. Please provide the Standard Operating Procedures (SOPs) for all types of reassays including those that describe criteria for identifying and reassaying pharmacokinetically anomalous samples. The SOP(s) should clearly state objective criteria for defining pharmacokinetic anomalies, the method of reassay, and acceptance criteria for selecting which value to report for the reassayed sample. This SOP should be in place prior to the start of the study; otherwise, the Division of Bioequivalence may not accept reassayed values of samples. Finally, please conduct all pharmacokinetic and statistical analyses using both the original as well as reassayed values.

6. The bioequivalence data to be submitted in an ANDA should be provided in a diskette or CD in SAS Transport format in two separate files as described below:

   a. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE Thalf
   b. SUBJ SEQ PER TRT C1 C2 C3 ..... . Cn

   Please separate each field with a blank space and indicate missing values with a period (.).

   Please refer to the Guidance for Industry: "Providing Regulatory Submissions in Electronic Format-ANDAs" for information regarding the proper format at: www.fda.gov/cder/guidance/index.htm (under electronic submissions).

If you have any questions, please call Steven Mazzella, R.Ph., Project Manager, Division of Bioequivalence at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

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

OGD 04-854

Section III. Patent Certification and Exclusivity Statement

2. Exclusivity Statement

According to information published in the current (24th Edition) of the "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book), Wellbutrin XL is not entitled to a period of marketing exclusivity under section 5050(j)(4)(D) of the Act. Copies of the applicable pages for the "Prescription and OTC Drug Product and Exclusivity Data" listing from the Orange Book) were submitted with the original ANDA.

ABRIKA
PHARMACEUTICALS

PARAGRAPH IV CERTIFICATION

I, Abrika Pharmaceuticals, LLLP, certify that, to the best of its knowledge, U.S. Patent No. 6,096,341 and U.S. Patent No. 6,143,327 will not be infringed by the manufacture, use, or sale of Abrika Pharmaceuticals, LLLP's Bupropion HCl Extended-release Tablets, 300 mg. for which this abbreviated new drug application (ANDA) is submitted, or in the alternative, that U.S. Patent No. 6,096,341 and/or U.S. Patent No. 6,143,327 are invalid and/or unenforceable.

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The notices will be sent by registered or certified mail, return receipt requested, and meet the requirements of 21 CFR§ 314.95(a, c).

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ABRIKA PHARMACEUTICALS, LLLP

By: _____
Monique Weitz
Associate Director, Project Management

EXCLUSIVITY STATEMENT

In accordance with 21 CFR § 314.94(a)(3)(ii), information published in *Approved Drug Products with Therapeutic Equivalence Evaluations* ("the Orange Book"), Electronic Version updated as of June 25, 2008, lists the following information regarding exclusivity for Wellbutrin XL®:

I-497 PREVENTION OF SEASONAL MAJOR DEPRESSIVE EPISODES IN PATIENTS WITH SEASONAL AFFECTIVE DISORDER, listed as expiring June 12, 2009.

Actavis South Atlantic LLC (Actavis) certifies that it does not intend to market the Actavis proposed products for the indication listed above before June 12, 2009, the date on which the I-497 exclusivity term expires. Hence, Actavis has removed any language associated with the above indication from our labeling.

ACTAVIS SOUTH ATLANTIC LLC

By: _____
Monique Weitz
Sr. Director, Project and Site Management

1.3.3.1 Debarment Certification

Debarment/Non-conviction Certification

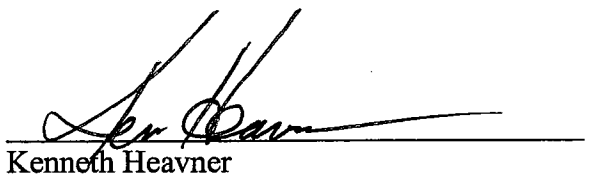
CERTIFICATION REQUIRED BY GENERIC DRUG ENFORCEMENT ACT OF 1992

Pursuant to Section 306(K) of the Federal Food, Drug and Cosmetic Act ("the Act"), as amended by the Generic Drug Enforcement Act of 1992, Abrika Pharmaceuticals, Inc. hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under Sections 306(a) or (b) of the Act in connection with this ANDA.

Abrika Pharmaceuticals, Inc. certifies that, during the previous five years, it has not sustained a conviction that is described in Sections 306(a) or (b) of the Act. In addition, no person affiliated with Abrika Pharmaceuticals, Inc. nor affiliated persons responsible for the development or submission of this application have been convicted of an offense described in Sections 306(a) or (b) of the Act.

Furthermore, Abrika Pharmaceuticals, Inc. agrees to notify the Food and Drug Administration of any changes in status of any employee with respect to Sections 306(a) or (b) of the Act.

Due diligence for this purpose includes the keeping of a current list of companies and individuals debarred by the FDA. Notice of debarment is published in the *Federal Register*, and FDA issues a quarterly list. In addition, we have a questionnaire for new hires and certification statements for outside contractors.



04/27/07

Kenneth Heavner
Executive Director of Quality Operations
Abrika Pharmaceuticals, Inc.

Date

1.3.3.2 List of Convictions Statement
Debarment/Non-conviction Certification

CERTIFICATION REQUIRED BY GENERIC DRUG ENFORCEMENT ACT OF 1992

Pursuant to Section 306(K) of the Federal Food, Drug and Cosmetic Act ("the Act"), as amended by the Generic Drug Enforcement Act of 1992, Abrika Pharmaceuticals, Inc. hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under Sections 306(a) or (b) of the Act in connection with this ANDA.

Abrika Pharmaceuticals, Inc. certifies that, during the previous five years, it has not sustained a conviction that is described in Sections 306(a) or (b) of the Act. In addition, no person affiliated with Abrika Pharmaceuticals, Inc. nor affiliated persons responsible for the development or submission of this application have been convicted of an offense described in Sections 306(a) or (b) of the Act.

Furthermore, Abrika Pharmaceuticals, Inc. agrees to notify the Food and Drug Administration of any changes in status of any employee with respect to Sections 306(a) or (b) of the Act.

Due diligence for this purpose includes the keeping of a current list of companies and individuals debarred by the FDA. Notice of debarment is published in the *Federal Register*, and FDA issues a quarterly list. In addition, we have a questionnaire for new hires and certification statements for outside contractors.

Scott Lodin
SVP and General Counsel
Abrika Pharmaceuticals, Inc.

4/27/07
Date

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-285 Applicant Actavis South Atlantic LLC
Drug Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg
Strength(s) _____

APPROVAL ☒ **TENTATIVE APPROVAL** ☒ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: | **DRAFT Package** | **FINAL Package**

1. **Martin Shimer** — Date 26 June 2008 — Date 8/15/08
Chief, Reg. Support Branch — Initials MHS — Initials rlw

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = XL NDA# 21-515
Date Checked N/A
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

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 ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval for 300 mg strength; T/A for 150 mg sttength.
Comments: ANDA submitted on 9/23/2004 for the 150 mg strength, BOS=Wellbutrin XL TAblets NDA 21-515, PIV to '341, '327. Before OGD acted on the 150 mg strength the sponsor submitted the 300 mg strength on 10/1/2004, same BOS, same patent certs. 150 mg strength ack for filing with PIV on 9/23/2004(LO dated 11/10/2004). XP submitted 11/18/2004-Notice sent to GSK dated 11/12/2004, sent to Biovail dated 11/12/2004, second set of notices sent to same entities dated 11/16/04. On 1/6/2005 firm submitted XP-RR from GSK signed and dated 11/16/04, RR from Biovail signed and dated 12/3/04 RR from GSK signed and dated 11/23/2004, RR from Biovail signed and dated 12/3/2004. XP submitted on 1/14/2005, Copy of CA 04-61704 filed in Southern District of FL on 12/21/2004 for infringement of the '341 and '327 patents. On 8/8/2007 the firm submitted a XP-CA noted earlier was dismissed with prejudice, case now closed. Anchen the sponsor of ANDA 77-284 was granted 180 day exclusivity for both the 150 mg and 300 mg strengths. In a letter dated 12/14/2006, Anchen informed FDA that they initiated commercial marketing of 77-284 for the 300 mg strength only. Anchen did this in order to selectively waive their exclusivity to IMPAX permitting the approval of ANDA 77-415 for the 300 mg strength. Therefore, 180 day exclusivity for the 300 mg product has long since expired. On 6/26/2008 Marty spoke with David Quiggle(949-639-8102). Marty asked Mr. Quiggle if Anchen had ever launched their 150 mg product. Mr. Quiggle immediately responded that he had just finished drafting a letter to be sent to the Agency confirming that marketing of the 150 mg strength began on 5/30/2008. This letter will be transmitted to the Agency shortly. Therefore, Anchen's still retains 180 day exclusivity.

ANDA is eligible for Full approval on the 300 mg strength and TA on the 150 mg strength.

2. Project Manager, Thomas Hinchliffe Team 10 — Date 6/20/08 — Date _____
Review Support Branch — Initials TOH — Initials _____

Original Rec'd date September 23, 2004
Date Acceptable for Filing September 23, 2004
Patent Certification (type) P4
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☐ No ☐
Bio Review Filed in DFS: Yes ☐ No ☐
Suitability Petition/Pediatric Waiver Yes ☐
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 5/2/2008
Date of Office Bio Review 4/3/08
Date of Labeling Approv. Sum 7/11/2008
Labeling Acceptable Email Rec'd Yes ☐ No ☐
Labeling Acceptable Email filed Yes ☐ No ☐
Date of Sterility Assur. App. _____
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:DATE OF APPLICATION: September 23, 2004

3. Labeling Endorsement
Reviewer: Labeling Team Leader:
Date_____ Date8/15/08
Name/Initials_____ Name/Initialsrlw/for

Comments:

From: Golson, Lillie D
Sent: Monday, August 04, 2008 10:37 PM
To: Hinchliffe, Thomas; Golson, Lillie D
Subject: FW: 77-285 Needs AP Endorsement

Hi Tom,

From a labeling standpoint, labeling is acceptable for approval. Please endorse the AP routing form on behalf of Michelle and me.

Thanks

From: Dillahunt, Michelle
Sent: Monday, August 04, 2008 11:49 AM
To: Golson, Lillie D
Subject: FW: 77-285 Needs AP Endorsement

Labeling is acceptable.

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 01Aug08
OGD Regulatory Counsel, Post-MMA Language Included ☐ InitialsDTR
Comments:Changes to AP/TA ltr saved to V drive.

5. Div. Dir./Deputy Dir. Date8/12/08
Chemistry Div. II InitialsFF

Comments: CMC ok Commitment to conduct dose dumping studies post approval.

6. Frank Holcombe **First Generics Only** Date8/15/08
Assoc. Dir. For Chemistry Initialsrlw/for
Comments: (First generic drug review)
N/A. Multiple ANDAs have been approved for the 300 mg tablet strength. In addition, Anchen's ANDA 77-284 for the 150 mg tablet strength was approved on December 14, 2006.

7. Vacant Date_____
Deputy Dir., DLPS Initials_____
RLD = Wellbutrin XL Extended-release Tablets 150 mg and 300 mg (Once-daily)
SmithKline Beecham (GlaxoSmithKline) NDa 21-515 (001, 002)

8. Peter Rickman Date 8/15/08
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐No ☐;Petition: Yes☐ No☐
Comments: Bioequivalence studies (fasting and non-fasting) on the 150 mg tablet strength found acceptable 12/23/05. In-vitro dissolution testing on both strengths also found acceptable. Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 12/23/05. [Review located in V:\drive 77285A1205.doc]. Commitment obtained to perform ethanol "dose-dumping" studies post-approval.

Final printed labeling (FPL) found acceptable for approval 7/11/08.

CMC found acceptable for approval (Chemistry Review #4) 7/25/08.

OR

8. Robert L. West — Date 8/15/08
Deputy Director, OGD — Initials RLWest
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EES dated 5/2/08 (Verified 8/15/08). No "OAI" Alerts noted.

Actavis (formerly Abrika) made paragraph IV certifications to the 341 and '327 patents listed in the Orange Book. Actavis was sued on both patents within the statutory 45-day period. The litigation was dismissed by the court on July 31, 2007. There are no other patents listed in the current Orange Book for this drug product. Actavis has choosen to "carve-out" information from its package insert labeling pertaining to the I-497 exclusivity (prevention of major depressive episodes in patients with SAD). This is acceptable.

Actavis's ANDA for the 300 mg tablet strength is recommended for approval. Actavis's 150 mg tablet strength may be tentatively approved at this time. Final approval for the 150 mg tablet strength is blocked by Anchen's 180-day generic drug exclusivity for the 150 mg tablet strength under ANDA 77-284. This exclusivity will expire on November 26, 2008.

9. Gary Buehler — Date 8/15/08
Director, OGD — Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Thomas Hinchliffe Team 10 — Date8/15/08
Review Support Branch — Initials TOH
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
8/15/08Time notified of approval by phone 8/15/08Time approval letter faxed

FDA Notification:
8/15/08Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
8/15/08Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

EES Data for: 077285

*** *Compliance Recommendations* ***

App No	Doc Seq No	Date	OC Recommendation
077285	000	5/2/2008	ACCEPTABLE
077285	000	11/29/2007	WITHHOLD
077285	000	3/14/2005	ACCEPTABLE

*** *EER Table* ***

CFN	Name	Profile Code	Last Milestone Name	Last Milestone Date	Last Status	Last Status Date	OAI Alert/ Effective Date	
		CTL	OC RECOMMENDATION	5/2/2008	AC	5/2/2008	None	b(4
		CTL	OC RECOMMENDATION	5/2/2008	AC	5/2/2008	None	
		CTL	REQUEST CANCELLED	5/2/2008	AC	6/26/2007	None	
		CTL	REQUEST CANCELLED	5/2/2008	WH	11/21/2007	None	b(4)
		TCT	REQUEST CANCELLED	3/5/2008	WH	11/21/2007	None	
	ABRIKA PHARMACEUTICALS LLLP	TCT	REQUEST CANCELLED	12/21/2007	WH	11/21/2007	None	
	ABRIKA PHARMACEUTICALS LLLP	CTL	REQUEST CANCELLED	12/21/2007	AC	6/21/2007	None	
			OC RECOMMENDATION	11/29/2007	AC	11/29/2007	None	
		TTR	OC	10/29/2007	AC	10/29/2007	None	b(4)

			RECOMMENDATION					
2249136	VPS CORPORATION	TCT	OC RECOMMENDATION	8/28/2007	AC	8/28/2007	None	
[redacted]		CTL	OC RECOMMENDATION	6/21/2007	AC	6/21/2007	None	

b(4)

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 021515 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
021515	001	6096341	Oct 30, 2018				
021515	001	6143327	Oct 30, 2018				Y

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021515	**001**	**I-497**	**Jun 12, 2009**

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

View a list of all patent use codes
View a list of all exclusivity codes
Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through July, 2008
Patent and Generic Drug Product Data Last Updated: August 14, 2008

Patent and Exclusivity Search Results from query on Appl No 021515 Product 002 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
021515	002	6096341	Oct 30, 2018				

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021515	**002**	**I-497**	**Jun 12, 2009**

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

View a list of all patent use codes
View a list of all exclusivity codes
Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through July, 2008
Patent and Generic Drug Product Data Last Updated: August 14, 2008

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

/s/

Thomas Hinchliffe
8/15/2008 11:05:45 AM

actavis
creating value in pharmaceuticals

July 25, 2008

ORIG AMENDMENT

N-000-AA

Thomas Hinchliffe, Pharm.D.
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Central Document Room
7500 Standish Place
Room East 150
Rockville, MD 20855

Reference: **ANDA 77-285**
Bupropion Hydrochloride Extended-Release Tablets, (XL), 150 mg and 300 mg
TELEPHONE AMENDMENT – Residual Solvents (Amendment 27) USP Chapter <467>

Dear Mr. Hinchliffe:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, which were submitted to the Agency on September 23, 2004 and October 1, 2004, respectively as well as:

- Telephone Amendment (Amendment 23) submitted on June 9, 2007.
- Fax sent to Tom Hinchliffe, Pharm. D. on July 16, 2008.
- Teleconference with Tom Hinchliffe, Pharm. D., Naigi Ya, Ph.D., Monique Weitz and Jim Huang, Ph. D. on July 17, 2008.
- Fax sent to Tom Hinchliffe, Pharm. D. on July 22, 2008
- Teleconference with Tom Hinchliffe, Pharm. D., Naigi Ya, Ph.D., Bing Wu, Ph.D., Monique Weitz, Jim Huang, Ph. D. and Diane Guo on July 23, 2008.

Actavis is submitting this Telephone Amendment via fax on July 24, 2008 and electronically on July 25, 2008 in response to the telephone conference fax received via fax on July 16, 2008. Our response follows this cover letter.

This amendment is being submitted according to the eCTD guidance.

RECEIVED

JUL 28 2008

OGD

Actavis SouthAtlantic LLC | 13800 NW 2nd Street, #190 Sunrise, FL 33325 | t (+1) 954 315 6600 f (+1) 954 315 6601 | www.actavis.com

The following original signature documents are being submitted both as paper and electronic PDF documents:

- FDA Form 356h
- Cover letter
- Field copy letter
- FDA Form 3674

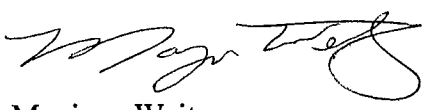
The size of the electronic submission is approximately 1.25 MB. The files are free of viruses as determined by using Trend Micro™ OfficeScan™ Version 7.3 (virus definition date July 25, 2008).

In addition, a letter is being sent to Actavis' FDA Field Office stating that this amendment has been filed with FDA electronically and can be found in FDA's electronic document room.

If there are any questions concerning this submission, please contact me at 954-315-6502.

Thank you.

Sincerely,



Monique Weitz
Senior Director, Project and Site Management
Actavis South Atlantic LLC

actavis
creating value in pharmaceuticals

July 25, 2008

Food and Drug Administration
District Office
555 Winderley Place
Maitland, FL 32751

Reference: ANDA 77-285
Bupropion Hydrochloride Extended-Release Tablets, (XL), 150 mg and 300 mg
Telephone Amendment – Residual Solvents (Amendment 27) USP Chapter <467>

Dear Sir/Madam:

Please be advised that Actavis has faxed and filed our Telephone Amendment (Amendment 27) for ANDA 77-285, Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, on July 24, 2008 and July 25, 2008 respectively. This amendment will be located in FDA's electronic document room for review.

Actavis commits to providing any updated information to the District Office as appropriate.

Please direct any questions to:

Monique Weitz, Sr. Director, Project and Site Management
Actavis South Atlantic, LLC
13800 N.W. 2nd Street, Suite 190
Sunrise, Florida 33325
Telephone: 954-313-6502 Fax: 954-315-66550

Thank you.

Sincerely,

Monique Weitz
Sr. Director, Project and Site Management
Actavis South Atlantic LLC

RECEIVED
JUL 28 2008
OGD

actavis
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Fax

To:	Tom Hinchliffe, Pharm.D.	**From:**	Monique Weitz
Fax:	(240) 276-8582	**Date:**	July 22, 2008
Phone:	(240) 276-8536	**Pages:**	16 , including cover
Re:	ANDA # 77-285 7/16/2008 <467> Telephone Amendment	**CC:**	Naiqi Ya, Ph.D.

-☐ **Urgent** ☐**For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

•Comments:

Tom,

As mentioned on my voicemail message, Actavis would like to set up a telephone conference to discuss the following proposal with respect to the 7/16/2008 <467> telephone amendment.

Please note that this is a different approach than discussed on our July 17, 2008 telephone conference.

Thank you for reviewing this proposal. We look forward to hearing from you.

Kind Regards,
Monique Weitz
(954) 315-6502

Cc: Jim Huang, Ph.D. (Actavis)

Residual solvents evaluation for Bupropion Hydrochloride Extended Release Tablets as per USP <467> guideline

Basic information about drug substances and excipients used in the drug product:

b(4)

b(4)

b(4)

Basis for proposed calculation for each residual solvent in the drug product:

b(4)

b(4)

b(4)

b(4)

b(4)

(4)

b(4)

Redacted 14 page(s)

of trade secret and/or

confidential commercial

information from

Administrative documents

actavis
creating value in pharmaceuticals

Fax

To:	Tom Hinchliffe	**From:**	Monique Weitz
Fax:	(240) 276-8582	**Date:**	July 16, 2008
Phone:	(240) 276-8536	**Pages:**	2 , including cover
Re:	ANDA # 77-285	**CC:**	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

•Comments:

Tom,

As mentioned on my voicemail message, Actavis would like clarification on the 7/16/2008 telephone amendment.

Background:
On June 9, 2008 Actavis submitted a report titled "Bupropion HCl Extended-Release Tablets: Evaluation for Residual Solvents TECHNICAL REPORT NO.: AS097" for the residual solvents in Bupropion Hydrochloride Extended-Release Tablets (XL) 150 mg and 300 mg.

We have taken a cumulative procedure (USP option 2) to calculate maximum daily exposure levels in the drug product based on residual solvents in its ingredients. If the calculation results are less than or equal to Permitted Daily Exposure (PDE) provided in USP <467>, then no test of the drug product is required. In the report, we calculated all possible residual solvents in all ingredients in Bupropion Hydrochloride Extended-Release Tablets (XL) 150 mg and 300 mg. A summary of residual solvents in the drug product is provided on page 19 of the report. They are far below permitted daily exposure.

- See page 22 of the report for information on residual solvents in _____ b(4)
- See page 24 of the report for information on residual solvents in _____
- See page 30 of the report for information on residual solvents in _____ b(4)
- See page 38 of the report for information on residual solvents in _____ b(4)
- See page 47 of the report for information on residual solvents in _____ b(4)

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Our question is the following:
Based on our understanding of USP <467>, communications with USP, the report that was submitted, and the additional background information provided above, Actavis would like clarification on why the test specifications for the inactive ingredients to include residual solvent specifications (solvent identity, acceptance criteria, and test methods) as listed in the Telephone Amendment is being requested.

Thank you for taking the time to review this request.

Kind Regards,
Monique Weitz
(954) 315-6502

Actavis SouthAtlantic LLC ¦ 13800 NW 2nd Street, Suite 190 ¦ Sunrise, FL 33325 ¦ t 954 315 6600 ¦ f 954 315 6601 ¦ www.actavis.com

TELEPHONE CONFERENCE FAX

ANDA 77-285

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Actavis South Atlantic LLC

TEL: 954-315-6502

ATTN: Monique Weitz

FAX: 954-315-6601

FROM: Thomas Hinchliffe

FDA CONTACT PHONE: (240) 276-8536

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated September 23, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Tablets, 150 mg and 300 mg.

The deficiencies presented below represent MINOR deficiencies identified during the ongoing review and the current review cycle will remain open. You should respond to these deficiencies with a "Telephone Amendment" within ten working days. If you have questions regarding these deficiencies please contact the Project Manager, Thomas Hinchliffe at (240) 276-8536. Please submit documentation by fax to the attention of the Project Manager at ENTER FAX NUMBER HERE. Please also submit official hard copies of any faxed documentation to the Document Room.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

CHEMISTRY REVIEW

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-285

APPLICANT: Actavis South Atlantic LLC

DRUG PRODUCT: Bupropion Hydrochloride Extended-Release Tablets (XL), 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 240-276-8536 Please submit documentation by fax to the attention of the Project Manager at 240-276-8582. Please also submit official hard copies of any faxed documentation to the Document Room.*

A. Deficiencies:

Regarding the Residual Solvents testing for the raw materials and the drug product per the USP < 467>:

- Please update the test specifications for the inactive ingredients [redacted] and [redacted] to include residual solvents specifications (solvent identity, acceptance criteria, and test methods). b(4)
- Test methods for the residual solvents testing should also be validated if non-USP methods are used.
- Please also update COAs for the excipients to include the residual solvents results.

22-1

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June 26, 2008

Thomas Hinchliffe, Pharm.D.
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
7500 Standish Place
Room East 150
Rockville, MD 20855

ORIG AMENDMENT
W/A

Reference: ANDA 77-285
Bupropion Hydrochloride Extended-Release Tablets, (XL), 150 mg & 300 mg
Final Printed Labeling & Exclusivity Statement Amendment (26)

Dear Mr. Hinchliffe:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, which were submitted to the Agency on September 23, 2004 and October 1, 2004, respectively as well as:

- FDA letter stating the ANDA received acceptable for filing November 10, 2004.
- Final Printed Labeling Amendment (9) submitted July 9, 2005.
- Final Printed Labeling Amendment (16) submitted April 2, 2008.
- Final Printed Labeling Amendment (22) submitted May 19, 2008
- Final Printed Labeling Amendment (24) submitted June 16, 2008
- Final Printed Labeling Amendment (25) submitted June 23, 2008

Reference is made to the June 25, 2008 telephone conversation between Monique Weitz, Senior Director, Project & Site Management and Michelle Dillahunt from the Office of Generic Drugs, Labeling Division. Ms. Dillahunt had requested that Actavis delete all references to seasonal affective disorder from the Outsert and Medication Guide due to the I-497 exclusivity term which expires June 12, 2009.

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Actavis is also submitting an exclusivity statement regarding the I-497 exclusivity. Please see Section 1.3.5.2.

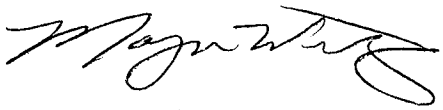
This amendment is being submitted to provide labeling with the 300 mg strength only. At approval, Actavis will only be given approval on the 300 mg strength with a tentative approval on the 150 mg due to exclusivity held by another firm. Therefore, Actavis has carved out the 150 mg from our labeling at this time. Once Actavis has been given the approval for the 150 mg, the labeling will be resubmitted to include the 150 mg strength.

This Labeling Amendment consists of one volume; one archival (blue) hard copy and CDROM will be sent via courier.

The final printed labeling for Bupropion Hydrochloride Extended-Release Tablets (XL), 300 mg, package outsert has been provided. In accord with the December 11, 2003, electronic labeling rule, the final printed labeling for the package outsert is being provided electronically as Adobe Acrobat PDF files and corresponding Microsoft Word files. The labeling is also being submitted in SPL format. The size of the electronic submission is approximately 2 MB. The files are free of viruses as determined by using Trend Micro™OfficeScan™ Version 7.3 (virus definition date June 26, 2008).

If there are any questions concerning this submission, please contact me at 954-315-6600.

Thank you,



Monique Weitz
Senior Director, Project and Site Management
Actavis South Atlantic LLC

Cc: Michelle Dillahunt

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June 23, 2008

Thomas Hinchliffe, Pharm.D.
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
7500 Standish Place
Room East 150
Rockville, MD 20855

N - 000 - AF

Reference: ANDA 77-285
Bupropion Hydrochloride Extended-Release Tablets, (XL), 150 mg & 300 mg
Final Printed Labeling Amendment (Amendment 25)

Dear Mr. Hinchliffe:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, which were submitted to the Agency on September 23, 2004 and October 1, 2004, respectively as well as:

- FDA letter stating the ANDA received acceptable for filing November 10, 2004.
- Final Printed Labeling Amendment (9) submitted July 9, 2005.
- Final Printed Labeling Amendment (16) submitted April 2, 2008.
- Final Printed Labeling Amendment (22) submitted May 19, 2008
- Final Printed Labeling Amendment (24) submitted June 16, 2008

Reference is made to the telephone conversation between Monique Weitz, Senior Director, Project & Site Management and Michelle Dillahunt from the Office of Generic Drugs, Labeling Division. Ms. Dilllahunt had requested that Actavis add the Medication Guide onto the Outsert.

Actavis has provided the amended Outsert discussed in the above mentioned telephone conversation.

This amendment is being submitted to provide labeling with the 300 mg strength only. At approval, Actavis will only be given approval on the 300 mg strength with a tentative approval on the 150 mg due to exclusivity held by another firm. Therefore, Actavis has carved out the 150 mg from our labeling at this time. Once Actavis has been given the approval for the 150 mg, the labeling will be resubmitted to include the 150 mg strength.

This Labeling Amendment consists of one volume; one archival (blue) hard copy and CDROM will be sent via courier.

The final printed labeling for Bupropion Hydrochloride Extended-Release Tablets (XL), 300 mg, package outsert has been provided. In accord with the December 11, 2003, electronic labeling rule, the final printed labeling for the package outsert is being provided electronically as Adobe Acrobat

Actavis SouthAtlantic LLC | 13800 NW 2nd Street, #190 Sunrise, FL 33325 | t (+1) 954 315 6600 f (+1) 954 315 6601 | www.actavis.com

PDF files and corresponding Microsoft Word files. The labeling is also being submitted in SPL format. The size of the electronic submission is approximately 600 KB. The files are free of viruses as determined by using Trend Micro™OfficeScan™ Version 7.3 (virus definition date June 16, 2008).

If there are any questions concerning this submission, please contact me at 954-315-6600.

Thank you,

Monique Weitz
Senior Director, Project and Site Management
Actavis South Atlantic LLC

Cc: Michelle Dillahunt

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June 16, 2008

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Thomas Hinchliffe, Pharm.D.
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
7500 Standish Place
Room East 150
Rockville, MD 20855

Reference: ANDA 77-285
Bupropion Hydrochloride Extended-Release Tablets, (XL), 150 mg & 300 mg
Final Printed Labeling Amendment (Amendment 24)

Dear Mr. Hinchliffe:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, which were submitted to the Agency
on September 23, 2004 and October 1, 2004, respectively as well as:

- FDA letter stating the ANDA received acceptable for filing November 10, 2004.
- Final Printed Labeling Amendment (9) submitted July 9, 2005.
- Final Printed Labeling Amendment (16) submitted April 2, 2008.
- Final Printed Labeling Amendment (22) submitted May 19, 2008

Labeling deficiency comments from FDA's June 13, 2008 telefax are provided in italicized text with responses from Actavis following each comment in normal bold text. A copy of the telefax is provided after this transmittal letter for ease of review.

This amendment is being submitted to provide labeling with the 300 mg strength only. At approval, Actavis will only be given approval on the 300 mg strength with a tentative approval on the 150 mg due to exclusivity held by another firm. Therefore, Actavis has carved out the 150 mg from our labeling at this time. Once Actavis has been given the approval for the 150 mg, the labeling will be resubmitted to include the 150 mg strength.

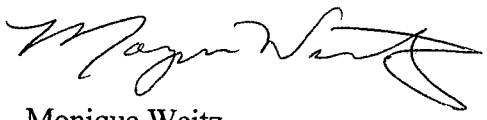
This Labeling Amendment consists of one volume; one archival (blue) hard copy and CDROM will be sent via courier.

The final printed labeling for Bupropion Hydrochloride Extended-Release Tablets (XL), 300 mg, package outsert has been provided. In accord with the December 11, 2003, electronic labeling rule, the final printed labeling for the package outsert is being provided electronically as Adobe Acrobat PDF files and corresponding Microsoft Word files. The labeling is also being submitted in SPL format. The size of the electronic submission is approximately 3.0 MB. The files are free of viruses

as determined by using Trend Micro™OfficeScan™ Version 7.3 (virus definition date June 16, 2008).

If there are any questions concerning this submission, please contact me at 954-315-6600.

Thank you,



Monique Weitz
Senior Director, Project and Site Management
Actavis South Atlantic LLC

Cc: Michelle Dillahunt

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June 9, 2008

Thomas Hinchliffe, Pharm.D.
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Central Document Room
7500 Standish Place
Room East 150
Rockville, MD 20855

ORIG AMENDMENT
N-000-AA

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Reference: ANDA 77-285
Bupropion Hydrochloride Extended-Release Tablets, (XL), 150 mg and 300 mg
Gratuitous Amendment – Residual Solvents (Amendment 23) USP Chapter <467>

Dear Mr. Hinchliffe:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, which were submitted to the Agency on September 23, 2004 and October 1, 2004, respectively. Please also reference our Chemistry Major Amendment submitted on April 27, 2007.

Actavis is submitting this Telephone Amendment in accord with the July 1, 2008 deadline for submission of Residual Solvents testing of our drug substance, excipients, and drug product, as required by USP Chapter <467>.

Actavis' attached report, AS-097, shows that ANDA 77-285 complies with the following:

- The drug substance, bupropion hydrochloride, and excipients comprising the Actavis' Bupropion Hydrochloride Extended-Release Tablets (XL) have residual solvent acceptance limits that fall within the ICH Q3C (option 1) limit.
- The drug substance, bupropion hydrochloride, and excipients comprising the Actavis' Bupropion Hydrochloride Extended-Release Tablets (XL) weighted by their amount in the drug product, results in a cumulative daily exposure for residual solvents that falls within the ICH Q3C (option 2) limit.

In addition to the above report, Actavis commits to re-assess our compliance with USP <467> if we change ingredient suppliers in the post approval period.

Please note that the ANDA was submitted by Abrika Pharmaceuticals, Inc. and there may be references to Abrika Pharmaceuticals, Inc. throughout the original submission and subsequent amendments. Abrika Pharmaceuticals, Inc. was purchased by Actavis Group, hf on April 18, 2007. The name change to Actavis South Atlantic LLC was certified on May 11, 2007. A New Correspondence as notification of this name change was submitted to FDA on March 19, 2008.

Actavis SouthAtlantic LLC | 13800 NW 2nd Street, #190 Sunrise, FL 33325 | t (+1) 954 315 6600 f (+1) 954 315 6601 | www.actavis.com

The enclosed telephone amendment is organized in Common Technical Document (CTD) format and is contained on one CDROM. On February 25, 2008, Actavis was granted a waiver by Virginia Ventura of CDER for submission in eCTD format under the condition that we submit using the "hybrid" method. As such, the documents have been arranged in folders according to the eCTD guidance. A hyperlinked PDF Table of Contents is located on the CDROM outside of the folders to act as a backbone and contains links the files contained in the folders. Hyperlinks within the table of contents and methods-validation files are indicated by blue text.

The following original signature documents are being submitted both as paper and electronic PDF documents:

- FDA Form 356h
- Cover letter
- Field copy letter

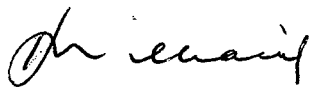
This amendment contains Module 1 as well as an Appendix 1, and is being submitted electronically in PDF format, with the exception of the above sections which are being submitted both as paper and electronic files, on one CDROM which is being submitted via overnight courier. The size of the electronic submission is approximately 10 MB. The files are free of viruses as determined by using Trend Micro™ OfficeScan™ Version 7.3 (virus definition date June 9, 2008).

In addition, a letter is being sent to Actavis' FDA Field Office stating that this amendment has been filed with FDA electronically and can be found in FDA's electronic document room.

If there are any questions concerning this submission, please contact me at 954-315-6502.

Thank you.

Sincerely,



Hindley Williams
Senior Manager, Quality Assurance
Actavis South Atlantic LLC

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June 9, 2008

Food and Drug Administration
District Office
555 Winderley Place
Maitland, FL 32751

Reference: ANDA 77-285
Bupropion Hydrochloride Extended-Release Tablets, (XL), 150 mg and 300 mg
Telephone Amendment – Residual Solvents (Amendment 23) USP Chapter <467>

Dear Sir/Madam:

Please be advised that Actavis has filed our Telephone Amendment (Amendment 23) for ANDA 77-285, ANDA Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, via overnight courier today, June 9, 2008, with FDA on one CDROM. This amendment will be located in FDA's electronic document room for review.

Actavis commits to providing any updated information to the District Office as appropriate.

Please direct any questions to:

Monique Weitz, Sr. Director, Project and Site Management
Actavis South Atlantic, LLC
13800 N.W. 2nd Street, Suite 190
Sunrise, Florida 33325
Telephone: 954-313-6502 Fax: 954-315-66550

Thank you.

Sincerely,

Hindley Williams
Senior Manager, Quality Assurance
Actavis South Atlantic LLC

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May 19, 2008

ORIG AMENDMENT
N-AF

Thomas Hinchliffe, Pharm.D.
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
7500 Standish Place
Room East 150
Rockville, MD 20855

Reference: ANDA 77-285
Bupropion Hydrochloride Extended-Release Tablets, (XL), 150 mg & 300 mg
Final Printed Labeling Amendment (Amendment 22)

Dear Mr. Hinchliffe:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, which were submitted to the Agency on September 23, 2004 and October 1, 2004, respectively as well as:

- FDA letter stating the ANDA received acceptable for filing November 10, 2004.
- Final Printed Labeling Amendment (9) submitted July 9, 2005.
- Final Printed Labeling Amendment (16) submitted April 2, 2008.

This amendment is being submitted to provide labeling with the 300 mg strength only. At approval, Actavis will only be given approval on the 300 mg strength with a tentative approval on the 150 mg due to exclusivity held by another firm. Therefore, Actavis has carved out the 150 mg from our labeling at this time. Once Actavis has been given the approval for the 150 mg, the labeling will be resubmitted to include the 150 mg strength.

This Labeling Amendment consists of one volume; one archival (blue) hard copy and CDROM will be sent via courier.

The final printed labeling for Bupropion Hydrochloride Extended-Release Tablets (XL), 300 mg, package outsert has been provided. In accord with the December 11, 2003, electronic labeling rule, the final printed labeling for the package outsert is being provided electronically as Adobe Acrobat PDF files and corresponding Microsoft Word files. The labeling is also being submitted in SPL format. The size of the electronic submission is approximately 4.5 MB. The files are free of viruses as determined by using Trend Micro™OfficeScan™ Version 7.3 (virus definition date May 19, 2008).

If there are any questions concerning this submission, please contact me at 954-315-6600.

Thank you,

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Monique Weitz
Senior Director, Project and Site Management
Actavis South Atlantic LLC

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April 1, 2008

Thomas Hinchliffe, Pharm.D.
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
7500 Standish Place
Room East 150
Rockville, MD 20855

ORIG AMENDMENT
N. AF

Reference: ANDA 77-285
Bupropion Hydrochloride Extended-Release Tablets, (XL), 150 mg and 300 mg
Final Printed Labeling Amendment (Amendment 16)

Dear Mr. Hinchliffe:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, which were submitted to the Agency on September 23, 2004 and October 1, 2004, respectively. Please also reference our Chemistry Major Amendment submitted on April 27, 2007.

This amendment is being submitted in response to updated labeling for the RLD, Wellbutrin® XL, which was approved by FDA on August 2, 2007 as well as FDA's labeling amendment facsimile received on June 12, 2006. Because the RLD has updated their labeling multiple times since Actavis last submitted labeling on July 8, 2005, Actavis has used the current RLD labeling as the basis to create the attached submitted labeling as opposed to our most recently submitted labeling (July 8, 2005).

Deficiency comments from FDA's June 12, 2006 facsimile are provided in Attachment 1 in italicized text with responses from Actavis following each comment in normal bold text.

This Labeling Amendment consists of one volume; one archival (blue) hard copy and CDROM will be sent via courier.

The final printed labeling for Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, package insert has been provided. In accord with the December 11, 2003, electronic labeling rule, the final printed labeling for the package insert is being provided electronically as Adobe Acrobat PDF files and corresponding Microsoft Word files. The labeling is also being submitted in SPL format. The size of the electronic submission is approximately 4.5 MB. The files are free of viruses as determined by using Trend Micro™OfficeScan™ Version 7.3 (virus definition date April 1, 2008).

If there are any questions concerning this submission, please contact me at 954-315-6600.

Thank you,

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APR 02 2008
OGD

Monique Weitz
Senior Director, Project and Site Management
Actavis South Atlantic LLC

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Attachment 1
Responses to Requested Information

Labeling Deficiencies:

CONTAINER: 30s / ——— (150 mg and 300 mg)

Satisfactory in final print as of September 28, 2005 submission.

Response:

Actavis acknowledges that the 30s container labels submitted as of September 28, 2005 are accepted as satisfactory.

——————————————————————— b(4)
——————————————————————— **In accord with unit of use rules, as of this time Actavis is submitting a 30 count and 90 count packaging configuration for both 150 mg and 300 mg.**

PHYSICIAN INSERT

Add the following paragraph under the WARNINGS section after the 4th paragraph:

"Adults with MDD or co-morbid depression in the ... 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 suicidal attempts, and should receive careful monitoring during treatment. [American Psychiatric Association Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors, 2003] [Brown, 2000]."

Response:

Actavis has added the following paragraph under the WARNINGS section after the 4th paragraph:

"Adults with MDD or co-morbid depression in the ... 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 suicidal attempts, and should receive careful monitoring during treatment. [American

Psychiatric Association Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors, 2003] [Brown, 2000].”

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March 27, 2008

Thomas Hinchliffe, Pharm.D.
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Central Document Room
7500 Standish Place
Room East 150
Rockville, MD 20855

N-000-AA

Reference: ANDA 77-285
Bupropion Hydrochloride Extended-Release Tablets, (XL), 150 mg and 300 mg
Gratuitous Amendment – Analytical Site Change (Amendment 21)

Dear Mr. Hinchliffe:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, which were submitted to the Agency on September 23, 2004 and October 1, 2004, respectively. Please also reference our Chemistry Major Amendment submitted on April 27, 2007.

In accord with 21 CFR 314.70 and a Guidance published September 2003 on a Stand-Alone - Analytical Testing Laboratory Site Change (SUPAC-MR), Actavis is submitting a Gratuitous Amendment for an Analytical Testing Laboratory Site Change.

Actavis is proposing an Analytical Testing Laboratory Site Change to ——————— for drug b(4)

b(4)

information and will not be used in the future for this ANDA. Please see Section 1.12.11 Basis for Submission for additional details.

Please note that the ANDA was submitted by Abrika Pharmaceuticals, Inc. and there may be references to Abrika Pharmaceuticals, Inc. throughout the original submission and subsequent amendments. Abrika Pharmaceuticals, Inc. was purchased by Actavis Group, hf on April 18, 2007. The name change to Actavis South Atlantic LLC was certified on May 11, 2007. A New Correspondence as notification of this name change was submitted to FDA on March 19, 2008.

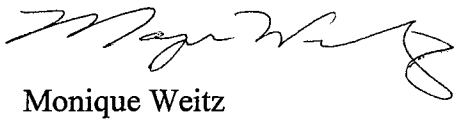
Actavis SouthAtlantic LLC | 13800 NW 2nd Street, #190 Sunrise, FL 33325 | t (+1) 954 315 6600 f (+1) 954 315 6601 | www.actavis.com

This Gratuitous Amendment consists of one volume; three hard copies, archival (blue), review-chemistry (red), and field (maroon) are being submitted via overnight courier. In accordance with 21 CFR 314.96, or 314.94, the field copy of the technical section of the amendment has been sent directly to the FDA District Office in Maitland, Florida. Please note an updated field copy certification is provided.

If there are any questions concerning this submission, please contact me at 954-315-6502.

Thank you.

Sincerely,



Monique Weitz
Senior Director, Project and Site Management
Actavis South Atlantic LLC

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March 27, 2008

Food and Drug Administration
District Office
555 Winderley Place
Maitland, FL 32751

Reference: ANDA 77-285
Bupropion Hydrochloride Extended-Release Tablets, (XL), 150 mg and 300 mg
Gratuitous Amendment – Analytical Site Change (Amendment 21)

Dear Sir/Madam:

Pursuant to the requirements in 21 CFR 314.94(d)(5), and concurrent with the filing of our original gratuitous amendment for ANDA 77-285, enclosed please find the "Field Copy" in support of Abrika Pharmaceuticals' ANDA Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg. The Field Copy contains:

- A Field Copy Certification
- A true copy of the Form FDA 356h filed with the subject gratuitous amendment
- A true copy of the Technical Sections provided in the submission of the subject gratuitous amendment

Abrika commits to providing any updated information to the District Office as appropriate.

Please direct any questions to:

Monique Weitz, Sr. Director, Project and Site Management
Actavis South Atlantic, LLC
13800 N.W. 2nd Street, Suite 190
Sunrise, Florida 33325
Telephone: 954-313-6502 Fax: 954-315-66550

Thank you.

Sincerely,

Monique Weitz
Senior Director, Project and Site Management
Actavis South Atlantic LLC

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March 20, 2008

Thomas Hinchliffe, Pharm.D.
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Central Document Room
7500 Standish Place
Room East 150
Rockville, MD 20855

AMENDMENT
N/AB

Reference: ANDA 77-285
Bupropion Hydrochloride Extended-Release Tablets, (XL), 150 mg and 300 mg
Bioequivalence Amendment (Amendment 18)

Dear Mr. Hinchliffe:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, which were submitted to the Agency on September 23, 2004 and October 1, 2004, respectively. Please also reference our Chemistry Major Amendment submitted on April 27, 2007.

This amendment is being submitted in response to FDA's Bioequivalency Amendment facsimile received on July 2, 2007. Deficiency comments from FDA's July 2, 2007 facsimile are provided in Attachment 1 in italicized text with responses from Actavis following each comment in normal bold text.

Please note that the ANDA was submitted by Abrika Pharmaceuticals, Inc. and there may be references to Abrika Pharmaceuticals, Inc. throughout the original submission and subsequent amendments. Abrika Pharmaceuticals, Inc. was purchased by Actavis Group, hf on April 18, 2007. The name change to Actavis South Atlantic LLC was certified on May 11, 2007. A New Correspondence as notification of this name change was submitted to FDA on March 19, 2008.

In accordance with 21 CFR 314.96, this Bioequivalency Amendment consists of one volume; two hard copies, archival (blue) and review-bioequivalence (orange) are being submitted via overnight courier.

If there are any questions concerning this submission, please contact me at 954-315-6502.

Thank you.

Sincerely,

RECEIVED
MAR 21 2008
OGD

Monique Weitz
Senior Director, Project and Site Management
Actavis South Atlantic LLC

Attachment 1
Responses to Requested Information

Due to concern that some extended-release drug products may release drug quickly ("dose dumping") when ingested with alcoholic beverages, the Agency currently requests that you 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 alcohol:*

- ***Test 1:*** *12 units of the drug products tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours.*
- ***Test 2:*** *12 units of the drug products analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collected every 15 minutes for a total of 2 hours.*
- ***Test 3:*** *12 units of the drug products analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collected every 15 minutes for a total of 2 hours.*
- ***Test 4:*** *12 units of the drug products analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.*

Please submit standard operating procedures (SOPs) for the dissolution testing above, individual dissolution data, mean values, standard deviations, coefficient of variation (CV%), and plots of the percent dissolved data.

We ask that these studies be performed as post-approval commitments, and completed within 6 months of approval.

Please acknowledge your agreement to perform the aforementioned dissolution studies.

Response:

Actavis acknowledges and agrees to completing and submitting the above studies within six months of approval of our ANDA 77-285, Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg.

actavis
creating value in pharmaceuticals

March 19, 2008

NEW CORRESP
N/XA

Thomas Hinchliffe, Pharm.D.
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
7500 Standish Place
Room East 150
Rockville, MD 20855

RECEIVED
MAR 20 2008
OGD

Reference: New Correspondence – Name Change

Dear Mr. Hinchliffe:

This new correspondence is being submitted to notify FDA that Abrika Pharmaceuticals, Inc. was purchased by Actavis Group, hf on April 18, 2007. The name change to Actavis South Atlantic LLC (Actavis) was certified on May 11, 2007.

This name change affects the following ANDA's which were submitted under the Abrika Pharmaceuticals, Inc. name and registration:

ANDA	Product Name
77-062	Fentanyl Transdermal System 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr
77-285	Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg
77-455	Bupropion Hydrochloride Extended-Release Tablets, USP (SR), 150 mg
77-475	Bupropion Hydrochloride Extended-Release Tablets, USP (SR), 150 mg
77-899	Nifedipine Extended-Release Tablets, 30 mg and 60 mg
[redacted]	[redacted]

b(4)

The following ANDA's were submitted under the Actavis South Atlantic, LLC name and registration, with reference throughout to the Abrika Pharmaceuticals, Inc. name:

ANDA	Product Name
[redacted]	[redacted]

b(4)

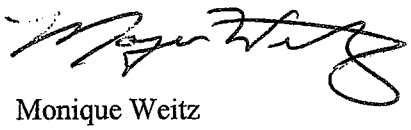
Per a conversation between Christina Provo of Actavis and Thomas Hinchliffe of FDA on March 14, 2008, this New Correspondence consists of one archival (blue) hard copy for each ANDA listed above, which will be sent via courier. In addition, one CDROM will be sent which contains the electronic copies of the 356h forms for each of the above listed ANDAs. The CDROM is being sent in a separate jacket labeled *New Correspondence, Electronic Copy* with the original copy of this cover letter. The size of the electronic

Actavis SouthAtlantic LLC | 13800 NW 2nd Street, #190 Sunrise, FL 33325 | t (+1) 954 315 6600 f (+1) 954 315 6601 | www.actavis.com

submission is approximately 6 MB. The files are free of viruses as determined by using Trend Micro™OfficeScan™ Version 7.3 (virus definition date March19, 2008).

If there are any questions concerning this submission, please contact me at 954-315-6600.

Thank you,



Monique Weitz
Senior Director, Project and Site Management
Actavis South Atlantic LLC

MINOR AMENDMENT

ANDA 77-285

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: Abrika Pharmaceuticals LLLP TEL: 954-315-6502

ATTN: Monique Weitz FAX: 954-315-6601

FROM: Thomas Hinchliffe PROJECT MANAGER: (301) 827-5771

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated September 23, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Tablets, 150 mg and 300 mg.

Reference is also made to your amendment dated April 27, 2007.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (____ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

In an effort to improve document flow and availability to review staff, please submit your response in electronic PDF format, with a signed cover letter and 356h form.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-285
APPLICANT: Abrika Pharmaceuticals, Inc.
DRUG PRODUCT: Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg

The major amendment dated April 27, 2007 has been reviewed, and the following deficiencies presented below represents minor deficiencies:

A. Deficiencies:

1. There are a number of places where the drug product "[redacted] appears instead of "Bupropion Hydrochloride Extended-Release Tablets". Please correct the mistake where necessary. b(4)

2. Regarding the raw materials controls:

   - Please provide a full testing of the raw material Hydrochloric acid NF (Mfr. lot# C40046) per the monograph specifications.
   - The [redacted] (Mfr. lot# WP252277) is not tested in accordance with the in-house specifications. Please provide complete test data for the [redacted] material. b(4)
   - Please provide a clear copy of the manufacturer's COA for Colloidal Silicon dioxide NF [redacted] (Mfr. lot# 550442). b(4)

3. The facility at [redacted], was previously proposed as a packaging site of the drug product. Please clarify if [redacted] will be used for any future commercial production batches.

4. Low [redacted] yield [redacted] and [redacted] yield [redacted], were observed for the 300 mg strength, and low packaging yields (below [redacted]) were reported for both the 150 mg and 300 mg tablets packaged in the bottles of 30's and 90's. Please explain/discuss. b(4)

5. Please provide an LOA for DMF [redacted] for the [redacted] b(4)

6. Please provide test data for the HDPE bottles and the [redacted] caps from [redacted] per the USP <661> and <671> requirements. b(4)

7. Out-of-specification results were observed for Tablet Thickness for the [redacted] of the 300 mg (lot# CM6CY03P33). Please provide explanation/discussion for the OOS results. b(4)

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

1. The Division of Bioequivalence has requested that you conduct additional dissolution testing to address the potential "dose dumping" issue.

2. Please provide available long-term controlled room temperature stability data for the drug product.

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
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/

Naiqi Ya
11/1/2007 01:31:27 PM
for Florence S. Fang

actavis
creating value in pharmaceuticals

ORIGINAL

August 07, 2007

Thomas Hinchliffe, Pharm.D.
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Central Document Room
7500 Standish Place
Room East 150
Rockville, MD 20855

ORIG AMENDMENT
N / XP

Reference: ANDA 77-285
Bupropion Hydrochloride Extended-Release Tablets, (XL), 150 mg and 300 mg
Patent Amendment; Final Judgment

Dear Mr. Hinchliffe:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, which were submitted to the Agency on September 23, 2004 and October 1, 2004, respectively.

This Patent Amendment is being submitted per 21 CFR 314.107(e) to notify FDA of Final Judgment received in the lawsuit of Biovail Laboratories International SRL vs Abrika, LLP Case Number 04-61704-CIV-ALTONAGA/Bandstra. The Order of Dimissal with Prejudice is located in Attachment 1 to this cover letter.

Please note that the original ANDA was submitted in the name Abrika, LLLP. Abrika, LLLP was purchased by Actavis Group, hf on April 18, 2007. The name change to Actavis South Atlantic, LLC was certified on May 11, 2007.

One Archival (blue) copy of this amendment is being provided to the Agency.

If there are any questions concerning this submission, please contact me at 954-315-6600.

Thank you.

Sincerely,
for Monique Weitz

RECEIVED
AUG 08 2007
OGD

Monique Weitz
Director, Regulatory Affairs / Project Management
Actavis South Atlantic, LLC

BIOEQUIVALENCY AMENDMENT

ANDA 77-285

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: Abrika Pharmaceuticals TEL: 954-315-6502

ATTN: Monique Weitz FAX: 954-315-6601

FROM: Keri Suh PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on September 23, 2004, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Extended Release Tablets, 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 __two__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCY

ANDA: 77-285 APPLICANT: Abrika

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

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

Due to concern that some extended-release drug products may release drug quickly ("dose dumping") if ingested with alcoholic beverages, the Agency currently requests that you conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL of 0.1 N HCl using apparatus I (basket) at 75 rpm, with and without alcohol:

Test 1: 12 units of the drug products analyzed according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units of the drug products analyzed by substituting 5% (v/v) of test medium with Alcohol USP, with data collected every 15 minutes for a total of 2 hours.

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

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

Please submit standard operating procedures (SOPs) for the dissolution testing above, individual dissolution data, mean values, standard deviations, coefficient of variation (CV%), and plots of the percent dissolved data.

We ask that these studies be performed as post-approval commitments, and completed within 6 months of approval.

Please acknowledge your agreement to perform the aforementioned dissolution studies.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
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/

Barbara Davit
6/29/2007 05:12:38 PM

ABRIKA
PHARMACEUTICALS

April 27, 2007

Thomas Hinchliffe, Pharm.D.
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Central Document Room
7500 Standish Place
Room East 150
Rockville, MD 20855

ORIG AMENDMENT
N/A C

Reference: ANDA 77-285
Bupropion Hydrochloride Extended-Release Tablets, (XL), 150 mg and 300 mg
Major Amendment Response; Packager Site & Container/Closure Change

Dear Mr. Hinchliffe:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, which were submitted to the Agency on September 23, 2004 and October 1, 2004, respectively.

This Major Amendment is based upon the letter received by Abrika on April 26, 2006 and a Packager Site and Container/Closure Change. Please see section 1.12, Other Correspondence, for a copy of the Major Amendment facsimile and related correspondences between Abrika and FDA. Please find in Section 1.12.11, Basis for Submission, a summary of the investigation based on the major amendment received.

This amendment is organized in Common Technical Document (CTD) format and consists of a total of 5 paper volumes. Four copies of the ANDA are being provided to the Agency: the Archival (blue), Review [Chemistry (red) and Bioequivalence (orange)], and Field (burgundy) copies. The volumes associated with each copy are listed in the following table. In accordance with 21 CFR 314.94, the Field Copy of the amendment has been submitted to the appropriate FDA District Office in Maitland, Florida. For the convenience of the Reviewer, a copy of the Comprehensive Table of Contents (Section 1.2) is included at the beginning of each volume.

Module	Number of Volumes per Module	Archival Copy	Review Copy		Field Copy[a]
		Blue Binder	Red Binder (Chemistry)	Orange Binder (Bioequivalence)	Burgundy Binder
Module 1	1	X	X	X	X
Module 2	1	X	X	X	
Module 3	3	X	X		X
Total Volumes	5	5	5	2	4
[a] = Field Copy has been sent to FDA District Office in Maitland, Florida					

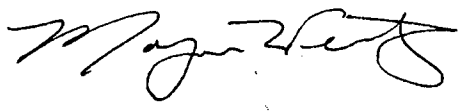
RECEIVED
APR 30 2007
OGD / CDER

13800 N.W. 2nd St • Suite 190 • Sunrise, Florida 33325 • Phone: 954-315-6600 • Fax: 954-315-6601

If there are any questions concerning this submission, please contact me at 954-315-6600.

Thank you.

Sincerely,



Monique Weitz
Director, Regulatory Affairs / Project Management
Abrika Pharmaceuticals, Inc.

ABRIKA
PHARMACEUTICALS

October 6, 2006

Thomas Hinchliffe, Pharm. D., Project Manager
Division of Chemistry II, Team 10
Office of Generic Drug Products
Food and Drug Administration
HFD-600
Metro Park North 2
7500 Standish Place
Rockville, MD 20855

RE: **NEW CORRESPONDENCE**
ANDA # 77-285, Bupropion Hydrochloride Extended-Release Tablets. 150 mg and 300 mg Major Deficiency Response Received on April 26, 2006
ANDA # 77-455, Bupropion Hydrochloride Extended-Release Tablets ——— 150 mg and ——— Major Deficiency Response Received on April 26, 2006 b(4)
ANDA # 77-475, Bupropion Hydrochloride Extended-Release Tablets. 150 mg Major Deficiency Response Received on April 26, 2006

Dear Mr. Hinchliffe:

Abrika Pharmaceuticals Inc. acknowledges the April 26, 2006 receipt of the three major deficiency letters for ANDAs, # 77-285, # 77-455, # 77-475 as listed above and would like to inform you that we are compiling the information to appropriately respond.

We anticipate responding to:

- ANDA # 77-285 in April 2007
- ANDA # 77-455 in October 2006
- ANDA # 77-475 in November 2006

Best regards,

Monique Weitz
Director, Regulatory Affairs / Project Management
Abrika Pharmaceuticals, Inc.

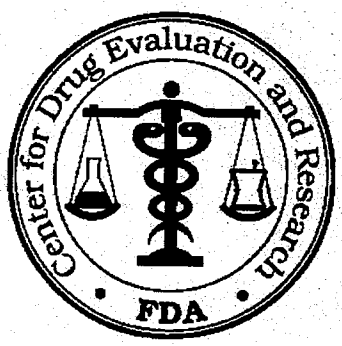
13800 N.W. 2nd St • Suite 190 • Sunrise, Florida 33325 • Phone: 954-315-6600 • Fax: 954-315-6601

MAJOR AMENDMENT

ANDA 77-285

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)

APR 2 6 2006



APPLICANT: Abrika Pharmaceuticals LLP TEL: 954-315-6600

ATTN: Monique Weitz FAX: 954-315-6601

FROM: Thomas Hinchliffe PROJECT MANAGER: (301) 827-5771

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 20, 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.

Reference is also made to your amendment dated June 28, 2005; February 15, 2006; and March 14, 2006.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__1__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

Chemistry comments provided here.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-285

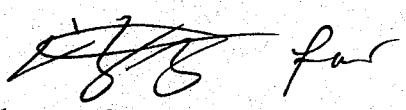
APPLICANT: Abrika Pharmaceuticals, Inc.

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

The deficiency presented below represents a MAJOR deficiency.

We have reviewed all available stability data you provided for Bupropion Hydrochloride Extended-Release Tablets USP, 150 mg and 300 mg, and concluded that the drug product failed to meet the dissolution specification recommended by the Division of Bioequivalence in the accelerated, intermediate, and long-term stability studies. The dissolution failures, upon which you have not provided any investigation report, may be indications of problems in the drug formulation and/or manufacturing process. Therefore, the drug product is not recommended for approval for marketing in its current formula. It is recommended that a new drug product batch be manufactured to address the dissolution failures. Supporting documents and data in Chemistry, manufacturing and Controls should be provided for the drug product, along with a minimum of three months of accelerated stability data.

Sincerely yours,



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

ABRIKA
PHARMACEUTICALS

ORIG AMENDMENT

N/Am

March 14, 2006

Thomas Hinchliffe, Pharm.D.
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

Re: Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg
ANDA 77-285
MINOR AMENDMENT

Mr. Hinchliffe:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, which were submitted to the Agency on September 23, 2004 and October 1, 2004, respectively. Reference is also made to our Chemistry Telephone Amendment submitted on February 15, 2006 and our Labeling Amendment submitted on July 8, 2005. In accord with 21 CFR 314.96, we are amending this application to provide information which you requested via facsimile.

Minor deficiency comments from FDA's February 27, 2006 telefax are provided in Attachment I in italicized text with responses from Abrika following each comment in normal bold text. A copy of the telefax is provided after this transmittal letter for ease of review.

This Minor Amendment consists of one volume; three hard copies, archival (blue), review-chemistry (red) and field (maroon) have been sent via courier. The field copy of the technical section of the ANDA Amendment has been sent directly to the Maitland, Florida, FDA District Office. Please note an updated field copy certification is provided.

If there are any questions concerning this submission, please contact me at (954) 315-6600.

Thank you.

Sincerely,

Monique Weitz
Director, Regulatory Affairs / PM
Abrika Pharmaceuticals

RECEIVED
MAR 15 2006
OGD / CDER

MINOR AMENDMENT

ANDA 77-285

FEB 27 2006

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: Abrika Pharmaceuticals LLLP TEL: 954-315-6502

ATTN: Monique Weitz FAX: 954-315-6601

FROM: Thomas Hinchliffe PROJECT MANAGER: (301) 827-5771

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated September 23, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Tablets, 150 mg and 300 mg.

Reference is also made to your amendments dated April 14, 2005; September 28, 2005; and February 15, 2006.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__2__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
CMC comments provided.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-285

APPLICANT: Abrika Pharmaceuticals, Inc.

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

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please discuss and/or explain in detail the significant trend in the amount of drug product released in 8 and/or 16 hours observed for the drug product stored at both the intermediate (30°C/60%RH) and long term controlled room temperature (CRT) stability conditions (25°C/60% RH). [redacted] b(4) lease provide an investigation report for the out-of-specification dissolution data.

2. The proposed -- month expiry for the drug product is not justified based on available long term stability data for the drug product packaged in the 30's [redacted] configurations. Please revise the expiration dating for the drug product. b(4)

3. [redacted] b(4) Please revise your post-approval stability protocol to reflect the proposed change. We would also remind you that the drug product labeling should also be revised to reflect the change.

Sincerely yours,

for

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

ABRIKA
PHARMACEUTICALS

FACSIMILE TRANSMITTAL SHEET

TO: Thomas Hinchliffe	FROM: Monique Weitz
COMPANY: FDA	DATE: 2/15/2006
FAX NUMBER: 301-443-3839	TOTAL NO. OF PAGES INCLUDING COVER: 43
PHONE NUMBER:	SENDER'S REFERENCE NUMBER: N/A
RE: ANDA 77-285	YOUR REFERENCE NUMBER: N/A

☐ URGENT ☐ FOR REVIEW ☐ PLEASE COMMENT ☐ PLEASE REPLY ☐ PLEASE RECYCLE

NOTES/COMMENTS:

Tom,

Please find attached a facsimile copy of Abrika Pharmaceuticals Telephone Amendment for Bupropion Hydrochloride Extended-Release Tablets (XL) based on a facsimile call on February 14, 2006. A hard copy is being sent via courier for delivery on February 16, 2006.

Kind Regards,
Monique Weitz

FDA FAX

ANDA 77-285

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: Abrika Pharmaceuticals LLLP

TEL: 954-315-6502

ATTN: Monique Weitz

FAX: 954-315-6601

FROM: Thomas Hinchliffe

PROJECT MANAGER: (301) 827-5771

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated September 23, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Tablets, 150 mg and 300 mg.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

*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.*

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-285

APPLICANT: Abrika 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. You have accepted the following dissolution method and acceptance criteria recommended by the Division of Bioequivalence:

Stage I: Acid stage

Medium:	750 ml of 0.1N HCl
Apparatus:	USP Paddle
Rotation Speed:	50 rpm
Specification:	——— (Q) of the labeled amount of bupropion in the dosage form is dissolved in 120 minutes.

b(4)

Stage II: Buffer stage

Medium:	pH 6.8 Sodium Phosphate buffer, 0.05M
Volume:	1000 ml (250 ml of 0.20 M tribasic sodium phosphate added to the acid stage media, adjust pH if necessary)
Apparatus:	USP Paddle
Rotation Speed:	50 rpm
Specification:	3 hours: ——— 8 hours: ——— 16 hours: ———

b(4)

Please revise the dissolution specification for the drug product release and stability testing accordingly.

2. The dissolution data provided for the drug product stored at both the intermediate (30°C/60%RH) and the long term controlled room temperature

(CRT) stability conditions (25°C/60%RH) show significant trends in the amount of drug product released in 8 and/or 16 hours, and out-of-specification data are observed at 9 and/or 12 months test points at the intermediate (30°C/60%RH) storage condition. Please discuss.

3. Since the dissolution data from the accelerated and intermediate stability studies failed the dissolution acceptance criteria, the expiration dating of the drug product can only be supported by long term (CRT) stability data. Please revise your proposed expiry of the drug product based on available long term data.

4. Please update the post-approval stability protocol for the drug product in accordance with the revised drug product stability specification.

ABRIKA
PHARMACEUTICALS

ORIG AMENDMENT
N/AM

February 15, 2006

Thomas Hinchliffe, Pharm.D.
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

Re: Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg
ANDA 77-285
Chemistry Telephone Amendment

Mr. Hinchliffe:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, which were submitted to the Agency on September 23, 2004 and October 1, 2004, respectively. In accord with 21 CFR 314.96, we are amending this application to provide information which you requested via facsimile.

Chemistry telephone deficiency comments from FDA's February 14, 2006 telefax are provided in italicized text with responses from Abrika following each comment in normal text. A copy of the telefax is provided after this transmittal letter for ease of review.

This Telephone Amendment consists of one volume; four hard copies, archival (blue), review-bioequivalence (orange), review-chemistry (red) and field (maroon) will be sent via courier. The field copy of the technical section of the ANDA Amendment has been sent directly to the Maitland, Florida, FDA District Office. Please note an updated field copy certification is provided.

If there are any questions concerning this submission, please contact me at (954) 315-6600.

Thank you.

Sincerely,

Monique Weitz
Director, Regulatory Affairs / PM
Abrika Pharmaceuticals

RECEIVED
FEB 16 2006
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ABRIKA
PHARMACEUTICALS

February 15, 2006

Food and Drug Administration
District Office
555 Winderley Place
Maitland, FL 32751

Re: Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg
ANDA 77-285
Chemistry Telephone Amendment

Dear Sir/Madam:

Pursuant to the requirements in 21 CFR 314.94(d)(5), and concurrent with the filing of our original telephone amendment for ANDA 77-285, enclosed please find the "Field Copy" in support of Abrika Pharmaceuticals' ANDA Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg. The Field Copy contains:

- A Field Copy Certification
- A true copy of the Form FDA 356h filed with the subject ANDA
- A true copy of the Technical Sections provided in the submission of the subject ANDA

Abrika commits to providing any updated information to the District Office as appropriate.

Please direct any questions to:

Monique Weitz, Director
Abrika Pharmaceuticals
13800 N.W. 2nd Street, Suite 190
Sunrise, Florida 33325
Telephone: 954-313-6600 Fax: 954-315-6500

Thank you.

Sincerely,

Monique Weitz,
Director Regulatory Affairs/Project Management
Abrika Pharmaceuticals

ABRIKA PHARMACEUTICALS

February 15, 2006

Food and Drug Administration
District Office
555 Winderley Place
Maitland, FL 32751

Re: Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg
ANDA 77-285
Chemistry Telephone Amendment

Dear Sir/Madam:

Pursuant to the requirements in 21 CFR 314.94(d)(5), and concurrent with the filing of our original telephone amendment for ANDA 77-285, enclosed please find the "Field Copy" in support of Abrika Pharmaceuticals' ANDA Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg. The Field Copy contains:

- A Field Copy Certification
- A true copy of the Form FDA 356h filed with the subject ANDA
- A true copy of the Technical Sections provided in the submission of the subject ANDA

Abrika commits to providing any updated information to the District Office as appropriate.

Please direct any questions to:

Monique Weitz, Director
Abrika Pharmaceuticals
13800 N.W. 2nd Street, Suite 190
Sunrise, Florida 33325
Telephone: 954-313-6600 Fax: 954-315-6500

Thank you.

Sincerely,

Monique Weitz,
Director Regulatory Affairs/Project Management
Abrika Pharmaceuticals

ABRIKA
PHARMACEUTICALS

December 21, 2005

ORIG AMENDMENT
N/A

Aaron Sigler, Pharm. D.
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg
ANDA 77-285
Bioequivalency Amendment

Mr. Sigler:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, which was submitted to the Agency on September 29, 2004.

Reference is made the conversations between Monique Weitz and David Zhao, Ph.D. of Abrika Pharmaceuticals and Aaron Sigler, Pharm.D., Ethan Shire, Pharm.D., and Daniel Tran of the Division of Bioequivalence on December 20, 2005 and December 21, 2005.

Abrika Pharmaceuticals has provided complete responses to the items discussed in the above conversations in attachment 1. To aid in the review of this information, we have listed the specific items in italics followed by the response in bold.

This Bioequivalency Amendment consists of one volume. Three hard copies (chemistry, archive, and reviewer copies) are being sent via courier.

If there are any questions concerning this submission, please contact me at (954) 315-6600.

Thank you.

Sincerely,

Monique Weitz
Director, Regulatory Affairs / Project Management
Abrika Pharmaceuticals

RECEIVED
DEC 27 2005
OGD/CDER

cc: Thomas Hinchliffe, Pharm.D.

13800 N.W. 2nd St • Suite 190 • Sunrise, Florida 33325 • Phone: 954-315-6600 • Fax: 954-315-6601

ABRIKA
PHARMACEUTICALS

ORIG AMENDMENT
N/AB

December 7, 2005

Thomas Hinchliffe, Pharm. D.
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: Bupropion Hydrochloride Extended-Release Tablets 150 mg and 300 mg
ANDA 77-285
Bioequivalency Amendment

Mr. Hinchliffe:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets 150 mg and 300 mg, which was submitted to the Agency on September 29, 2004.

Reference is made to the Bioequivalency Deficiency telefax that was issued to Abrika Pharmaceuticals on December 6, 2005. A copy of the December 6th facsimile is included for your convenience.

Abrika Pharmaceuticals has provided complete responses to the items listed in the December 6th facsimile in Attachment 1. To aid in the review of this information, we have listed the specific items in italics followed by the response in bold. These responses reference various sections in the ANDA updated in this Amendment. A Comprehensive Table of Contents for this Amendment is provided in Section I., which lists all of the sections that have been revised and are included in this Amendment.

This Bioequivalency Amendment consists of one volume. Three hard copies (chemistry, archive and reviewer copies) are being sent via courier.

If there are any questions concerning this submission, please contact me at (954) 315-6600.

Thank you.

Sincerely,

Monique Weitz
Director, Regulatory Affairs / Project Management
Abrika Pharmaceuticals

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DEC 08 2005
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13800 N.W. 2nd St • Suite 190 • Sunrise, Florida 33325 • Phone: 954-315-6600 • Fax: 954-315-6601

Attachment 1
Responses to Requested Information

The following pieces of information were not found in the submitted application, and they are requested for completeness of our review of your application:

a) the potency of the RLD batch

Response:

A copy of the Certificate of Analysis for the Reference Listed Drug (RLD) that was used in the bioequivalence study, which contains the potency is included. See SECTION VI. Bioavailability/Bioequivalence.

b) the content uniformity of the test product

Response:

A copy of the Certificate of Analysis for the Test Product that was used in the bioequivalence study, which contains the content uniformity is included. See SECTION VI. Bioavailability/Bioequivalence.

c) the dates of analysis (e.g. starting and ending dates) for plasma samples

Response:

The dates of analysis for plasma samples were July 31, 2004 to August 12, 2004 for Project No. 40140 and August 7, 2004 to August 28, 2004 for Project No. 40140. See SECTION VI. Bioavailability/Bioequivalence.

d) a detailed SOP describing your proposed in vitro dissolution method

Response:

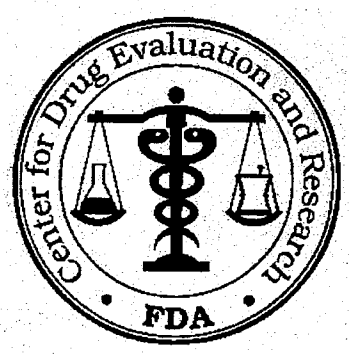
A detailed STP (SOP), STP-031-03, Drug Release and UV Analysis for 150 mg and 300 mg Bupropion HCL Extended-Release Tablets (QD) describing our proposed in vitro dissolution method has been provided. See SECTION VI. Bioavailability/Bioequivalence.

BIOEQUIVALENCY AMENDMENT

ANDA 77-285

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)

DEC 0 6 2005



APPLICANT: Abrika Pharmaceuticals LLP TEL: 954-315-6600

ATTN: Monique Weitz FAX: 954-315-6601

FROM: Keri Suh PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on September ~~29~~ 23, 2004, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion HCl ER Tablets, 150 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 __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:

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-285 APPLICANT: Abrika

DRUG PRODUCT: Bupropion XL Tablet
150 mg and 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:

The following pieces of information were not found in the submitted application, and they are requested for completeness of our review of your application:

a) the potency of the RLD batch

b) the content uniformity of the test product

c) the dates of analysis (e.g. starting and ending dates) for plasma samples

d) a detailed SOP describing your proposed in vitro dissolution method

Sincerely yours,

Barbara M Davit for

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

ABRIKA
PHARMACEUTICALS

October 6, 2006

Thomas Hinchliffe, Pharm. D., Project Manager
Division of Chemistry II, Team 10
Office of Generic Drug Products
Food and Drug Administration
HFD-600
Metro Park North 2
7500 Standish Place
Rockville, MD 20855

RECEIVED
OCT 1 0 2006
OGD / CDER

MC.

RE: **NEW CORRESPONDENCE**
ANDA # 77-285, Bupropion Hydrochloride Extended-Release Tablets. 150 mg and 300 mg Major Deficiency Response Received on April 26, 2006
ANDA # 77-455, Bupropion Hydrochloride Extended-Release Tablets. [redacted] 150 mg and [redacted] Major Deficiency Response Received on April 26, 2006 b(4)
ANDA # 77-475, Bupropion Hydrochloride Extended-Release Tablets. 150 mg Major Deficiency Response Received on April 26, 2006

Dear Mr. Hinchliffe:

Abrika Pharmaceuticals Inc. acknowledges the April 26, 2006 receipt of the three major deficiency letters for ANDAs, # 77-285, # 77-455, # 77-475 as listed above and would like to inform you that we are compiling the information to appropriately respond.

We anticipate responding to:

- ANDA # 77-285 in April 2007
- ANDA # 77-455 in October 2006
- ANDA # 77-475 in November 2006

Best regards,

Monique Weitz
Director, Regulatory Affairs / Project Management
Abrika Pharmaceuticals, Inc.

13800 N.W. 2nd St • Suite 190 • Sunrise, Florida 33325 • Phone: 954-315-6600 • Fax: 954-315-6601

8.1

rmaceuticals
3800 N.W. 2nd Street, Suite 190
Sunrise, Florida 33325
Ph. 954-315-6600
Fax 954-315-6601

ABRIKA PHARMACEUTICALS

B,MS

Fax

To:	Thomas Hinchliffe	**From:**	Monique Weitz
Fax:	(301) 443-3839	**Date:**	September 28, 2005
Phone:	(301) 827-5771	**Pages:**	67 , including cover
Re:	ANDA # 77-285 Chemistry Minor Telephone Amendment	**CC:**	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

•Comments:

Thomas,

Hello!

Please find attached Abrika's response to ANDA # 77-285 Chemistry Minor Telephone Amendment dated September 21, 2005.

Please note that for the insert only the page that contained the labeling change (site of manufacturer) is included in this facsimile. The entire comparison (no other changes were made) will be included in the hard copy and electronically that will be sent out tomorrow via FedEx.

Also, Final Printed Labeling (FPL) cannot be faxed; therefore, FPL will be included in the hard copy to also be sent via FedEx tomorrow.

You should receive the hard copy with the FPL and electronic labeling on Friday, September 30, 2005.

Kind Regards,
Monique Weitz

ABRIKA PHARMACEUTICALS

September 28, 2005

Thomas Hinchliffe, Pharm.D.
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

Re: Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg
ANDA 77-285
Chemistry Minor Telephone Amendment

Mr. Hinchliffe:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, which were submitted to the Agency on September 23, 2004 and October 1, 2004, respectively and telephone amendment submitted on October 25, 2004. In accord with 21 CFR 314.96, we are amending this application to provide information which you requested via facsimile.

Chemistry Minor deficiency comments from FDA's September 21 2005 telefax are provided in italicized text with responses from Abrika following each comment in normal text. A copy of the telefax is provided after this transmittal letter for ease of review.

This Telephone Amendment consists of one volume; four hard copies, archival (blue), review (orange), chemistry (red) and CDROM will be sent via courier. The field copy of the technical section of the ANDA Amendment has been sent directly to the Maitland, Florida, FDA District Office. Please note an updated field copy certification is provided.

The final printed labeling for Bupropion HCL Extended-Release Tablets (XL), 150 mg and 300 mg container labels and package inserts have been provided. In accordance with the December 11, 2003, electronic labeling rule, the final printed labeling for the container labels and package insert are also being provided electronically as Adobe Acrobat PDF files and corresponding Microsoft Word files. The size of the electronic submission is approximately 2 M. The files are free of viruses as determined by using Symantec Antivirus Corporate Edition 8.0 virus definition date September 28, 2005

If there are any questions concerning this submission, please contact me at (954) 315-6600.

Thank you.

Sincerely,

Monique Weitz
Director, Regulatory Affairs / PM
Abrika Pharmaceuticals

MINOR AMENDMENT

ANDA 77285

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: Abrika Pharmaceuticals LLP TEL: 954-315-6600

ATTN: Monique Weitz FAX: 954-315-6601

FROM: Thomas Hinchliffe PROJECT MANAGER: (301) 827-5771

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated September 29, 2004, submitted pursuant to Section 505(J) of the Federal Food, Drug, and Cosmetic Act for Bupropion HCl ER Tablets, 150 and 300 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__1__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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.

SPECIAL INSTRUCTIONS:

CHEMISTRY REVIEW

Chemistry Assessment Section

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-285

APPLICANT: Abrika 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. Please revise the Drug Release specifications in accordance with the USP monograph Test 1 for the release and stability testing of Bupropion Hydrochloride Extended-Release Tablets, as recommended by the Division of Bioequivalence, and provide test data accordingly.

2. It is recommended that you provide a test limit for Moisture in the stability specification for the drug product based on the stability data.

3. Please provide available long-term controlled room temperature stability data for the drug product.

4. The name and address of the manufacturer provided in the labeling amendment dated July 8, 2005 is actually for a contract analytical facility ———, not the manufacturing facility at ——————. Please revise the labeling accordingly. b(4)

ABRIKA
PHARMACEUTICALS

July 8, 2005

ORIG AMENDMENT
N/AF

Thomas Hinchliffe, Pharm.D.
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

Re: Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg
ANDA 77-285
LABELING AMENDMENT

Mr. Hinchliffe:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg, which were submitted to the Agency on September 23, 2004 and October 1, 2004, respectively and telephone amendment submitted on October 25, 2004. In accord with 21 CFR 314.96, we are amending this application to provide information which you requested via facsimile.

Labeling deficiency comments from FDA's June 9, 2005 telefax are provided in italicized text with responses from Abrika following each comment in normal text. A copy of the telefax is provided after this transmittal letter for ease of review.

This Labeling Amendment consists of one volume; two hard copies, archival (blue), review (orange), and CDROM will be sent via courier.

The final printed labeling for Bupropion HCL Extended-Release Tablets (XL), 150 mg and 300 mg container labels and package inserts have been provided. In accordance with the December 11, 2003, electronic labeling rule, the final printed labeling for the container labels and package insert are also being provided electronically as Adobe Acrobat PDF files and corresponding Microsoft Word files. The size of the electronic submission is approximately 2 M. The files are free of viruses as determined by using Norton Antivirus Corporate Edition 8.0 (virus definition date July 8, 2005.

If there are any questions concerning this submission, please contact me at (954) 315-6600.

Thank you.

Sincerely,

Monique Weitz
Director, Regulatory Affairs / PM
Abrika Pharmaceuticals LLLP

RECEIVED
JUL 11 2005
OGD/CDER

13800 N.W. 2nd St • Suite 190 • Sunrise, Florida 33325 • Phone: 954-315-6600 • Fax: 954-315-6601

Attachment 1
Responses to Requested Information

GENERAL

- *The Division of Neruopharmacological Drug Products and the Office of New Drug Evaluation 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.*

Response:
Abrika acknowledges the determination of the Division of Neruopharmacological Drug Products and the Office of New Drug Evaluation, and commits to dispense Bupropion Hydrochloride Extended-Release Tablets based on one month's unit-of-use configuration of 30 tablets b(4) **In addition, a medication guide (MedGuide) has been added to the Prescribing Information on the insert, which will be affixed to the container that comprises of a child-resistant closure.**

- *Please 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

XXX Tablets Rx only

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

Response:
The principal display panel has been reformatted to include the information shown above.

- *Put "ATTENTION: Dispense with Medication Guide" on the side display panel if it's not possible to put it on the principal display panel due to space limitation.*

Response:
"ATTENTION: Dispense with Medication Guide" has been added to the side display panel because of space limitation on the principal display panel.

- *Revise the storage temperature recommendation as follows:*

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

Response:
The storage recommendation has been revised to the following: "Store at 20° - 25°C (68° - 77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]"

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

- *See comment under **GENERAL***

"The Division of Neruopharmacological Drug Products and the Office of New Drug Evaluation 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."

Response:
Abrika acknowledges the determination of the Division of Neruopharmacological Drug Products and the Office of New Drug Evaluation, and commits to dispense Bupropion Hydrochloride Extended-Release Tablets based on one month's unit-of-use configuration of 30 tablets b(4)

PHYSICIAN INSERT

- *See comment under **GENERAL***

"The Division of Neruopharmacological Drug Products and the Office of New Drug Evaluation 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."

Response:
Abrika acknowledges the determination of the Division of Neruopharmacological Drug Products and the Office of New Drug Evaluation, and a medication guide (Med Guide) has been added to the Prescribing Information on the insert, which will be affixed to the container that comprises of a child-resistant closure.

- *Update your insert labeling based on the attached approved labeling for the reference listed drug, Wellbutrin XL. Please note that all antidepressants are now required to be dispensed with a medication guide, and we need you to submit your proposal for dissemination of the medication guide for review.*

Response:
Abrika acknowledges that the medication guide (MedGuide) is to be dispensed with the unit-of-use container. The approved labeling for the reference listed drug, Wellbutrin XL® was not attached to the facsimile so Abrika took the currently approved labeling from FDA's website and made the changes to our Physician Insert using that material as a reference, and submits the attached as the proposed plan for dissemination of the medication guide.

ABRIKA
PHARMACEUTICALS

June 14, 2005

Thomas Hinchliffe, Pharm. D.
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: Bupropion Hydrochloride Extended-Release Tablets 150 mg and 300 mg
ANDA 77-285
Bioequivalency Amendment

Mr. Hinchliffe:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets 150 mg and 300 mg, which was submitted to the Agency on September 29, 2004 and Chemistry Amendment dated April 14, 2005.

Reference is made to Controlled Correspondence Reference Number: OGD #04-854 received on November 18, 2004.

Reference is made to the Minor Amendment Bioequivalency Deficiency telefax that was issued to Abrika Pharmaceuticals LLLP on June 2, 2005, received on June 6, 2005. A copy of the June 2nd letter is included for your convenience.

Abrika Pharmaceuticals has provided complete responses to the items listed in the June 2nd letter in Attachment 1. To aid in the review of this information, we have listed the specific items in italics followed by the response. These responses reference various sections in the ANDA updated in this Amendment. A Comprehensive Table of Contents for this Amendment is provided in Section I., which lists all of the sections that have been revised and are included in this Amendment.

In addition to the requested items, Abrika is including SFBC Final Clinical Study Report Amendments for Projects 40140 and 40141.

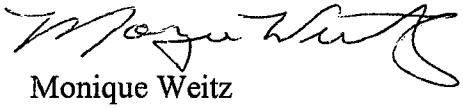
This Bioequivalency Amendment consists of one volume. Two hard copies (archive and reviewer copies) are being sent via courier.

13800 N.W. 2nd St • Suite 190 • Sunrise, Florida 33325 • Phone: 954-315-6600 • Fax: 954-315-6601

If there are any questions concerning this submission, please contact me at (954) 315-6600.

Thank you.

Sincerely,



Monique Weitz
Director, Regulatory Affairs
Abrika Pharmaceuticals LLLP

Enclosure

Attachment 1
Responses to Requested Information

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

Medium: *water*
Volume: *900 mL*
Temperature: *37°C*
Apparatus: *Apparatus II (paddles)*
Rotation: *50 RPM*
Specification: [redacted] *in 1 hour*
[redacted] *in 4 hours* b(4)
[redacted] *in 8 hours*

Response:

Monique Weitz had telephone conversation with Keri Suh on June 8, 2005 in which Ms. Suh stated that the Reviewer and Division Director had a meeting on June 7th with a final decision that Abrika did not need to repeat the dissolution as stated in this deficiency letter. Instead, FDA will review the information that Abrika had submitted the comparative disso studies in the April 14, 2005 Chemistry Amendment, Section VI, Table 4, specifically 4a, which included dissolution condition using USP apparatus I (baskets) at 75 rpm in Water (900 mL).

Background information: The dissolution condition using apparatus II (paddle) with rotation speed of 50 rpm is similar or equivalent to apparatus I (basket) with rotation speed of 75 rpm. Therefore, we believe the dissolution data provided in *Table1 Summary Dissolution Test Results for USP apparatus I (basket) at 75 rpm in Water* under Section VI in this amendment should provide sufficient information requested in your letter dated June 02, 2005. As shown in the table, both Abrika products and reference products Wellbutrin XL (150 mg and 300 mg) released [redacted] in 2 hours and [redacted] b(4)
in 4 hours. Neither product released [redacted] in 8 hours as specified in the specification provided in the deficiency letter. Please advise after you further review the information provided here if any additional dissolution data is still desired. Also included in Section VI 1. of this amendment is a copy of controlled correspondence from FDA to Abrika Pharmaceuticals with a recommendation for comparative dissolution testing.

2) *In order to improve the review process, the Division of Bioequivalence requests that you provide 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.*

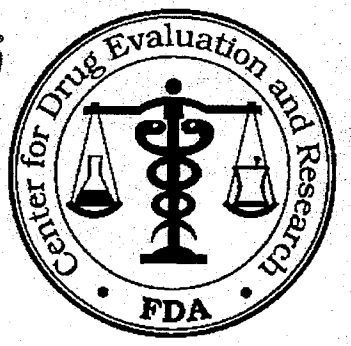
Response:

In-vivo study data, dissolution data, and formulation data are provided using the format supplied in the attached templates. These tables have also been included on a CDROM in both Word and PDF format, which are identical to the included data with the exception of page numbers. These electronic media have been scanned for viruses and are virus-free. This virus scan was performed using Norton Antivirus Corporate Edition 8.0 (virus definition date June 14, 2005). The approximate size of the electronic submission is 24 MB. See SECTION VI. BA/BE Part 2.

BIOEQUIVALENCY AMENDMENT

ANDA 77-285

JUN 0 2 2005



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Abrika Pharmaceuticals LLLP TEL: 954-315-6502

ATTN: Monique Weitz FAX: 954-315-~~6601~~ 6500

FROM: Keri Suh PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on September 23, 2004, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Tablets, 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 ten pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES JUN 0 2 2005

ANDA: 77-285 APPLICANT: Abrika

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:

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

Medium:	water
Volume:	900 mL
Temperature:	37ºC
Apparatus:	Apparatus II (paddles)
Rotation:	50 rpm
Specification:	[redacted] in 1 hour [redacted] in 4 hours [redacted] in 8 hours

b(4)

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: 77-285

ABRIKA
PHARMACEUTICALS

April 14, 2005

Thomas Hinchliffe
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
4/14/05

Re: ANDA 77-285
Bupropion Hydrochloride Extended-Release Tablets 150 mg and 300 mg
Chemistry Minor Amendment
Response to CMC Deficiency Letter

Mr. Hinchliffe:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets 150 mg and 300 mg, which was submitted to the Agency on September 29, 2004 and amendments dated October 1 and October 25, 2004. Reference is made to the Minor Amendment CMC Deficiency Letter that was issued to Abrika Pharmaceuticals LLLP on March 16, 2005. A copy of the March 16 letter is included for your convenience.

Abrika Pharmaceuticals has provided complete responses to the items listed in the March 16 letter in Attachment 1. To aid in the review of this information, we have listed the specific items in italics followed by the response. These responses reference various sections in the ANDA updated in this Amendment. A Comprehensive Table of Contents for this Amendment is provided in Section I., which lists all of the sections that have been revised and are included in this Amendment.

This Minor Amendment consists of one volume. Four copies (archive, reviewer, chemistry, and field copies) of this Minor Amendment are being submitted. In accordance with 21 CFR 314.96, a field copy of this Minor Amendment has been submitted directly to the FDA District Office in Maitland, Florida. An updated field copy certification is provided in Section XXI. of the Amendment.

This Telephone Amendment also contains Bioequivalence deficiency comments from FDA's January 14, 2005 telefax. A copy of the telefax is provided after this transmittal letter for ease of review.

If there are any questions regarding this submission, please contact me at (954) 315-6600.

Sincerely,

Monique Weitz
Director, Regulatory Affairs
Abrika Pharmaceuticals LLLP

RECEIVED
APR 15 2005
OGD / CDER

13800 N.W. 2nd St • Suite 190 • Sunrise, Florida 33325 • Phone: 954-315-6600 • Fax: 954-315-6601

Attachment 1
Responses to Requested Information

1. *Regarding the test specifications for the drug substances:*

- *Please add a test limit for Total Unidentified Impurities in the drug substance specifications in accordance with the USP monograph requirement.*

Response:

"Total Unidentified Impurities: ——— has been added to the drug substance specifications in accordance with the USP monograph requirement. See SECTION VIII Raw Materials, 1C. b(4)

- *Please revise the test specification for Identification by HPLC in accordance with the USP monograph or provide justification that the retention time of drug substance in the sample is ——— minutes in the standard. The same comment applies to the drug product.* b(4)

Response:

The drug substance and drug product test specification for Identification by HPLC has been revised in accordance with the USP monograph. See SECTION VIII Raw Materials, 1C and SECTION XV, 2C, respectively.

- *It is recommended that a ——— particle size specification be added into the drug substance specifications to characterize particle size distribution. Please provide your test method and test results for the two drug substance lots as well.* b(4)

Response:

A ——— particle size specification has been added to the drug substance specifications to characterize particle size distribution. The test method is USP<786> and the specific instructions (i.e. air pressure, testing time and sample amount) are listed in the revised specifications. The test results for the two drug substance lots are also included in the certificate of analysis. See SECTION VIII Raw Materials, 1C. b(4)

- *Please tighten the test limit for the Residual Solvent ——— to be consistent with the revised test limit from the API manufacturer.* b(4)

Response:

The test limit for the Residual Solvent ——— in the drug substance specification has been tightened to be consistent with the test limit from the API manufacturer, " ———See SECTION VIII Raw Materials, 1C. b(4)

2. *Regarding the inactive ingredients used in the manufacture of the drug product:*

- *Please provide your acceptance criteria for ———— It is not acceptable that Copovidone EP monograph is used as the official regulatory specifications for the excipient. Test methods should also be provided.* b(4)

Response:

Copovidone USP monograph recently appears in 1st supplement of USP 28-NF 23 which became official on April 1, 2005. All the acceptance criteria in the current USP/NF Copovidone ———— monograph will be adopted as Abrika's regulatory specifications for the excipients. Since the test methods are available in the monograph, a copy of the methods is not provided in this response. See SECTION VIII Raw Materials, 2C. b(4)

- *Please provide your acceptance test data or COA for ———— (Manufacturer lot# 14407). A clear copy of supplier COA for the excipient should also be provided.* b(4)

Response:

———— Manufacturer lot # 144076 did not undergo full monograph testing prior to batch manufacturing and consequently the COA for ———— issued by ———— was not provided in the original submission of ANDA 77-285; however, based on the deficiency as stated above, Abrika requested full testing on ———— Manufacturer lot # 144076 as per Colloidal Silicon Dioxide monograph in the current USP/NF at ———— A copy of the COA is submitted. b(4) b(4)
See SECTION VIII Raw Materials, 2D.
A clear copy of supplier COA for the excipient has also been provided.
See SECTION VIII Raw Materials, 2D.

- ———— *contains several other inactive ingredients in addition to Methacrylic Acid Copolymer———— Please clarify if all of these ingredients are compendial products.* b(4)

Response:

All of the other inactive ingredients of ———— manufactured by ————, are compendial products. Documentation for clarification has been provided. See SECTION VIII Raw Materials, 2B. b(4)

- *Please provide your acceptance criteria for ———— and provide test data accordingly. Test methods should also be described in detail.* b(4)

Response:

The acceptance criteria for [redacted] are listed in Abrika's specification E019-01 effective 6/9/04. The test data has been provided. Test methods are also described in detail. See SECTION VIII Raw Materials, 2C. b(4)

3. *It appears that [redacted] is involved in raw materials testing. Please provide the full address, its function, and cGMP/GLP certification for the analytical facility.* b(4)

Response:

For clarification, the company that performed the manufacturing and release testing with respect to the Purified Water, USP is [redacted] is a different company than [redacted] full address, its function, and cGMP/GLP certification for the analytical facility has been provided. See below and SECTION IX Description of Manufacturing Facility. b(4)

[redacted]

b(4)

[redacted]

Registration Number: [redacted]
FEI Number: [redacted] b(4)
Labeler Code: [redacted]

[redacted] is the manufacturing site for the finished dosage form [redacted] performed the manufacturing, release testing with respect to the USP Purified Water, incoming identity testing of raw materials, and all in-process controls except for bulk tablet testing. b(4)

4. *The bulk tablets manufactured and packaged in the bottles of 30's shown in the table on page 4703 for the 150 mg tablets are inconsistent with those provided in the packaging records. Please clarify.*

Response:

Please find below clarification of the bulk tablets manufactured and packaged in the bottles of 30's shown in the table on page 4703 for the 150 mg tablets are consistent with those provided in the packaging records.

Weight of average coated tablets [redacted]
Based on weight [redacted] sent [redacted] b(4)
Based on weight, [redacted] received [redacted]
Difference of [redacted] or [redacted]

issued the tablets to Order No. 500424.
bottles of 30 count plus bottles of 30 counts for b(4)
Customer Samples with were produced. Additional tablets for QA and Reject totaled tablets. For a total of
= b(4)

issued tablets to Order No. 500430
bottles of 30 count plus bottles of 30 count for Customer b(4)
Samples with were produced. Additional tablets for QA and Reject which totaled tablets. For a total of tablets.
= versus on the packaging batch record. Note that the b(4)
batch record percent reconciliation states which corresponds to the discrepancy.

Abrika received a of tablets for bulk holding study, Based on the weight of the b(4)
each tablet this represents tablets.

Order No.	Configuration	Number of Bottles	Number of Tablets Bottled	Additional Tablets Used QA and Reject
500424	30 count			
500423	30 count			
Total Count	NA	NA		
Bulk Holding				
Grand Total Count	or based on the number used for bulk holding			

b(4)

5. *Regarding the container/closures used in the packaging of the drug product:*

- *Please provide clear copies of the engineering drawings for the bottles and the* b(4)

Response:

Clear copies of the engineering drawings for the 75 cc, 150 cc, and 200 cc bottles and the 38 mm CRC cap have been provided. See SECTION XIII Packaging Materials Controls, 4.

- *It is recommended that the acceptance criteria for Dimension, Identification, and Cap Fit Test be provided in detail in the container/closure testing. Test methods for acceptance testing of the bottles and cap should also be provided.*

Response:

The acceptance criteria for Dimension, Identification, and Cap Fit Test have been provided in detail in the container/closure testing. Test methods for acceptance testing of the bottles and cap have also been provided. See SECTION XIII Packaging Materials Controls, 4.

6. *Regarding the in-process controls and finished drug product, we have the following comments:*

- *Please provide your analytical protocol including sampling size, sampling location and test procedure for blend uniformity testing.*

Response:

The requested information is provided in the original submission. To assist the Reviewer, the following table may be of assistance:

	150mg Executed	150mg Proposed	300mg Executed	300mg Proposed
Sampling Instructions			Located in — Batch Record, step D.7. (pg.s 7 and 10 of 14) (ANDA Amendment pg. #'s 00475 and 000478)	Located in Blend Batch Record, step D.7. (pg.s 7, 8 and 10 of 14) (ANDA Amendment pg. #'s 000316, 000317 and 000320)
Sample Size			(ave. =	
Sample Locations			See Figure 1 in — Batch Record (pg. 10 of 14) (ANDA Amendment pg # 000478)	See Figure 1 in — Batch Record (pg. 11 of 14) (ANDA Amendment pg # 000320)
Analytical Test Method			STP-029-03 (ANDA pg.s 004966 – 004978) See specifically sections 8.4 and 12.5.	STP-029-03 (ANDA pg.s 004966 – 004978) See specifically sections 8.4 and 12.5.

b(4)

b(4)

b(4)

Note to Reviewer: The proposed batch records had been enhanced prior to submission. The revisions included a requirement that ten samples in triplicate be collected and provided a more detailed diagram for their locations. These revisions were discussed in the original submission on ANDA pg. 004596, and October 1, 2004 ANDA Amendment pg. 000289.

- *Please provide explanation or justification for the in-process acceptance criteria for — ablet weight gain and — ablet weight gain. Are the same criteria proposed for future production batches?*

b(4)

Response:

The in-process acceptance criteria for — tablet weight gain and — tablet weight gain was determined based on prior experience of extended-release solid dosage formulation and functionality of both — Each of these — re not critical components of the extended-release profile of the product. —

b(4)

— As stated in the ANDA, pg.4376,

The range of ' which is set for the tablet weight gain and the range of which is set for tablet weight gain, are based on the process control from the ANDA batches. b(4)

This will be the same process control acceptance criteria proposed for future production batches as stated in the proposed batch records, ANDA pg. 004654 and pg. 004657 for reasons stated above. See SECTION XI Manufacturing and Processing Instructions, 3.

- *Please add additional tests for Identification by IR and for Water Content in the drug product release specifications.*

Response:

Additional tests for Identification by IR and for Water Content in the drug product release specifications have been added. See SECTION XV Analytical Methods, 2C.

- *Please note that the Division of Bioequivalence will establish the test specification and test method for the Drug Release/Dissolution testing of the drug product, which will be communicated separately.*

Response:

Abrika acknowledges that the Division of Bioequivalence will establish the test specification and test method for the Drug Release/Dissolution testing of the drug product, which will be communicated separately.

7. Regarding the GC method for the Residual Solvents in the drug substance and the HPLC method for Related Substances in the drug product and method validation:

- *In a GC chromatogram of sample solution on page 5055, there are additional peaks between 2 to 4 minutes that may interfere with the determination of the residual solvents and . Please discuss.* b(4)

Response:

The peaks between 2 to 4 minutes in the GC chromatogram of sample solution on page 5055 have been manually integrated and analyzed for the purpose of this discussion. Peak area response and resolution between adjacent peaks are reported. See SECTION XV Analytical Methods, 1A.

The resolution between each pair of adjacent peaks is greater than 1.0, which is adequate for GC analysis of residual solvents based on the resolution requirement of " in Method I, USP<467> Organic Volatile Impurities, page 2326, USP28. Moreover, the minor peak next to the peak and the minor peak next to the peak is b(4) b(4)

[redacted], respectively (assuming they have the same response factor). We believe that these additional peaks between 2 to 4 minutes do not affect the quantitation of the residual solvents, [redacted] and [redacted]

b(4)

- *The HPLC method for Assay and Related Substances has not been appropriately validated for Related Substances. Please include the USP specified and identified impurities, Bupropion Related Compounds C, E and F in your method validation.*

Response:

As discussed with Thomas Hinchliffe, Bing Wu, and Dave Schanchy on March 21, and after their further review, the mongraph method and validation as originally submitted is acceptable and no additional response is required.

- *Please include an additional system suitability test for the resolution between Bupropion Related Compound C and Bupropion Related Compound F in the HPLC method.*

Response:

An additional system suitability test for the resolution between Bupropion Related Compound C and Bupropion Related Compound F has been included in the HPLC method, STP-029. See SECTION XV Analytical Methods, 2D.

8. Regarding the Description and How Supplied section of the drug product labeling:

- *Please revise the storage statement to "Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature]".*

Response:

Abrika acknowledges and commits revising the storage statement to "Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature]" when we receive the labeling deficiency. We note that the labeling deficiency letter will contain the final decision on what the storage statement should state.

- *The name and address of the contract drug product manufacturer should be provided in the product labeling.*

Response:

Abrika acknowledges and commits to adding the name and address of the contract drug product manufacturer when we receive the labeling deficiency. We note that the labeling deficiency letter will contain the final decision on the addition of the name and address of

deficiency letter will contain the final decision on the addition of the name and address of the contract drug manufacturer to be added on the label.

Response to Telefax, Dated January 14, 2005, Requested Information

1) *In order to improve the review process, the Division of Bioequivalence requests that you provide 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.*

Response:

In-vivo study data, dissolution data, and formulation data are provided using the format supplied in the attached templates. These tables have also been included on a CDROM in both Word and PDF format, which are identical to the included data with the exception of page numbers. These electronic media have been scanned for viruses and are virus-free. This virus scan was performed using Norton Antivirus Corporate Edition 8.0 (virus definition date April 14, 2005). The approximate size of the electronic submission is 23 MB. See SECTION VI. BA/BE, 2.

MINOR AMENDMENT

3.1

ANDA 77-285

MAR 16 2005

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Abrika Pharmaceuticals LLP TEL: 954-315-6600

ATTN: Monique Weitz FAX: 954-315-6601

FROM: Thomas Hinchliffe PROJECT MANAGER: (301) 827-5771

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated September 29, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloriode Extended-Release Tablets, USP, 150 mg and 300 mg.

Reference is also made to your amendment dated October 1, and October 25, 2004.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided here.

MAR 16 2005

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-285

APPLICANT: Abrika Pharmaceuticals, Inc.

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

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Regarding the test specifications for the drug substance:

- Please add a test limit for Total Unidentified Impurities in the drug substance specifications in accordance with the USP monograph requirement.

- Please revise the test specification for Identification by HPLC in accordance with the USP monograph or provide justification that the retention time of drug substance in the sample is [redacted] in the standard. The same comment applies to the drug product. b(4)

- It is recommended that a [redacted] particle size specification be added into the drug substance specifications to characterize particle size distribution. Please provide your test method and test results for the two drug substance lots as well. b(4)

- Please tighten the test limit for the Residual Solvent [redacted] to be consistent with the revised test limit from the API manufacturer. b(4)

2. Regarding the inactive ingredients used in the manufacture of the drug product:

- Please provide your acceptance criteria for [redacted] It is not acceptable that Copovidone EP monograph is used as the official regulatory specifications for the excipient. Test methods should also be provided. b(4)

- Please provide your acceptance test data or COA for [redacted] (Manufacturer lot# 14407). A clear copy of supplier COA for the excipient should also be provided. b(4)

- [redacted] contains several other inactive ingredients in addition to Methacrylic Acid Copolymer [redacted] Please clarify if all of these ingredients are compendial products. b(4)

- Please provide your acceptance criteria for [redacted] and provide test data accordingly. Test methods should also be described in detail. b(4)

3. It appears that [redacted] is involved in raw materials testing. Please provide the full address, its function, and cGMP/GLP certification for the analytical facility. b(4)

4. The bulk tablets manufactured and packaged in the bottles of 30's shown in the table on page 4703 for the 150 mg tablets are inconsistent with those provided in the packaging records. Please clarify.

5. Regarding the container/closures used in the packaging of the drug product:

   - Please provide clear copies of the engineering drawings for the [redacted] bottles and the [redacted] b(4)

   - It is recommended that the acceptance criteria for Dimension, Identification, and Cap Fit Test be provided in detail in the container/closure testing. Test methods for acceptance testing of the bottles and cap should also be provided.

6 Regarding the in-process controls and finished drug product, we have the following comments:

   - Please provide your analytical protocol including sampling size, sampling location and test procedure for [redacted] uniformity testing.

   - Please provide explanation or justification for the in-process acceptance criteria for [redacted] tablet weight gain and [redacted] tablet weight gain. Are the same criteria proposed for future production batches? b(4)

   - Please add additional tests for Identification by IR and for Water Content in the drug product release specifications.

   - Please note that the Division of Bioequivalence will establish the test specification and test method for the Drug Release/Dissolution testing of the drug product, which will be communicated separately.

7 Regarding the GC method for the Residual Solvents in the drug substance and the HPLC method for Related Substances in the drug product and method validation:

- In a GC chromatogram of sample solution on page 5055, there are additional peaks between 2 to 4 minutes that may interfere with the determination of the residual solvents [redacted] and [redacted] b(4) Please discuss.

- The HPLC method for Assay and Related Substances has not been appropriately validated for Related Substances. Please include the USP specified and identified impurities, Bupropion Related Compounds C, E and F in your method validation.

- Please include an additional system suitability test for the resolution between Bupropion Related Compound C and Bupropion Related Compound F in the HPLC method.

8 Regarding the Description and How Supplied section of the drug product labeling:

- Please revise the storage statement to "Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature]".

- The name and address of the contract drug product manufacturer should be provided in the product labeling.

Sincerely yours,

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

ABRIKA
PHARMACEUTICALS

January 13, 2005

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

N/xP

Re: Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg
ANDA 77-285
PATENT AMENDMENT

Mr. Margand:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg, which were submitted to the Agency on September 23, 2004 and October 1, 2004, respectively and telephone amendment submitted on October 25, 2004. Also, please refer to the Patent Amendments submitted on November 17, 2004, which contains the original signatures for the amended Paragraph IV Patent Certification and Certifications of Noninfringement as well as January 5, 2005 which contains the proof of receipt of the notices by Glaxosmithkline on November 16, 2004 (for the 150 mg) and November 23, 2004 (for the 300 mg) and Biovail Laboratories, Inc. on December 3, 2004 (for both the 150 mg and 300 mg).

In accordance with section 505 (j)(5)(B)(iii) of the Act, copies of summons to serve which were delivered to Abrika Pharmaceuticals, Inc, Abrika, LLLP, and Abrika Pharmaceuticals LLLP on December 29, 2004 are provided.

If anything further is required at this time, please contact us.

Sincerely,

Monique Weitz
Director, Regulatory Affairs
Abrika Pharmaceuticals

RECEIVED
JAN 14 2005
OGD / CDER

13800 N.W. 2nd St • Suite 190 • Sunrise, Florida 33325 • Phone: 954-315-6600 • Fax: 954-315-6601

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Abrika Pharmaceuticals
Attention: Monique Weitz
13800 N.W. 2nd St., Suite 190
Sunrise, Fl 33325

RECEIVED
NOV 1 8 2004

Reference Number: OGD #04-854

Dear Ms. Weitz:

This letter is in response to your correspondence dated August 23, 2004. You request that the Office of Generic Drugs (OGD) provide bioequivalence recommendations regarding Bupropion Hydrochloride Extended Release Tablets, 150 mg and 300mg. OGD provides the following comments:

1. The following studies are recommended to establish bioequivalence of bupropion hydrochloride extended release tablets:

   a. A single-dose, two-way crossover fasting *in-vivo* bioequivalence study comparing Bupropion Hydrochloride Extended Release Tablets, 150 mg, to the reference listed drug (RLD), Wellbutrin XL® (Bupropion Hydrochloride Extended Release) Tablets, 150 mg. Due to safety concerns, studies using the 300 mg dose are not recommended.

   b. A single-dose, two-way crossover fed *in-vivo* bioequivalence study comparing Bupropion Hydrochloride Extended Release Tablets, 150 mg, to the RLD.

2. Please measure bupropion and hydroxybupropion in plasma.

3. Bupropion Hydrochloride Extended Release Tablets, 300 mg, may be considered for a waiver of *in-vivo* bioequivalence testing based on (1) acceptable bioequivalence studies on the 150 mg strength, (2) acceptable dissolution testing of the 150 mg and 300 mg strengths, and (3) proportional similarity in the formulations of the 150 mg and 300 mg strengths.

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

Apparatus:	USP 27 apparatus I (basket)
Speed:	75 rpm
Medium:	0.1N Hydrochloric Acid
Volume:	900 mL

Sampling times: 1, 2, 4, 6 and 8 hours and until at ——— of the labeled content is dissolved. b(4)

1. Paragraph IV Patent Certification

PARAGRAPH IV CERTIFICATION

I, Abrika Pharmaceuticals LLLP, certify that, to the best of its knowledge, U.S. Patent No. 6,096,341 and U.S. Patent No. 6,143,327, both due to expire on October 30, 2018, will not be infringed by the manufacture, use, or sale of Abrika Pharmaceuticals LLLP's Bupropion Hydrochloride Extended-Release Tablets USP, 150 mg and 300 mg, for which the abbreviated new drug application (ANDA) number 77-285 was submitted, or in the alternative, that U.S. Patent No. 6,096,341 and/or U.S. Patent No. 6,143,327 are invalid and/or unenforceable.

As required by Section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)) and 21 C.F.R.§§ 314.94 and 314.95, Abrika Pharmaceuticals LLLP hereby states that this ANDA is sufficiently complete to permit substantive review.

Furthermore, on November 12, 2004 and November 16, 2004, in accordance with 21 C.F. R. §§314.95(a) and (b), Abrika Pharmaceuticals LLLP sent a "Patent Certification Under 21 U.S.C. §355 and Notice of Certification of Invalidity or Noninfringement of a Patent Under 21 U.S.C. §355" (hereinafter "the Notice") to GLAXOSIMITHKLINE, as NDA holder for Wellbutrin XL 150 mg and 300 mg, respectively, and Biovail Laboratories, Inc., as owner of record of the above-referenced patents, via United States registered mail, return receipt requested. The Notice meets the content requirements under 21 C.F.R. §314.95(c). A copy is attached in Section III, Patent Certification. In addition, copies of the United States Postal Service receipts of mailing are also attached in Section III, Patent Certification.

ABRIKA PHARMACEUTICALS LLLP

By: _____

James S. New
Chief Executive Officer, Abrika Pharmaceuticals
November 17, 2004

Patent Certification Under 21 U.S.C. § 355 and Notice of Certification of Invalidity or Noninfringement of a Patent Under 21 U.S.C. § 355

I. Abrika Pharmaceuticals LLLP (Abrika), having a place of business at 13800 N.W. 2nd Street, Suite 190, Sunrise, Florida 33325 hereby certifies to the following persons that it has filed an Abbreviated New Drug Application (ANDA) under 21 U.S.C. § 355(j)(2)(B)(ii) (also referred to as Section 505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act) in order to obtain approval to engage in the commercial manufacture, use, or sale of Bupropion Hydrochloride Extended-Release Tablets USP, 150 mg that are bioequivalent to Wellbutrin XL® 150 mg tablets:

1. Holder of New Drug Application for Wellbutrin XL®, 150 mg:

GLAXOSMITHKLINE
5 Moore Drive
Research Triangle Park, NC 27709

2. On information and belief the owner of U.S. Letters Patent Nos. 6,096,341 and 6,143,327 is:

BIOVAIL LABORATORIES INC.
Building No. 2, Chelston Park
Collymore Rock, St. Michael
Barbados, West Indies

II. The United States Food and Drug Administration has received an ANDA from Abrika which contains the required bioequivalence data showing that the Abrika Bupropion Hydrochloride Extended-Release Tablets USP, 150 mg, is bioequivalent to Wellbutrin XL® Tablets 150 mg.

III. The Abrika Abbreviated New Drug Application Number is ANDA 77-285.

IV. The established name for the proposed drug product is Bupropion Hydrochloride Extended-Release Tablets USP, 150 mg.

V. The active ingredient for the proposed drug product is bupropion hydrochloride; the dosage form is an oral tablet that will be sold in 150 mg strength.

VI. The following patents (the "listed patents") which have been listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") are known to Abrika and will not be infringed by the making, using, or selling of the Abrika Bupropion Hydrochloride Extended-Release Tablet USP product (Abrika proposed product):

U.S. Patent No.	Expiration Date
6,096,341	October 30, 2018.
6,143,327	October 30, 2018.

VII. The ANDA indicates that Abrika intends to engage in the commercial manufacture, use, or sale of the proposed product before the expiration dates of U.S. Patent Nos. 6,096,341 and 6,143,327.

VIII. The above U.S. patents, which have been listed in the Orange Book, will not be infringed by the Abrika proposed product for the detailed factual and legal reasons set forth below or, in the alternative, would be invalid and/or unenforceable against the Abrika proposed product.

A. Noninfringement of U.S. Patent No. 6,096,341

All of the claims of the '341 patent require a delayed release tablet including bupropion hydrochloride and exhibiting a dissolution profile such that "after 1 hour, from 0 up to 30% of the bupropion hydrochloride is released, after 4 hours, from 10 to 60% of the bupropion hydrochloride is released, after 6 hours, from 20 to 70% of the bupropion hydrochloride is released, after 8 hours, more than 40% of the bupropion hydrochloride is released." The table below compares these claimed dissolution rates with the dissolution rates of the Abrika proposed product, tested under the same conditions -- 0.1N HCl, USP Apparatus I at 75 RPM. These dissolution testing conditions are specified in the Examples of the '341 patent and were relied upon by the patentee during prosecution of the '341 patent:

TABLE I. Dissolution Profile Comparison: '341 Patent Formulation v. Abrika Proposed Product

Time	% Released in 0.1N HCl, USP Apparatus I @ 75 RPM **Claims of the '341 Patent**	% Released in 0.1N HCl, USP Apparatus I @ 75 RPM **Abrika Proposed Product**
1hr	0-30	
4 hrs	10-60	
6 hrs	20-70	
8 hrs	>40	

b(4)

The claims of the '341 patent, themselves, do not specify any dissolution testing conditions. However, a proper claim interpretation limits the claims of the '341 patent not just to the claimed dissolution profile, but to the claimed dissolution profile *as obtained using the same dissolution testing conditions used by the patentee*. In situations where the results of a test or assay are claimed, but the actual test conditions are not, courts have limited the claims to those test results as performed under the same testing conditions; this is especially true where, like here, the results may vary greatly depending upon the test conditions. See Genentech v. Wellcome Found., 29 F.3d 1555 (Fed. Cir. 1994); J.T. Eaton & Co. v. Atlantic Paste & Glue Co., 106 F.3d 1563, 1565 (Fed. Cir. 1997).

In the '341 patent, the patentee emphasized these dissolution testing conditions, and their importance to the claims, during prosecution. In response to a 35 U.S.C. §102(a) rejection, the Applicant argued that "Claim 1 requires a specific dissolution profile," that the prior art was "silent on the dissolution medium and conditions that are used," and the prior art's failure "to teach the dissolution medium and conditions that are used" rendered "its disclosure deficient." '341 Patent File History, Paper No. 6, page 6. The Applicant then directed the examiner to its own dissolution medium and conditions, stating "***[t]he dissolution medium and conditions that are used in the invention is***, on the contrary, ***disclosed in example 1, page 8. (It corresponds to gastric juice.)***" Id. Thus, the claimed release profile should be interpreted as being derived from using the same conditions as described in Example 1 of Applicant's specification., *i.e.*, in 1000 ml of 0.1N HCl at 75 rpm using USP Apparatus I. See '341 Patent, Col. 5, Lines 10-13.

For these reasons, it is clear that the Abrika proposed product fails to meet, or even come close to, the claimed dissolution at 4 hours, 6 hours, and 8 hours and therefore cannot infringe any claim of the '341 patent either literally or under the doctrine of equivalents.

B. Noninfringement of U.S. Patent No. 6,143,327

All of the claims of the '327 patent require the claimed tablets exhibit a dissolution profile such that "after 2 hours from 0 up to 30% of the bupropion hydrochloride is released, after 4 hours, from 3 to 22% of the bupropion hydrochloride is released, after 6 hours, from 15 to 38% of the bupropion hydrochloride is released, after 8 hours, more than 40% of the bupropion hydrochloride is released." The table below compares the claimed dissolution rates with the dissolution rates of the Abrika proposed product, tested under the same conditions -- 0.1N HCl, USP Apparatus I at 75 RPM. These dissolution testing conditions are specified in the Examples of the '327 patent and were relied upon by the patentee during prosecution of the '327 patent:

TABLE II. Dissolution Profile Comparison: '327 patent formulation v. Abrika Proposed Product

Time	% Released in 0.1N HCl, USP Apparatus I @ 75 RPM **Claims of the '341 Patent**	% Released in 0.1N HCl, USP Apparatus I @ 75 RPM **Abrika Proposed Product**
1hr	0-30	[redacted]
4 hrs	3-22	
6 hrs	15-38	
8 hrs	>40	

b(4)

Again, the claims of the '327 patent do not specify the dissolution testing conditions. Just as in the '341 patent, proper claim interpretation should include the limitation of the actual dissolution testing conditions used to obtain the claimed dissolution profile. See Genentech v. Wellcome Found., 29 F.3d 1555, 1561 (Fed. Cir.

1994); J.T. Eaton & Co. v. Atlantic Paste & Glue Co., 106 F.3d 1563, 1565 (Fed. Cir. 1997); discussed *supra*.

"When multiple patents derive from the same initial application, the prosecution history regarding a claim limitation in any patent that has issued applies with equal force to subsequently issued patents that contain the same claim limitation." Biovail Corp. Int'l. v. Andrx Pharmaceuticals, Inc., 239 F.3d 1297, 1301 (Fed. Cir. 2001), quoting Elkay Mfg. Co. v. Ebco Mfg. Co., 192 F.3d 973, 980 (Fed. Cir. 1999). Thus, statements made by the patentee of the '327 patent during prosecution of its parent, *i.e.*, the '341 patent, regarding the dissolution profiles apply "with equal force" to the claims of the '327 patent. As noted above, during prosecution of the '341 patent, the Applicant emphasized the importance of, not only the dissolution profile, but the dissolution medium and conditions, in distinguishing its claimed invention. The Applicant in arguing that the testing conditions need to be disclosed and read into the claimed dissolution profile unequivocally stated to the examiner that the dissolution medium and conditions are as disclosed in example 1, page 8. See '341 Patent File History, Paper No. 6.

For these reasons, it is clear that the Abrika proposed product fails to meet, or even come close to, the claimed dissolution at 4 hours, 6 hours, and 8 hours, and therefore cannot infringe any claim of the '327 patent either literally or under the doctrine of equivalents.

For the above reasons, the Abrika proposed product will not infringe the listed patents.

The information provided herein is supplied for the purpose of complying with the above-referenced statutes and regulations, and neither Abrika nor its attorneys waive any attorney-client privilege or attorney work product immunity concerning the subject matter of this communication.

In accordance with 21 U.S.C. § 355(j)(2)(B)(i), it is hereby certified that on November 12, 2004 a copy of this notice has been sent by United States registered mail, return receipt requested, to Biovail Laboratories as owner of U.S. Patent Nos. 6,096,341 and 6,143,327 as required by 21 U.S.C. § 355(j)(2)(B)(i)(I), and to GlaxoSmithKline as the holder of the approved application for Welbutrin XL® as required by 21 U.S.C. § 355(j)(2)(B)(i)(II), in envelopes addressed to:

GLAXOSMITHKLINE
5 Moore Drive
Research Triangle Park, NC 27709

BIOVAIL LABORATORIES INC.
Building No. 2, Chelston Park
Collymore Rock, St. Michael
Barbados, West Indies

By: _____
Dr. James New
Chief Executive Officer
Abrika Pharmaceuticals LLLP
13800 N.W. 2nd Street, Suite 190
Sunrise, Florida 33325

ANDA 77-285

Abrika Pharmaceuticals, LLLP
Attention: Monique Weitz
13800 N.W. 2nd Street
Suite 190
Sunrise, Florida 33325

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 18, 2004 and your correspondence dated October 25, 2004.

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

DATE OF APPLICATION: September 23, 2004

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 23, 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 77-285
DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/G. Davis
HFD-92

Endorsement: HFD-615/MShimer, Chief, RSB _____ date 8 Nov 04
HFD-615/IMargand, CSO _____ date 10/27/04
Word File V:\Filesam\Ltrs&rev\77285.ack
FT/ 10/26/04
ANDA Acknowledgment Letter!

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 77-285 **FIRM NAME:** ABRIKA PHARMACEUTICALS

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

RELATED APPLICATION(S):

First Generic Product Received? NO

DRUG NAME: BUPROPION HYDROCHLORIDE
DOSAGE FORM: EXTENDED-RELEASE TABLETS, 150 MG AND 300 MG (NEW STRENGTH 300 MG)

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

Letter Date: OCTOBER 01, 2004	**Received Date**: OCTOBER 01, 2004
Comments: EC- 1+1= 2 YES	**On Cards:** YES
Therapeutic Code: 2020100 ANTIDEPRESSANTS	
Archival Format: PAPER **Sections** I **(356H Sections per EDR Email)**	
Review copy: YES E-Media Disposition: NA 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 [signature] **Date 10/26/04**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: [signature]	**Date:** 26 Oct 2004

ADDITIONAL COMMENTS REGARDING THE ANDA:
Information not directly pertaining to the new strength in sections I thru X is located in original strength (150mg) application dated 9/23/04 and is therefore not reviewed in this supplemental application.
See T-con dated 10/18/04.

Top 200 Drug Product:

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES (Statement regarding Rx/OTC Status) YES RX	☒
Sec. II	**Basis for Submission** **NDA# : 21-515** Ref Listed Drug: WELLBUTRIN XL Firm: GLAXO SMITH KLINE 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? 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) NO 3454 WAS SUBMIITED ON ORIGINAL APPLICATION 9/23/04. **2. Request for Waiver of In-Vivo Study(ies): YES** **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) Dosage formulations are proportional (150mg and 300mg) **4. Lot Numbers of Products used in BE Study(ies):** CF4CY03Q18 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 WAS DONE ON ORIGINAL APPLICATION DATED 9/23/04 a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) Refer to OGD CTL 04-344 for Anchen Parm. for BE recommendations. b. EDR Email: Data Files Submitted: NO c. In-Vitro Dissolution: Yes Pg. 258	☒
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. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. <u>Solutions</u> (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. <u>Suspensions</u> (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 Y 2. Inactive ingredients as appropriate Excipiens acceptable	☒

Sec. VIII	**Raw Materials Controls** Information unchanged from 150mg application 1. **Active Ingredients** a. Addresses of bulk manufacturers b. Type II DMF authorization letters or synthesis c. COA(s) specifications and test results from drug substance mfgr(s) d. Applicant certificate of analysis e. Testing specifications and data from drug product manufacturer(s) f. Spectra and chromatograms for reference standards and test samples g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified b. Testing specifications (including identification and characterization) c. Suppliers' COA (specifications and test results) d. Applicant certificate of analysis	☒
Sec.IX	**Description of Manufacturing Facility** Information unchanged from 150mg application 1. Full Address(es)of the Facility(ies) Y 2. CGMP Certification: NO WAS SUBMITTED ON ORIGINAL APPLICATION DATED 9/23/04 3. CFN numbers	☒
Sec. X	**Outside Firms Including Contract Testing Laboratories** Information unchanged from 150mg application. 1. Full Address 2. Functions 3. CGMP Certification/GLP 4. CFN numbers	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) Y 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified 3.If sterile product: Aseptic fill / Terminal sterilization N/A 4.Filter validation (if aseptic fill) N/A 5. Reprocessing Statement	☒
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 See Attached 2. In-process Controls - Specifications and data Y	☒
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) Y 2. Components Specification and Test Data (Type [redacted] DMF References) Only provide information for [redacted] bottle. 30 count size [redacted] information in original strength application. 3. Packaging Configuration and Sizes 30 [redacted] count bottles 4. Container/Closure Testing Y Testing for [redacted] done in original strength application 5. Source of supply and suppliers address Y	☒

b(4)

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 b(4) 2. Post Approval Commitments Y 3. Expiration Dating Period ——months 4. Stability Data Submitted a. 3 month accelerated stability data Y b. Batch numbers on stability records the same as the test batch CF4CY03Q18	☒
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	☒
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): NO WAS SUBMITTED ON ORIGINAL APPLICATION DATE 9/23/04 3. List of Convictions statement (original signature) N/A 4. Field Copy Certification (original signature) located in original strength application	☒

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

ANDA 77-285 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.

N/A 9) If first generic, copy BE review and file.

✓ 10) Sign Check List.

✓ 11) Check electronic Orange Book to verify current patent information and correct RLD. Wellbutrin XL 150mg

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. Wellbutrin XL 21-515

✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer. M-10 supp.

✓ 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 Martha A. Johnson date 26 Oct 2004

Telecon Record

Date: 10/18/04

ANDA: 77-285

Firm: Abrika Pharmaceuticals

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

FDA Participants: Iain Margand

Industry Participants: Jim New

Phone: 954-313-6600

Agenda:

1. Iain requested the following:

Please remove proprietary name from 356H form.

Have established name changed to USP designation on 356H form.

Correctly address patents expiration dates on Patent Certification letter.

Please provide composition of [redacted] b(4)

Provide electronic labeling as required.

Provide contact person for Active Pharmaceutical Ingredient manufacturer.

Provide DMF [redacted] letters from [redacted] manufacturer, and [redacted], [redacted] manufacturer. b(4)

Provide either FDA form 3454 or 3455 Financial Certification.

Please clarify largest intended production runs on Master Batch Records (scale-up).

Abrika Pharmaceuticals
13800 N.W. 2nd Street, Suite 190
Sunrise, Florida 33325
Ph. 954-315-6600
Fax 954-315-6601

ABRIKA PHARMACEUTICALS

Fax

To:	Ian Margand	**From:**	Monique Weitz
Fax:	(301) 594-1174	**Date:**	October 15, 2004
Phone:		**Pages:**	29 , including cover
Re:	ANDA : 77-285 Telephonic Amendment	**CC:**	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

•Comments:

Mr. Margand,

Good afternoon.

Attached is the Telephonic Amendment in response to a request for additional information.

Abrika is shipping the hard copy in binders that contain the CD-ROM for your files overnight.

Best Regards,
Monique Weitz

ABRIKA PHARMACEUTICALS

October 25, 2004

Ian Margand
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855
Fax Number: (301) 594-1174

Re: Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg
ANDA 77-285
Telephone Amendment (New Correspondence)

Mr. Margand:

Please reference our Abbreviated New Drug Application (ANDA) No. 77-285 for Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg, which was submitted to the Agency on September 23, 2004 and October 1, 2004, respectively. We are amending this application to provide information which you requested during our telephone discussion on October 18, 2004. Responses to the requested information are provided in Attachment 1. This Telephone Amendment contains replacement and updated pages as presented in Comprehensive Table of Contents for ANDA 77-285.

This Telephone Amendment consists of one volume, and is being sent via facsimile. In addition, three hard copies (archive, reviewer, and field copies) will also be sent via courier. The field copy of the technical section of the ANDA Amendment has been sent directly to the Maitland, Florida, FDA District Office. Please note an updated field copy certification is provided.

If there are any questions concerning this submission, please contact me at (954) 315-6600

Thank you.

Sincerely,

James S. New
Chief Executive Officer
Abrika Pharmaceuticals LLLP

Enclosure

ABRIKA
PHARMACEUTICALS

October 25, 2004

Food and Drug Administration
District Office
555 Winderley Place
Maitland, FL 32751

Re: Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300mg
ANDA 77-285
Telephone Amendment (New Correspondence)

Dear Sir/Madam:

Pursuant to the requirements in 21 CFR 314.94(d)(5), and concurrent with the filing of our original telephone amendment for ANDA 77-285, enclosed please find the "Field Copy" in support of Abrika Pharmaceuticals' ANDA Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg. The Field Copy contains:

- A Field Copy Certification
- A true copy of the Form FDA 356h filed with the subject ANDA
- A true copy of the Technical Sections provided in the submission of the subject ANDA

Abrika commits to providing any updated information to the District Office as appropriate.

Please direct any questions to:

Monique Weitz, Associate Director
Abrika Pharmaceuticals LLLP
13800 N.W. 2nd Street, Suite 190
Sunrise, Florida 33325
Telephone: 954-313-6600 Fax: 954-315-6601

Thank you.

Sincerely,

James New, Chief Executive Officer
Abrika Pharmaceuticals LLLP

Margand, Iain

From: Rosencrance, Susan M
Sent: Monday, October 18, 2004 1:52 PM
To: Margand, Iain
Subject: RE: Methacrylic copolymer [redacted] b(4)

Hi Iain,

I scanned the formulations for all the bupropion (ext-release) applications we have and none contain methacrylic copolymer [redacted] at this amount ([redacted] per tablet). If the IIG also shows no products with this amount, then I suggest asking for the safety data. b(4)

Susan

-----Original Message-----
From: Margand, Iain
Sent: Friday, October 15, 2004 10:20 AM
To: Rosencrance, Susan M
Subject: Methacrylic copolymer [redacted]

Hello Susan,

I am reviewing an application for Bupropion HCl Extended-release 150mg and 300mg tablets. The applicant is using methacrylic copolymer [redacted] as the [redacted] for the tablets. The 300mg strength uses [redacted] per tablet. I have searched in COMIS, DFS, IIG search website and Inactive Ingredient Query website and the largest amount I could find is [redacted] per tablet. I am trying to find out if you or your department may have some information on higher amounts or have a suggestion of somewhere else I could look. If not, I will contact the applicant to have them send me safety studies. Thank you for your help. b(4)

Iain

ABRIKA
PHARMACEUTICALS

October 1, 2004

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Central Document Room
7500 Standish Place
Room East 150
Rockville, MD 20855

RECEIVED
OCT 0 1 2004
OGD/CDER

Major Amendment
New Strength of Product
NEW CORRESP

MC

Reference: **Abrika Pharmaceuticals LLLP**
Bupropion Hydrochloride Extended-Release Tablets
ANDA 77-285

Dear Mr. Buehler:

Abrika Pharmaceuticals LLLP is submitting a major amendment to the above reference ANDA pursuant to 21 CFR §314.60. This amendment is being submitted to request FDA approval for an additional strength for Bupropion Hydrochloride Extended-Release Tablets, ANDA 77-285. The original ANDA for Bupropion Hydrochloride Extended-Release Tablets was submitted on September 23, 2004 and included the 150 mg strength. This amendment is being filed to add the 300 mg strength.

For ease of review both 150 mg and 300 mg side-by-side labeling comparisons and the proposed labeling have been included in this amendment. Please disregard the labeling information previously submitted in the original ANDA.

There have been no changes to the analytical methods used in support of the application.

A biowaiver is being requested for the 300 mg strength, so no clinical data is being submitted with this amendment .

The enclosed ANDA consists of two (2) volumes. Abrika Pharmaceuticals is filing an archival copy (in blue folders) that contains all the information required in the ANDA, a technical review copy (in red folders) containing all the information in the archival copy with the exception of the bioequivalence section (Section VI.), and a bioequivalence review copy (in orange folders) containing all information in the archival copy from the beginning of the ANDA through Section VII.

13800 N.W. 2nd St • Suite 190 • Sunrise, Florida 33325 • Phone: 954-315-6600 • Fax: 954-315-6601

We certify that, concurrently with filing this ANDA, a true copy of the technical sections of the ANDA (including a copy of the Form FDA 356h and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) was sent to our local district office. This field copy was contained in burgundy folders.

Please direct any written, telephone or fax communication regarding this application to:

Monique Weitz, Associate Director
Abrika Pharmaceuticals LLLP
13800 N.W. 2nd Street, Suite 190
Sunrise, Florida 33325
Telephone: 954-313-6600 Fax: 954-315-6601

Thank you.

Sincerely,

Monique Weitz, Head of Regulatory
Abrika Pharmaceuticals LLLP

Enclosure: Executive Summary

ABRIKA
PHARMACEUTICALS

505(j)(2)(A)(ii) ok on 9/23/2004 for the 150mg strength only
[signature]
26 Oct 2004

77-285

September 23, 2004

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Central Document Room
7500 Standish Place
Room East 150
Rockville, MD 20855

RECEIVED
SEP 2 3 2004
OGD/CDR

Re: Abrika Pharmaceuticals LLLP - Abbreviated New Drug Application for Bupropion Hydrochloride Extended-Release Tablets, 150 mg Original Submission

Dear Sir/Madam:

Abrika Pharmaceuticals LLLP is submitting this original abbreviated new drug application (ANDA), pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, seeking approval to market Abrika Pharmaceuticals' Bupropion Hydrochloride Extended-Release Tablets, 150 mg. Abrika Pharmaceuticals' Bupropion Hydrochloride Extended-Release Tablets, 150 mg is bioequivalent to the approved, reference listed drug, Wellbutrin XL (bupropion hydrochloride extended-release tablets) 150 mg, the subject of NDA No. 21-515, held by GlaxoSmithkline, Research Triangle Park, North Carolina 27709.

Two bioequivalence studies were performed in support of this ANDA. One study was designed as a randomized, single-dose, two-way crossover study under fasting conditions. The other study was designed as a randomized, single-dose, two-way crossover study under fed conditions. Both studies were managed on behalf of Abrika Pharmaceuticals by [redacted] b(4)

[redacted]. The studies were conducted by one principal investigator at a single site in the United States. The study reports and supporting documentation, are contained in the bioequivalence section (Section VI) of this application. The SAS Data Set diskettes (one for each study) are located at the front of the first binder for Section VI for both the Archival (blue) and Review (orange) copies.

The enclosed ANDA consists of twenty-nine (29) volumes. Abrika Pharmaceuticals is filing an archival copy (in blue folders) that contains all the information required in the ANDA, a technical review copy (in red folders) containing all the information in the archival copy with the exception of the bioequivalence section (Section VI.), and a bioequivalence review copy (in orange folders) containing all information in the archival copy from the beginning of the ANDA through Section VII.

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Although the drug substance, Bupropion Hydrochloride, is an USP compendial article, Abrika Pharmaceuticals is proposing an *alternative* method for determination of the impurity, ⌣ Abrika believes that this proposed HPLC method provides increased assurance for the purity of the drug substance. Additionally, the finished drug product that is the subject of this ANDA, Bupropion Hydrochloride Extended-Release Tablets (QD) is a non-USP article. Therefore, pursuant to FDA's February 1999, *Guidance for Industry, "Organization of an ANDA"*, Abrika Pharmaceuticals is submitting two additional separately bound copies of the Analytical Methods validation package (Section XV) for the proposed *alternative* analytical method and the non-compendial finished drug product. The package includes specifications, methods, and methods validation data for the drug substance and finished drug product. The specifications and methods are the same as those submitted in the ANDA. The package consists of pages copied from the original ANDA: 1) specifications and analytical methods for the drug substance, 2) specifications and analytical methods for the finished drug product, 3) methods validation data for the drug substance and finished drug product. The two separately bound copies are contained in red folders clearly marked as to contents.

b(4)

Abrika Pharmaceuticals commits to resolving any issues identified in the methods validation process after approval.

We certify that, concurrently with filing this ANDA, a true copy of the technical sections of the ANDA (including a copy of the Form FDA 356h and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) was sent to our local district office. This field copy was contained in burgundy folders.

Please direct any written, telephone or fax communication regarding this application to:

Monique Weitz, Associate Director
Abrika Pharmaceuticals LLLP
13800 N.W. 2nd Street, Suite 190
Sunrise, Florida 33325
Telephone: 954-313-6600 Fax: 954-315-6601

Thank you.

Sincerely,

Monique Weitz, Head of Regulatory
Abrika Pharmaceuticals LLLP

Enclosure: Executive Summary