CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 77-715

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

Sponsor: Watson Laboratories, Inc.

Approval Date: June 13, 2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-715

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-715

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-715

Watson Laboratories, Inc.
Attention: Ernest Lengle, Ph.D.
Executive Director, Regulatory Affairs
311 Bonnie Circle
Corona, CA 92880

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated May 19, 2005, 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 the tentative approval letter issued by this office on January 31, 2007, and to your amendments dated October 12, 2005; September 15, 2006; and March 15, and May 21, 2007. We acknowledge receipt of your correspondences dated March 23, 2006 and March 15, 2007, addressing the patent issues associated with this ANDA.

We have completed the review of this abbreviated application, 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) remain **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 has been satisfactorily resolved.

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:

> The dissolution testing should be conducted in 900 mL of 0.1 N HCl at 37 °C using USP Apparatus I (basket) at 75 rpm. The test product should meet the following specifications:
>
> | Time | Percent Dissolved |
> |---|---|
> | 2 hours | [redacted] b(4) |
> | 4 hours | |
> | 8 hours | |
> | 12 hours | |

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 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 the 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 Watson Laboratories, Inc. (Watson) for infringement of one or more of these patents that were the subjects of the paragraph IV certifications. This action must have been brought against Watson prior to the expiration of 45 days from the date the notice you provided under section 505 (j)(2)(B)(i) was received by the NDA/patent holder(s). You notified the agency that Watson 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 Watson in the United States District Court for the Southern District of New York [Biovail Laboratories International SRL v. Watson Laboratories, Inc., Civil Action No. 05CV7799]. You have informed the agency that on February 26, 2007, this litigation was dismissed with prejudice.

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.

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.

Our decision to retain the tentative approval status of 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 application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This decision is subject to change on the basis of new information that may come to our attention.

As noted previously, 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 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 to OGD prior to the submission of your application. Accordingly, your Bupropion Hydrochloride Extended-release Tablets (XL), 150 mg (Once-A-Day), will be eligible for final approval beginning on the date that is one-hundred eighty days after the date the agency received notice of the first commercial marketing of the 150 mg strength under the previous application. For additional information, we refer you to the Agency's guidance document entitled "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1988).

To reactivate this application to provide for final approval of your Bupropion Hydrochloride Extended-release Tablets (XL) 150 mg (Once-A-Day), you must submit a "Supplemental Application - Expedited Review Requested". This prior-approval supplemental application should be submitted approximately 90 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 501 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 301-827-5771.

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
6/13/2007 12:01:24 PM
for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-715

TENTATIVE APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-715

Watson Laboratories, Inc.
Attention: Christine Woods
Associate Director, Regulatory Affairs
311 Bonnie Circle
Corona, CA 92880

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated May 19, 2005, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Bupropion Hydrochloride Extended-release Tablets, 150 mg and 300 mg (Once-A-Day).

Reference is also made to your amendments dated July 27, July 28, and December 6, 2005; March 28, August 11, October 11, and November 13, 2006; and January 19, and January 26, 2007. We also acknowledge receipt of your correspondence dated March 23, 2006 addressing the patent issues associated with this ANDA.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the ongoing patent litigation noted below. Therefore, the ANDA is **tentatively approved.** This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention. This letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The reference listed drug (RLD) upon which you have based your ANDA, Wellbutrin XL 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 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 the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Bupropion Hydrochloride Extended-release Tablets, 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 Watson Laboratories, Inc. (Watson) for infringement of one or more of these patents that were the subjects of the paragraph IV certifications. This action must have been brought against Watson prior to the expiration of 45 days from the date the notice you provided under section 505 (j)(2)(B)(i) was received by the NDA/patent holder(s). You notified the agency that Watson complied with the requirements of section 505(j)(2)(B) of the Act, and litigation for infringement of the '341 and '327 patents was brought against Watson in the United States District Court for the Southern District of New York [Biovail Laboratories International SRL v. Watson Laboratories, Inc., Civil Action No. 05CV7799].

Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii), currently February 2, 2008,[1]

   b. the date the court decides[2] that the patents are invalid or not infringed (see sections

[1] Because information on the '341 and '327 patents was submitted to FDA before August 18, 2003, this reference to section 505(j)(5)(B)(iii) is to that section of the Act as in effect prior to December 8, 2003, when the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) was enacted. See MMA § 1101(c)(3).

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

505(j)(5)(B)(iii)(I), (II), and (III) of the Act) or,

c. the listed patents have expired, and

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

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED.

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

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

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 501 of the Act. Also, until the agency issues the final

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

For further information on the status of this application, or prior to submitting additional amendments, please contact Thomas Hinchliffe, Project Manager, at 301-827-5771.

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
1/31/2007 09:55:58 AM
for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-715

LABELING

PRESCRIBING INFORMATION

Bupropion Hydrochloride Extended-Release Tablets (XL)

Issued: May 2007

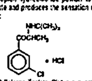
Rx only

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, is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is $C_{13}H_{18}ClNO \cdot HCl$. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



Bupropion Hydrochloride Extended-Release Tablets (XL) are supplied for oral administration as 300 mg, white to off-white extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: colloidal silicon dioxide, ethylcellulose, hydroxypropyl cellulose, methacrylic acid copolymer, microcrystalline cellulose, stearic acid, talc, titanium dioxide, hydrochloric acid and triethyl citrate. The tablets are printed with edible black ink. USP drug release test is pending.

CLINICAL PHARMACOLOGY

Pharmacodynamics: Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine and dopamine, and does not inhibit monoamine oxidase or the re-uptake of serotonin. While the mechanism of action of bupropion, as with other antidepressants, is unknown, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

... 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 4400 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 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Drug-Related Increases
<18	14 additional cases
18-24	5 additional cases
	Drug-Related Decreases
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. ...

... seizure, or patients treated with other agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold.

Hepatic Impairment: Bupropion hydrochloride extended-release tablets (XL) should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required, as peak bupropion, as well as AUC, levels are substantially increased and accumulation is likely to occur in such patients to a greater extent than usual. The dose should not exceed 150 mg every other day in these patients (see CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted.

PRECAUTIONS

General: ***Agitation and Insomnia:*** Increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment, have been associated with treatment with bupropion. Patients in placebo-controlled trials of major depressive disorder with the sustained-release formulation of bupropion, experienced agitation, anxiety, and insomnia as shown in Table 2.

Table 2. Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials of sustained-release formulation of bupropion for Major Depressive Disorder

Adverse Event Term	Bupropion Hydrochloride Sustained-Release Formulation 300 mg/day (n=376)	Bupropion Hydrochloride Sustained-Release Formulation 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 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 the sustained-release formulation of bupropion for Major Depressive Disorder

Weight Change	Bupropion Hydrochloride Sustained-Release Formulation 300 mg/day (n=339)	Bupropion Hydrochloride Sustained-Release Formulation 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 ...

MEDICATION GUIDE
Bupropion Hydrochloride Extended-Release Tablets (XL)
Rx only

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

IMPORTANT: Be sure to read the section of this Medication Guide beginning with "What is the most important information I should know about bupropion hydrochloride extended-release tablets (XL)?" It contains important information about this medication. It immediately follows the next section called "Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions."

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

Read the Medication Guide that comes with you or your family member's antidepressant medicine. This 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 when the medicine is first started.**
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 first 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.

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

There is a chance of having a seizure (convulsion, fit) with bupropion hydrochloride extended-release tablets (XL), especially in people:

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

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

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

What is important information I should know and share with my family about taking antidepressants?

Patients and their families should watch out for worsening depression or thoughts of suicide. Also watch out for sudden or severe changes in feelings such as feeling anxious, agitated, panicky, irritable, hostile, aggressive, impulsive, severely restless, overly excited and hyperactive, not being able to sleep, or other unusual changes in behavior. If this happens, especially at the beginning of antidepressant treatment or after a change in dose, call your doctor. For additional information see section above entitled "Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions." 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 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® (bupropion hydrochloride tablets) or WELLBUTRIN SR® (bupropion hydrochloride extended-release tablets (SR).** Bupropion is the same active ingredient that is in bupropion hydrochloride extended-release tablets (XL).
- drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- 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, 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 can harm your unborn baby.
- **are breastfeeding.** Bupropion passes through your milk. It is not known if bupropion can harm your baby.
- **have liver problems,** especially cirrhosis of the liver.
- have kidney problems.
- have an eating disorder such as anorexia nervosa or bulimia.
- have had a head injury.
- have had a seizure (convulsion, fit).
- have a tumor in your nervous system (brain or spine).
- have had a heart attack, heart problems, or high blood pressure.

- are a diabetic taking insulin or other medicines to control your blood sugar.
- drink a lot of alcohol.
- abuse prescription medicines or street drugs.
- **Tell your doctor about all the medicines you take**, including prescription and non-prescription medicines, vitamins and herbal supplements. Many medicines increase your chances of having seizures or other serious side effects if you take them while you are using bupropion hydrochloride extended-release tablets (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 their tightly closed bottle.
- Bupropion hydrochloride extended-release tablets (XL) may have an odor.

General information about bupropion hydrochloride extended-release tablets (XL)

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

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

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

Active ingredient: bupropion hydrochloride.

Inactive ingredients: colloidal silicon dioxide, ethylcellulose, hydroxypropyl cellulose, methacrylic acid copolymer, microcrystalline cellulose, stearic acid, talc, titanium dioxide, hydrochloric acid and triethyl citrate. The tablets are printed with edible black ink.

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tain the same active ingredient found in ZYBAN®, used as an aid to smoking cessation treatment, and that bupropion hydrochloride extended-release tablets (XL) should not be used in combination with ZYBAN®, or any other medications that contain bupropion (such as WELLBUTRIN SR® (bupropion hydrochloride extended-release tablets (SR)), the sustained-release formulation, or WELLBUTRIN® (bupropion hydrochloride tablets), the immediate-release formulation.

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, coadministration of bupropion with drugs that are metabolized by CYP2D6 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index.

MAO Inhibitors: Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Levodopa and Amantadine: Limited clinical data suggest a higher incidence of adverse experiences in patients receiving bupropion concurrently with either levodopa or amantadine. Administration of bupropion 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/m^2 basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day (approximately 2 to 7 times the MRHD on a mg/m^2 basis); lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a positive response (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/m^2 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/m^2 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/m^2 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 [illegible]

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

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

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

[†] Incidence based on the number of female patients.

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

Additional events to those listed in Table 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%), [illegible]

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® (bupropion hydrochloride tablets) or from Wellbutrin SR® (bupropion hydrochloride extended-release tablets (SR)): When switching patients from Wellbutrin® (bupropion hydrochloride tablets) to bupropion hydrochloride extended-release tablets (XL) or from Wellbutrin SR® (bupropion hydrochloride extended-release tablets (SR)) to [illegible]

HOW SUPPLIED

[illegible]

Storage

Store at 20°-25°C (68°-77°F). [See USP controlled room temperature.]

[illegible]

Watson Laboratories, Inc.
Corona, CA 92880 USA

Issued: May 2007

MEDICATION GUIDE
Bupropion Hydrochloride Extended-Release Tablets (XL)
Rx only

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

IMPORTANT: Be sure to read the section of this Medication Guide beginning with "What is the most important information I should know about bupropion hydrochloride extended-release tablets (XL)?" It contains important information about this medication. It immediately follows the next section called "Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions."

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

Read the Medication Guide that comes with you or your family member's antidepressant medicine. This 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 when the medicine is first started.**
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 first 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.

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

There is a chance of having a seizure (convulsion, fit) with bupropion hydrochloride extended-release tablets (XL), especially in people:

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

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

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

What is important information I should know and share with my family about taking antidepressants?

Patients and their families should watch out for worsening depression or thoughts of suicide. Also watch out for sudden or severe changes in feelings such as feeling anxious, agitated, panicky, irritable, hostile, aggressive, impulsive, severely restless, overly excited and hyperactive, not being able to sleep, or other unusual changes in behavior. If this happens, especially at the beginning of antidepressant treatment or after a change in dose, call your doctor. For additional information see section above entitled "Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions." 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 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® (bupropion hydrochloride tablets) or WELLBUTRIN SR® (bupropion hydrochloride extended-release tablets (SR).** Bupropion is the same active ingredient that is in bupropion hydrochloride extended-release tablets (XL).
- drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- 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, 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 can harm your unborn baby.
- **are breastfeeding.** Bupropion passes through your milk. It is not known if bupropion can harm your baby.

- **have liver problems,** especially cirrhosis of the liver.
- have kidney problems.
- have an eating disorder such as anorexia nervosa or bulimia.
- have had a head injury.
- have had a seizure (convulsion, fit).
- have a tumor in your nervous system (brain or spine).
- have had a heart attack, heart problems, or high blood pressure.
- are a diabetic taking insulin or other medicines to control your blood sugar.
- drink a lot of alcohol.
- abuse prescription medicines or street drugs.
- **Tell your doctor about all the medicines you take,** including prescription and non-prescription medicines, vitamins and herbal supplements. Many medicines increase your chances of having seizures or other serious side effects if you take them while you are using bupropion hydrochloride extended-release tablets (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 their tightly closed bottle.
- Bupropion hydrochloride extended-release tablets (XL) may have an odor.

General information about bupropion hydrochloride extended-release tablets (XL)

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

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

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

Active ingredient: bupropion hydrochloride.

Inactive ingredients: colloidal silicon dioxide, ethylcellulose, hydroxypropyl cellulose, methacrylic acid copolymer, microcrystalline cellulose, stearic acid, talc, titanium dioxide, hydrochloric acid and triethyl citrate. The tablets are printed with edible black ink.

The following are registered trademarks of their respective manufacturers: Prozac®/Eli Lilly and Company; Zoloft®/Pfizer Pharmaceuticals; Luvox®/Solvay Pharmaceuticals, Inc.; Anafranil®/Mallinckrodt Inc.; Nardil®/Warner Lambert Company; Parnate®/GlaxoSmithKline; Marplan®/Oxford Pharmaceutical Services, Inc.; Zyban®/GlaxoSmithKline; Wellbutrin®/GlaxoSmithKline; Wellbutrin SR®/GlaxoSmithKline.

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

Watson Laboratories, Inc.
Corona, CA 92880 USA

Issued: May 2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-715

LABELING REVIEWS

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

ANDA Number: 77-715
Date of Submissions: May 21, 2007
Applicant's Name: Watson Laboratories, Inc.
Established Name: Bupropion Hydrochloride Extended-release Tablets (XL) 300 mg (Once Daily)

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

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

CONTAINER LABELS (300 mg= 30s and 1000s)

Satisfactory in final print as of October 11, 2006 submission

PROFESSIONAL PACKAGE INSERT/MEDICATION GUIDE
Satisfactory in final print as of May 21, 2007 submission.

MEDICATION GUIDE
Satisfactory in final print as of May 21, 2007 submission.

Revisions needed post approval:
INSERT
DESCRIPTION, second paragraph, move last sentence on a separate line, "USP drug release test is pending.

BASIS OF APPROVAL:

PATENTS/EXCLUSIVITIES
Patent Data – NDA 21-515

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

Exclusivity Data– NDA 21-515

Code	Reference	Expiration	Labeling Impact
I-497	Prevention of seasonal major depressive episodes in patients with seasonal affective disorder	June 12, 2009	None Carve Out- AF dated 8/11/06

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.

NDA Firm: GlaxoSmithKline

Date of Approval of NDA Insert and supplement #: S-014 (approved 7/3/06); S-10, S-018 (approved 6/12/06)

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

Was this approval based upon an OGD labeling guidance? No

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

1. MODEL LABELING

This review was based on the labeling for Wellbutrin® XL (GlaxoSmithKline; Approved 7-3-06 and 6-12-06) NDA 21-515/S-014 and S-10, S-018. The firm has revised their suicidal Warnings and their Medication Guide per the Psychopharmacologic Drugs Advisory Committee's recommendations. This template can be found on the following website, http://www.fda.gov/cder/drug/antidepressants/default.htm

- Per memo from Kim Dettelbach, [redacted] b(5)
- S-014 provides for a larger and more prominent font to state the number of times a day that the bupropion formulation should be taken. S-018 was used for the text for the generics (revision of pregnancy category from a Category B to a Category C).
- For consistency in the generic labeling, the following revisions should be made to all bupropion hydrochloride extended-release tablets (XL);

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

WARNINGS
Screening Patients for Bipolar Disorder, second paragraph, revised to read;
Patients should be made aware that bupropion hydrochloride extended release tablets (XL) contain the same active ingredient found in ZYBAN®, used as an aid to smoking cessation treatment, and that bupropion hydrochloride extended release tablets (XL) should not be used in combination with ZYBAN®, or any other medications that contain bupropion, such as WELLBUTRIN SR (bupropion hydrochloride extended release tablets (SR), the sustained-release formulation or WELLBUTRIN (bupropion hydrochloride tablets), the immediate-release formulation.

PRECAUTIONS
Clinical Worsening and Suicide Risk, second paragraph, revised as follows:

Patients should be made aware that bupropion hydrochloride extended release tablets (XL) contain the same active ingredient found in ZYBAN®, used as an aid to smoking cessation treatment, and that bupropion hydrochloride extended release tablets (XL) should not be used in combination with ZYBAN®, or any other medications that contain bupropion, such as WELLBUTRIN SR (bupropion hydrochloride extended release tablets (SR), the sustained-release formulation or WELLBUTRIN (bupropion hydrochloride tablets), the immediate-release formulation.

DOSAGE AND ADMINISTRATION
Switching Patients from Wellbutrin® (bupropion hydrochloride tablets) or from Wellbutrin® SR (bupropion hydrochloride extended-release tablets (SR), revise subsection as follows:
When switching patients from Wellbutrin® (bupropion hydrochloride tablets) to bupropion hydrochloride extended-release tablets (XL) or from Wellbutrin ®SR (bupropion hydrochloride extended-release tablets (SR)) to bupropion hydrochloride extended release tablets (XL), give the same total daily dose when possible. Patients who are currently being treated with Wellbutrin® (bupropion hydrochloride tablets) at 300 mg/day (for example, 100 mg 3 times a day) may be switched to bupropion hydrochloride extended-release tablets (XL) 300 mg once daily. Patients who are currently being treated with Wellbutrin® SR (bupropion hydrochloride extended-release tablets (SR) at 300 mg/day (for example, 150 mg twice daily) may be switched to bupropion hydrochloride extended release tablets (XL) 300 mg once daily.

MEDICATION GUIDE

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

Do not take bupropion hydrochloride extended-release tablets if you:

- have or had a seizure disorder or epilepsy.
- are taking ZYBAN® (used to help people stop smoking) or any other medicines that contain bupropion hydrochloride, such as WELLBUTRIN® (bupropion hydrochloride tablets) or WELLBUTRIN SR® (bupropion hydrochloride extended-release tablets (SR). Bupropion is the same active ingredient that is in bupropion hydrochloride extended-release tablets (XL).
- drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these make you sleepy) or benzodiazepines and you stop using them all of a sudden.

2. Bupropion extended release tablets for Wellbutrin XL will contain "(XL)" and "Once Daily" on the labeling to distinguish from the Wellbutrin SR generic products. Watson was instructed to use the Tall-Man lettering for the established name as recommended in the Name Differentiation Project.

Per Lillie Golson's email dated 9/11/06, the labeling should state Wellbutrin SR and Wellbutrin when referencing the immediate-release and sustained release formulations in the CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, DOSAGE AND ADMINSTRATION sections and the Med Guide. Wellbutrin SR and Wellbutrin were added because of safety/confusion issue when all three formulations are referenced in the same paragraph. I requested Watson to add the trademarks and corresponding manufacturer of Zyban, Wellbutrin and Wellbutrin SR.

3. USP ISSUE: There is a Bupropion Hydrochloride Extended-Release Tablets monograph in USP 29. However, according to the bio review (V:\firmsam\impax\ltrs&rev\77415D1104.doc), the monograph is not for Wellbutrin® XL:

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

For this ANDA, D. Patel noted (V:\firmsam\watson\ltrs&rev\77715D0505.doc) that the firm conducted dissolution testing using the NDA 21-515 method. I emailed D. Patel on 4/25/06 to see if Watson needs to add "Drug Release Test and Dissolution Test pending" to their labeling. D. Patel replied on 4/27/06.

Ann,

Since there is no USP dissolution method for bupropion extended release tablet (Wellbutrin XL), Watson conducted dissolution testing using the RLD method. Dissolution method for this product may not be submitted to be placed in the USP. Therefore, I would think it may not be necessary to include the statement.

Thanks
Dev

From: Vu, Thuyanh (Ann)
Sent: Tuesday, April 25, 2006 11:50 AM
To: Patel, Devvrat
Subject: Question about USP and ANDA 77-715

Devvrat,

Could you advise me on the labeling for ANDA 77-715 (Watson's bupropion XL tabs). Your review stated that Watson followed the RLD's dissolution testing method. I realized that the USP 29 dissolution testing methods only pertains to bupropion IR and SR formulations. Should Watson put in the Labeling, the statement: "USP Drug Release Test is pending."? USP 29 also specified dissolution test in the labeling section. Do I also need to ask Watson to add in : "USP Dissolution Test is pending."?

Thanks
Ann

Latest email about USP issue from Lillie Golson and Nhan Tran dated 9/1/06:

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

From: Tran, Nhan L
Sent: Thursday, August 31, 2006 4:24 PM
To: Golson, Lillie D
Cc: Seo, Paul
Subject: RE: Wellbutrin XL

Lillie:

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

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

I hope I have answered your questions. If you need further clarifications, please let me know.

Thanks,

I asked Watson to delete "USP" from their labeling and labels. I will ask Watson to add "USP drug release test is pending" in their Description section since Watson could not currently meet USP specifications for test 1.

Watson deleted "USP" and added ""USP drug release test is pending" in their Description section in their 10/11/06 amendment.

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

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

Exclusivity Data– NDA 21-515

Code	Reference	Expiration	Labeling Impact
I-497	Prevention of seasonal major depressive episodes in patients with seasonal affective disorder	June 12, 2009	None Carve Out- AF dated 8/11/06

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
   Watson Laboratories, Inc.

1033 Stoneleigh Avenue
Carmel, NY 10512 [Vol 1.2, pg. 356]

6. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A3.1, pp. 56 & 57] **Component/ Function**
Bupropion Hydrochloride/API
Hydroxypropyl Cellulose
Microcrystalline Cellulose and colloidal silicon dioxide/
Stearic Acid/
[redacted]
Triethyl Citrate/
Methacrylic Acid Copolymer/
[redacted]
[redacted] Black Ink/Printing Ink

b(4)

7. CONTAINER/CLOSURE
30's: [redacted] bottle [redacted] [Vol 1.3, pg. 757]
1000's: [redacted] bottle [redacted], [Vol 3.2, pg 670]

b(4)

8. PACKAGING CONFIGURATIONS
RLD: 150 mg: Bottles of 30s and 90s 300 mg: Bottles of 30s
ANDA: 300 mg: Bottles of 30s and 1000s
Watson has stated in their 5/21/07 submission that they have removed reference to the 150 mg strength, per discussion with Peter Rickman.

9. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
RLD: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
ANDA: Store at 20-25°C (68-77°F). [See USP Controlled Room Temperature].

10. DISPENSING RECOMMENDATIONS:
NDA – Dispense in tight containers as defined in the USP.
ANDA –Dispense in a tight, light-resistant container as defined in the USP.

USP- Packaging and storage- Preserve in well-closed containers

11. TABLET IMPRINT (Vol 1.3, pg. 1110 for the 150 mg strength, Vol 3.2, pg. 798 for the 300 mg strength)
RLD: unscored
ANDA: The tablet descriptions are satisfactory as seen in the HOW SUPPLIED section.
- 150 mg: White to off-white, round, biconvex, film coated tablets with "WPI" over "3331" on one side and plain on the other side.
- 300 mg: White to off-white, round, biconvex, film coated tablets with "WPI" over "3332" on one side and plain on the other side.

12. BIOAVAILABILITY/BIOEQUIVALENCE: As of 10/25/06 the Division of Bioequivalence review is pending.

	Labeled	Sponsor Bio Study	
		Fasting	Fed
C_{max}	Not listed in RLD labeling	68.93 mcg/mL	77.81 mcg/mL
T_{max}	5 hours	4.79 hours	6.48 hours

$T_{1/2}$	21 hours	18.22 hours	20.14 hours

13. MED GUIDE/PATIENT INFORMATION LEAFLET: Watson stated in AF dated 8/11/06 that for each 1,000 count bottle, Watson will ship a tear-off pad of 50 Med Guides/Patient Information Leaflets per tear-off pad. Watson's 30 count containers have one Med Guide/Patient Information Leaflet affixed to the container.

MEDICATION GUIDE
Bupropion Hydrochloride Extended-Release Tablets (XL)

Rx only

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

IMPORTANT: Be sure to read the section of this Medication Guide beginning with "What is the most important information I should know about bupropion hydrochloride extended-release tablets (XL)?" It contains important information about this medication. It immediately follows the next section called "Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions."

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

Read the Medication Guide that comes with you or your family member's antidepressant medicine. This 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 when the medicine is first started.**
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 first 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.

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

There is a chance of having a seizure (convulsion, fit) with bupropion hydrochloride extended-release tablets (XL), especially in people:

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

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

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

What is important information I should know and share with my family about taking antidepressants?

Patients and their families should watch out for worsening depression or thoughts of suicide. Also watch out for sudden or severe changes in feelings such as feeling anxious, agitated, panicky, irritable, hostile, aggressive, impulsive, severely restless, overly excited and hyperactive, not being able to sleep, or other unusual changes in behavior. If this happens, especially at the beginning of antidepressant treatment or after a change in dose, call your doctor. For additional information see section above entitled "Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions." 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 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® (bupropion hydrochloride tablets) or WELLBUTRIN SR® (bupropion hydrochloride extended-release tablets (SR).** Bupropion is the same active ingredient that is in bupropion hydrochloride extended-release tablets (XL).
- drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- 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, 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 can harm your unborn baby.
- **are breastfeeding.** Bupropion passes through your milk. It is not known if bupropion can harm your baby.

- **have liver problems,** especially cirrhosis of the liver.
- have kidney problems.
- have an eating disorder such as anorexia nervosa or bulimia.
- have had a head injury.
- have had a seizure (convulsion, fit).
- have a tumor in your nervous system (brain or spine).
- have had a heart attack, heart problems, or high blood pressure.
- are a diabetic taking insulin or other medicines to control your blood sugar.
- drink a lot of alcohol.
- abuse prescription medicines or street drugs.
- **Tell your doctor about all the medicines you take,** including prescription and non-prescription medicines, vitamins and herbal supplements. Many medicines increase your chances of having seizures or other serious side effects if you take them while you are using bupropion hydrochloride extended-release tablets (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 their tightly closed bottle.
- Bupropion hydrochloride extended-release tablets (XL) may have an odor.

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

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

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

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

Active ingredient: bupropion hydrochloride.

Inactive ingredients: colloidal silicon dioxide, ethylcellulose, hydroxypropyl cellulose, methacrylic acid copolymer, microcrystalline cellulose, stearic acid, talc, titanium dioxide, hydrochloric acid and triethyl citrate. The tablets are printed with edible black ink.

The following are registered trademarks of their respective manufacturers: Prozac®/Eli Lilly and Company; Zoloft®/Pfizer Pharmaceuticals; Luvox®/Solvay Pharmaceuticals, Inc.; Anafranil®/Mallinckrodt Inc.; Nardil®/Warner Lambert Company; Parnate®/GlaxoSmithKline; Marplan®/Oxford Pharmaceutical Services, Inc.; Zyban®/GlaxoSmithKline; Wellbutrin®/GlaxoSmithKline; Wellbutrin SR®/GlaxoSmithKline.

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

Watson Laboratories, Inc.
Corona, CA 92880 USA

Issued: May 2007

PRESCRIBING INFORMATION

Bupropion Hydrochloride Extended-Release Tablets (XL)

Issued: May 2007

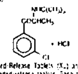
Rx only

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, is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is $C_{13}H_{18}ClNO \cdot HCl$. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



[illegible]

CLINICAL PHARMACOLOGY

[illegible]

CLINICAL TRIALS

[illegible]

INDICATIONS AND USAGE

[illegible]

CONTRAINDICATIONS

[illegible]

WARNINGS

[illegible]

Table 1	
Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Drug-Related Increases
<18	14 additional cases
18-24	5 additional cases
	Drug-Related Decreases
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) is 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, [illegible]

[illegible]

PRECAUTIONS

[illegible] Patients in placebo-controlled trials of major depressive disorder with the sustained-release formulation of bupropion, experienced agitation, anxiety, and insomnia as shown in Table 2.

Table 2. Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials of sustained-release formulation of bupropion for Major Depressive Disorder

Adverse Event Term	Bupropion Hydrochloride Sustained-Release Formulation 300 mg/day (n=376)	Bupropion Hydrochloride Sustained-Release Formulation 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 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 the sustained-release formulation of bupropion for Major Depressive Disorder

Weight Change	Bupropion Hydrochloride Sustained-Release Formulation 300 mg/day (n=339)	Bupropion Hydrochloride Sustained-Release Formulation 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 pre-existing hypertension.

Data from a comparative study of the sustained-release formulation of bupropion (Zyban® Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher [illegible]

[illegible]

MEDICATION GUIDE
Bupropion Hydrochloride Extended-Release Tablets (XL)
Rx only

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

IMPORTANT: Be sure to read the section of this Medication Guide beginning with "What is the most important information I should know about bupropion hydrochloride extended-release tablets (XL)?" It contains important information about this medication. It immediately follows the next section called "Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions."

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

Read the Medication Guide that comes with you or your family member's antidepressant medicine. This 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 when the medicine is first started.**
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 first 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.

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

There is a chance of having a seizure (convulsion, fit) with bupropion hydrochloride extended-release tablets (XL), especially in people:

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

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

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

What is important information I should know and share with my family about taking antidepressants?

Patients and their families should watch out for worsening depression or thoughts of suicide. Also watch out for sudden or severe changes in feelings such as feeling anxious, agitated, panicky, irritable, hostile, aggressive, impulsive, severely restless, overly excited and hyperactive, not being able to sleep, or other unusual changes in behavior. If this happens, especially at the beginning of antidepressant treatment or after a change in dose, call your doctor. For additional information see section above entitled "Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions." 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 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® (bupropion hydrochloride tablets) or WELLBUTRIN SR® (bupropion hydrochloride extended-release tablets (SR).** Bupropion is the same active ingredient that is in bupropion hydrochloride extended-release tablets (XL).
- drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- 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, 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 can harm your unborn baby.
- **are breastfeeding.** Bupropion passes through your milk. It is not known if bupropion can harm your baby.
- **have liver problems,** especially cirrhosis of the liver.
- have kidney problems.
- have an eating disorder such as anorexia nervosa or bulimia.
- have had a head injury.
- have had a seizure (convulsion, fit).
- have a tumor in your nervous system (brain or spine).
- have had a heart attack, heart problems, or high blood pressure.

- are a diabetic taking insulin or other medicines to control your blood sugar.
- drink a lot of alcohol.
- abuse prescription medicines or street drugs.
- **Tell your doctor about all the medicines you take**, including prescription and non-prescription medicines, vitamins and herbal supplements. Many medicines increase your chances of having seizures or other serious side effects if you take them while you are using bupropion hydrochloride extended-release tablets (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, cat, 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 their tightly closed bottle.
- Bupropion hydrochloride extended-release tablets (XL) may have an odor.

General information about bupropion hydrochloride extended-release tablets (XL)

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

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

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

Active ingredient: bupropion hydrochloride.

Inactive ingredients: colloidal silicon dioxide, ethylcellulose, hydroxypropyl cellulose, methacrylic acid copolymer, microcrystalline cellulose, stearic acid, talc, titanium dioxide, hydrochloric acid and triethyl citrate. The tablets are printed with edible black ink.

The following are registered trademarks of their respective manufacturers: Prozac®/Eli Lilly and Company; Zoloft®/Pfizer Pharmaceuticals; Luvox®/Solvay Pharmaceuticals, Inc.; Anafranil®/Mallinckrodt Inc.; Nardil®/Warner Lambert Company; Parnate®/GlaxoSmithKline; Marplan®/Oxford Pharmaceutical Services, Inc.; Zyban®/GlaxoSmithKline; Wellbutrin®/GlaxoSmithKline; Wellbutrin SR®/GlaxoSmithKline.

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

Watson Laboratories, Inc.
Corona, CA 92880 USA

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[illegible] same active ingredient as bupropion hydrochloride extended-release tablets (XL), should not be used in combination with bupropion hydrochloride extended-release tablets (XL), or should not be used in combination with any other bupropion product. Bupropion hydrochloride extended-release tablets (XL) should be discontinued and not prescribed if the patient experiences a seizure while on this medication.

Patients should not drink alcohol to excess (CNS sedative drug like bupropion hydrochloride extended-release tablets (XL) may lower the tolerance for alcohol in patients taking bupropion), or abruptly discontinue alcohol and sedative drugs.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised not to breastfeed an infant if they are receiving bupropion hydrochloride extended-release tablets (XL).

Patients should be advised to notify their physician if they develop symptoms of hypomania or mania.

Patients should be advised to swallow bupropion hydrochloride extended-release tablets (XL) whole and not to crush, chew, divide, or break the tablets.

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions: Few systematic data have been collected on the metabolism of bupropsion following concomitant administration with other drugs or, alternatively, the effect of concomitant administration of bupropion on the metabolism of other drugs.

Because bupropion is so 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 enzyme. Therefore, the potential exists for drug interactions between bupropion hydrochloride extended-release tablets (XL) and drugs that are substrates or inhibitors of the CYP2B6 enzyme (eg, cyclophosphamide, ticlopidine and cyclophosphamide). In addition, in vitro studies suggest that piperidine derivative metabolites of bupropion, but not bupropion itself, are inhibitors of reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent oxidation of the pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy male volunteers who received single doses of bupropion 150 mg tablets of the sustained-release formulation of bupropion and another 200 mg of ritonavir, the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and half-life, respectively, of the combined moieties of 4-hydroxybupropion and erythro-hydrobupropion.

While not systematically studied, certain drugs may induce the metabolism of bupropion (eg, carbamazepine, phenobarbital, phenytoin).

Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of ethinylestradiol or norethindrone.

Administration of ritonavir 100 mg every 8 hours or lopinavir 400 mg/ritonavir 100 mg every 12 hours for 14 days resulted in decreased bupropion concentrations. Bupropion dose adjustment should be considered in patients receiving concomitant ritonavir or lopinavir/ritonavir.

Administration of bupropion 150 mg sustained-release tablets once daily for 14 days resulted in a 50% increase in the AUC of hydroxybupropion. Bupropion dose adjustment should be considered in patients receiving concomitant ritonavir or lopinavir/ritonavir.

Coadministration of bupropion 150 mg sustained-release tablets once daily for 14 days resulted in a 23% increase in the AUC of the combined moieties of 4-hydroxybupropion and erythro-hydrobupropion. There is no known experience of the effects of this level of exposure to hydroxybupropion in humans.

Although in vitro studies indicate that bupropion is a competitive inhibitor of CYP2D6, the clinical significance of this finding is unknown. During clinical trials, bupropion was coadministered with a number of cardiovascular drugs that are predominantly metabolized by CYP2D6, including beta-blockers, antidepressants of the selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressant (TCA), and antihypertensive classes, without apparent adverse consequences. However, caution is advised in coadministering bupropion with these drugs.

Drugs Metabolized By Cytochrome P450isoenzyme 2B6 (CYP2B6): Many drugs, including most analgesics, sedatives, hypnotics, anticonvulsants, and antipsychotics, are metabolized by the CYP2B6 isoenzyme. Although bupropion is not metabolized by this isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2B6 isoenzyme activity. In a study of 15 male subjects (aged 19–32 years) who were extensive metabolizers of the CYP2B6 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 7-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 CYP2B6 has not been formally studied.

Transdermal nicotine and bupropion may both decrease seizure threshold. Concomitant administration should be considered only if the potential benefit outweighs the potential risk. Administration of bupropion hydrochloride extended-release tablets (XL) to patients receiving any other medication concurrently should be undertaken with caution, using small initial doses and careful dose escalation.

Drugs That Lower Seizure Threshold: Concurrent administration of bupropion hydrochloride extended-release tablets (XL) and agents (eg, antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low-dose initiation and gradual dose increase 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 persons who were drinking alcohol during treatment with bupropion. Patients should be advised to minimize or discontinue alcohol use during bupropion hydrochloride extended-release tablets (XL) therapy (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, (approximately 6 and 2 times the maximum recommended human dose [MRHD], respectively, on a mg/m² basis). In the rat study, there was a dose-related, statistically significant increase in adenomas and carcinomas (combined) of the liver and other organs was seen in other study.

Bupropion produced a positive response (2 of 5 tests conducted) only in 2 of 5 strains in the Ames bacterial mutagenicity test and also was positive in one mammalian cell test in 5 of 5 conducted. The clastogenic activity was observed only at concentrations associated with toxicity.

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 performed in rats and rabbits, bupropion 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 the rat study, there was a dose-related embryotoxicity (increased resorptions and decreased fetal weights) observed at doses greater than or equal to 150 mg/kg/day (approximately equal to the MRHD on a mg/m² basis) and greater. Decreased fetal weights were also seen at 50 mg/kg/day (approximately one-third the MRHD on a mg/m² basis).

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 developing normally.

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 during the first trimester of pregnancy. 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 antidepressors in the first trimester, or to 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 excreted 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 (the immediate-release formulation was not studied), 376 were 65 years old and older, and 75 were 75 years old and older. 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 was not substantially altered in elderly subjects given single doses. 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 reactions 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 safety information included under this subsection

is based primarily on data from six controlled clinical trials each for the sustained-release formulation of bupropion.

Adverse Events Leading to Discontinuation of Treatment With the Immediate-release or sustained-release formulation of bupropion: In placebo-controlled clinical trials, 9% and 11% of patients treated with 300 and 400 mg/day, respectively, of the sustained-release formulations of bupropion and 4% of patients treated with placebo discontinued treatment due to adverse events. The specific adverse events that contributed to dose discontinuation in at least 1% of patients treated with 300 mg/day or 400 mg/day of the sustained-release formulations of bupropion, and 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	Bupropion Hydrochloride Sustained-Release Formulations 300 mg/day (n=376)	Bupropion Hydrochloride Sustained-Release Formulations 400 mg/day (n=114)	Placebo (n=388)
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 discontinuations 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 Immediate and Sustained Release Formulations of Bupropion: Table 5 enumerates treatment-emergent adverse events that occurred among patients treated with 300 and 400 mg/day of the sustained-release formulations of bupropion and each 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, duration, reliance on spontaneous 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, the reported figures do not indicate the seriousness of the various adverse events nor the 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[a] Adverse Event	Bupropion Hydrochloride Sustained-Release Formulations 300 mg/day (n=376)	Bupropion Hydrochloride Sustained-Release Formulations 400 mg/day (n=114)	Placebo (n=388)
Body (General)			
Headache	26%	25%	23%
Infection	8%	9%	6%
Abdominal pain	3%	9%	2%
Asthenia	3%	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%	3%	2%
Dyspepsia	0%	2%	0%
Musculoskeletal			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	2%	3%	0%
Twitch	1%	2%	-
Nervous System			
Insomnia	13%	16%	6%
Dizziness	7%	11%	5%
Agitation	3%	6%	2%
Anxiety	5%	6%	3%
Tremor	6%	3%	1%
Nervousness	3%	3%	3%
Somnolence	2%	3%	2%
Irritability	3%	3%	2%
Memory decreased	-	3%	1%
Paresthesia	1%	2%	1%
Central nervous system stimulation	2%	1%	1%
Respiratory			
Pharyngitis	3%	5%	2%
Sinusitis	3%	1%	2%
Increased cough	1%	2%	1%
Skin			
Sweating	6%	5%	2%
Rash	5%	4%	1%
Pruritus	2%	4%	2%
Urticaria	2%	1%	0%
Special Senses			
Tinnitus	6%	6%	2%
Taste perversion	2%	4%	-
Amblyopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	-	2%	0%
Vaginal hemorrhage[b]	-	2%	-
Urinary tract infection	1%	0%	-

[a] Adverse events that occurred in at least 1% of patients treated with either 300 or 400 mg/day of the sustained-release formulations 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, hypertonia, neck pain, respiratory disorder, rhinitis, and sinus disorder.

[b] Incidence based on the number of female patients.

- Hypertension (see also WARNINGS and PRECAUTIONS)

Additional events to those listed in Table 5 that occurred in an incidence of at least 1% in controlled clinical trials of the immediate-release formulation of bupropion (150 to 600 mg/day) and that were numerically more frequent than placebo were: cardiac arrhythmias (3% vs. 4%), hypertension (4% vs. 2%), hypertonia (3% vs. 2%), tachycardia (11% vs. 6%), appetite increase (4% vs. 2%), dysgeusia (2% vs. 1%), hearing loss (2% vs. 1%), libido decreased (2% vs. 1%), impaired sleep quality (4% vs. 2%), sensory disturbance (4% vs. 3%), confusion (3% vs. 0%), decreased libido (3% vs. 2%), hostility (6% vs. 4%), auditory disturbance (5% vs. 3%), and gastritis 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 least twice the placebo rate are listed below for the 300 and 400 mg/day dose groups.

300 mg/day of the Sustained-Release Formulation: Abnormal dreams, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tremor, and tremor.

400 mg/day of the Sustained-Release Formulation: Abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tremor, and urinary frequency.

Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion: In addition to the adverse events listed above, the following events have been reported in clinical trials and postmarketing experience with bupropion hydrochloride in patients who were depressed or were treated for other conditions. The frequent events represent the proportion of patients who experienced a reaction in a therapeutic adverse event trial. At least one occurrence in placebo-controlled studies for depression (n = 681) or smoking cessation (n = 1,613), or patients who experienced an adverse event requiring discontinuation of treatment in an open-label exploratory study with the sustained-release formulation of bupropion (n=3100). All less frequent events that were observed are included except those listed in Tables 2 through 5, those events listed in other safety-related sections, those adverse events associated under COSTART terms that are so general as to be inherently 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 only remote clinical importance are discussed 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 in which a causal relationship is remote: Events are not necessarily reported 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: sore chills, facial edema, musculoskeletal chest pain, and gynecomastia.

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, pericarditis, and vasodilation. Rare was syncope. Also observed were complete atrioventricular block, extrasystoles, hypertension, hypertensive crisis (in some cases severe; see PRECAUTIONS), myocardial infarction, phlebitis, and pulmonary embolism.

Digestive: Infrequent: were abnormal liver function, bruxism, gastric reflux, gingivitis, glossitis, increased stomatitis, 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 secretion.

Hemic and Lymphatic: Infrequent: was ecchymosis. Also observed were anemia, leukopenia, leukocytosis, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhage or thrombotic complications, were observed when bupropion was coadministered with warfarin.

Metabolic and Nutritional: Infrequent: were edema and peripheral edema. Also observed was dysgeusia.

Musculoskeletal: Infrequent: were leg cramps. Also observed were muscle rigidity, rhabdomyolysis and muscle weakness.

Nervous System: Infrequent: were abnormal coordination, decreased libido, depersonalization, dysphoria, emotional lability, lethargy, hypertonia, hypesthesia, hypnagogic reaction, libido increased, and vertigo. Rare were amnesia, ataxia, dehydration, and hyperkinesia. Also observed were abnormal electroencephalogram (EEG), aggression, akathisia, delirium, delusions, dystonia, dyskinesia, dysphasia, epileptic status, extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid reaction, restlessness, and unsteady walking/ataxic dysfunction.

Respiratory: Rare was bronchospasm. Also observed were pneumonia.

Skin: Rare was alopecia/hair loss. Also observed were alopecia, pigmentation, exfoliative dermatitis, and melasma.

Special Senses: Infrequent: were acute angle-closure glaucoma and dry eye. Also observed were deafness, diplopia, increased intraocular pressure, and mydriasis.

Urogenital: Infrequent: were impotence, polyuria, and prostatic disorder. Also observed were abnormal ejaculation, cystitis, dysphagia, dysuria, genital moniliasis, hematuria, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Bupropion is not a controlled substance.

Human: Controlled clinical studies of bupropion immediate-release formulation in abuse and dependence potential, in subjects with a history of multiple drug abuse, and in depressed patients showed some increase in motor activity and impaired mental acuity.

In a population of individuals experienced with drugs of abuse, a single dose of 400 mg of bupropion produced mild euphoria similar to that produced by diethylpropion (Tenuate®) and significantly less than that produced by methamphetamine and zolpidem (Ambien®). The Addiction Research Center Inventories (ARCI), and a secret word-response category produced amphetamine-like and zolpidem-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 of one 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 EKG 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 uncomplicated seizures, cardiac dysrhythmia, and cardiac arrest preceded the death were reported in these patients.

Overdosage Management: Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. EKG monitoring is also recommended for at least 48 hours post-ingestion. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orotracheal 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, or hemoperfusion or exchange transfusion in the management of bupropion overdosage. 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 diazepam or lorazepam 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, sometimes the initial symptoms of a developing manic episode, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the temporary administration of an intermediate or long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first few weeks of treatment. Insomnia may be treated by sedating antidepressant doses. If dose lowering, a return to effective suppressant 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 administered once daily. Higher dosing (up to 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/day initial dose is adequately tolerated, an increase to the 300 mg/day target dose, given as one dose 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 a maximum of 400 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. Such a response to the acute episode, but unless 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 has not been systematically demonstrated. The physician should periodically reassess the need for maintenance treatment and the appropriate dose for such treatment.

Switching Patients from Wellbutrin® (bupropion hydrochloride) or from Wellbutrin SR® (bupropion hydrochloride extended-release tablets) or from Wellbutrin XL® (bupropion hydrochloride extended-release tablets (XL)) to bupropion hydrochloride extended-release tablets (XL): When switching patients from Wellbutrin® (bupropion hydrochloride tablets) to bupropion hydrochloride extended-release tablets (XL) or from Wellbutrin SR® (bupropion hydrochloride extended-release tablets (SR)) to bupropion hydrochloride extended-release tablets (XL), the same total daily dose will generally be appropriate. Patients who are currently being treated with Wellbutrin® (bupropion hydrochloride tablets) at 300 mg/day, for example, 100 mg 3 times a day, may be switched to bupropion hydrochloride extended-release tablets (XL) 300 mg once daily. Patients who are currently being treated with Wellbutrin SR® (bupropion hydrochloride extended-release tablets (SR)) at 300 mg/day, for example, 150 mg twice daily, may be switched to bupropion hydrochloride extended-release tablets (XL) 300 mg once daily.

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. Initiating and/or titrating dose of bupropion hydrochloride extended-release tablets (XL) should be used with caution 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 severe 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 white to off-white, round, film-coated tablets with WPI over 2332 printed in black ink in bottles of 30 tablets (NDC 0591-3329-30) and bottles of 1000 tablets (NDC 0591-3329-10).

Storage

Store at 20°-25°C (68°-77°F) [See USP controlled room temperature.]

The following are registered trademarks of their respective manufacturers: Zyban®/GlaxoSmithKline; Wellbutrin®/GlaxoSmithKline; Wellbutrin SR®/GlaxoSmithKline.

Watson Laboratories, Inc.
Corona, CA 92880 USA

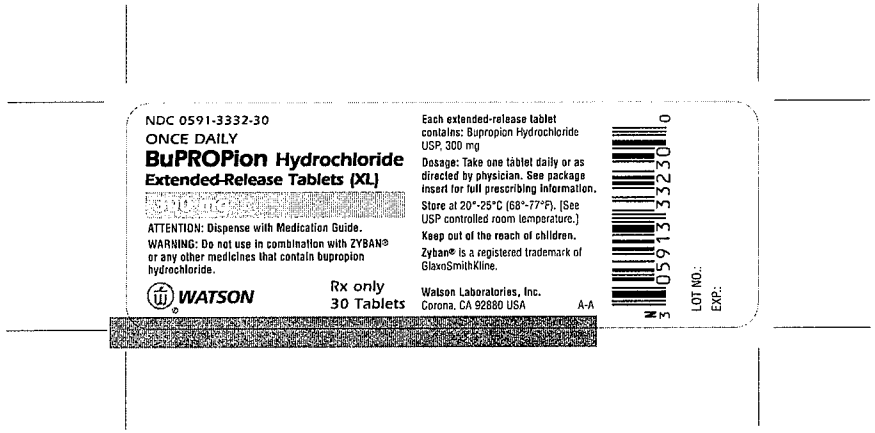
Issued: May 2007

PROOF-1

Artwork by [redacted]

b(4)

LABEL SIZE:
3.5" WIDE X 1.25" HIGH



BLACK TEXT

[redacted]
WATSON IMAGE

[redacted]
COLOR CODE LEVEL 2

b(4)

[redacted]
REFER TO SPEC SHEET

PROOF-1

Artwork by [redacted] b(4)

LABEL SIZE:
5.25" WIDE x 2.25" HIGH

NDC 0591-3332-10

ONCE DAILY

BuPROPion Hydrochloride
Extended-Release Tablets (XL)

300 mg

ATTENTION: Dispense with Medication Guide.

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

WATSON®

Rx only
1000 Tablets

Each extended-release tablet contains: Bupropion Hydrochloride USP, 300 mg

Dosage: Take one tablet daily or as directed by physician. See package insert for full prescribing information.

Store at 20°-25°C (68°-77°F). [See USP controlled room temperature.]

Keep out of the reach of children.

Zyban® is a registered trademark of GlaxoSmithKline.

Watson Laboratories, Inc.
Corona, CA 92880 USA A-A

3 05913 33210 2

LOT NO.:
EXP.:

BLACK TEXT

[redacted] WATSON IMAGE b(4)

[redacted] COLOR CODE LEVEL 2

[redacted] REFER TO SPEC SHEET

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
6/2/2007 02:15:19 PM
LABELING REVIEWER

Lillie Golson
6/4/2007 04:28:09 PM
LABELING REVIEWER

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

ANDA Number:	77-715	Dates of Submissions: October 11, 2006 & November 13, 2006
Applicant's Name:	Watson Laboratories, Inc.	
Established Name:	Bupropion Hydrochloride Extended-release Tablets (XL) 150 mg and 300 mg (Once Daily)	

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

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

CONTAINER LABELS (150 mg= 30s, 300 mg= 30s and 1000s)

Satisfactory in final print as of October 11, 2006 submission
150 mg (30s) : \\Cdsesub1\n77715\N_000\2006-10-11\labeling\proposed.pdf\150 mg 30s.pdf
300 mg (30s): \\Cdsesub1\n77715\N_000\2006-10-11\labeling\proposed.pdf\300 mg 30s.pdf
300 mg (1000s): \\Cdsesub1\n77715\N_000\2006-10-11\labeling\proposed.pdf\300 mg 1000s.pdf

PROFESSIONAL PACKAGE INSERT
Satisfactory in final print as of October 11, 2006 submission
\\Cdsesub1\n77715\N_000\2006-10-11\labeling\proposed.pdf\pi.pdf

MEDICATION GUIDE
Satisfactory in final print as of November 13, 2006 submission

Future Revisions:

General

Yana Mille has been consulted regarding whether this product (and its RLD) falls under the USP monograph. If so, it is allowable for the sponsor to include "USP" in the established name throughout labels and labeling. They may report a labeling change in the regard in an annual report.

Medication Guide (Second bullet under, "Who should not take...")

Revise "bupropion hydrochloride extended-release tablets (XL)" to read "Wellbutrin SR".

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.

NDA Firm: GlaxoSmithKline

Date of Approval of NDA Insert and supplement #s: S-014 (approved 7/3/06) and S-010 & S-018 (approved 6/12/06)

Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No

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

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

   - Per memo from Kim Dettelbach, [redacted] b(5)
   - S-014 provides for a larger and more prominent font to state the number of times a day that the bupropion formulation should be taken. S-018 was used for the text for the generics (revision of pregnancy category from a Category B to a Category C).

2. Bupropion extended release tablets for Wellbutrin XL will contain "(XL)" and "Once Daily" on the labeling to distinguish from the Wellbutrin SR generic products. Watson was instructed to use the Tall-Man lettering for the established name as recommended in the Name Differentiation Project.

Per Lillie Golson's email dated 9/11/06, the labeling should state Wellbutrin SR and Wellbutrin when referencing the immediate-release and sustained release formulations in the CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, DOSAGE AND ADMINSTRATION sections and the Med Guide. Wellbutrin SR and Wellbutrin were added because of safety/confusion issue when all three formulations are referenced in the same paragraph. I requested Watson to add the trademarks and corresponding manufacturer of Zyban, Wellbutrin and Wellbutrin SR.

3. USP ISSUE: There is a Bupropion Hydrochloride Extended-Release Tablets monograph in USP 29. However, according to the bio review (V:\firmsam\impax\ltrs&rev\77415D1104.doc), the monograph is not for Wellbutrin® XL:

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

   For this ANDA, D. Patel noted (V:\firmsam\watson\ltrs&rev\77715D0505.doc) that the firm conducted dissolution testing using the NDA 21-515 method. I emailed D. Patel on 4/25/06 to see if Watson needs to add "Drug Release Test and Dissolution Test pending" to their labeling. D. Patel replied on 4/27/06.

Ann,

Since there is no USP dissolution method for bupropion extended release tablet (Wellbutrin XL), Watson conducted dissolution testing using the RLD method. Dissolution method for this product may not be submitted to be placed in the USP. Therefore, I would think it may not be necessary to include the statement.

Thanks
Dev

From: Vu, Thuyanh (Ann)
Sent: Tuesday, April 25, 2006 11:50 AM
To: Patel, Devvrat
Subject: Question about USP and ANDA 77-715

Devvrat,

Could you advise me on the labeling for ANDA 77-715 (Watson's bupropion XL tabs). Your review stated that Watson followed the RLD's dissolution testing method. I realized that the USP 29 dissolution testing methods only pertains to bupropion IR and SR formulations. Should Watson put in the Labeling, the statement: "USP Drug Release Test is pending."? USP 29 also specified dissolution test in the labeling section. Do I also need to ask Watson to add in : "USP Dissolution Test is pending."?

Thanks
Ann

Latest email about USP issue from Lillie Golson and Nhan Tran dated 9/1/06:

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

From: Tran, Nhan L
Sent: Thursday, August 31, 2006 4:24 PM
To: Golson, Lillie D
Cc: Seo, Paul
Subject: RE: Wellbutrin XL

Lillie:

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

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

I hope I have answered your questions. If you need further clarifications, please let me know.

Thanks,

I asked Watson to delete "USP" from their labeling and labels. I will ask Watson to add "USP drug release test is pending" in their Description section since Watson could not currently meet USP specifications for test 1.

Watson deleted "USP" and added ""USP drug release test is pending" in their Description section in their 10/11/06 amendment.

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

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

Exclusivity Data– NDA 21-515

Code	Reference	Expiration	Labeling Impact
I-497	Prevention of seasonal major depressive episodes in patients with seasonal affective disorder	June 12, 2009	Carve Out- AF dated 8/11/06

It is not known at this time whether the sponsor is pursuing a pediatric exclusivity for the new indication.

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
   Watson Laboratories, Inc.
   1033 Stoneleigh Avenue
   Carmel, NY 10512 [Vol 1.2, pg. 356]

6. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A3.1, pp. 56 & 57]
Component/ Function
Bupropion Hydrochloride/API
Hydroxypropyl Cellulose/ [redacted]
Microcrystalline Cellulose and colloidal silicon dioxide [redacted]
Stearic Acid/ [redacted]
[redacted]
Methacrylic Acid Copolymer [redacted]
[redacted]
[redacted] Black Ink/Printing Ink

b(4)

7. CONTAINER/CLOSURE
   30's: [redacted] bottle [redacted] [Vol 1.3, pg. 757]
   1000's: [redacted] bottle [redacted] [Vol 3.2, pg 670]

b(4)

8. PACKAGING CONFIGURATIONS
   RLD: 150 mg: Bottles of 30s and 90s 300 mg: Bottles of 30s
   ANDA: 150 mg: Bottles of 30s 300 mg: Bottles of 30s and 1000s

9. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   RLD: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
   ANDA: Store at 20-25°C (68-77°F). [See USP Controlled Room Temperature].

10. DISPENSING RECOMMENDATIONS:
    NDA – Dispense in tight containers as defined in the USP.
    ANDA –Dispense in a tight, light-resistant container as defined in the USP.
    USP- Packaging and storage- Preserve in well-closed containers

11. TABLET IMPRINT (Vol 1.3, pg. 1110 for the 150 mg strength, Vol 3.2, pg. 798 for the 300 mg strength)
    RLD: unscored
    ANDA: The tablet descriptions are satisfactory as seen in the HOW SUPPLIED section.
    - 150 mg: White to off-white, round, biconvex, film coated tablets with "WPI" over "3331" on one side and plain on the other side.
    - 300 mg: White to off-white, round, biconvex, film coated tablets with "WPI" over "3332" on one side and plain on the other side.

12. BIOAVAILABILITY/BIOEQUIVALENCE: As of 10/25/06 the Division of Bioequivalence review is pending.

	Labeled	Sponsor Bio Study	
		Fasting	Fed
C_{max}	Not listed in RLD labeling	68.93 mcg/mL	77.81 mcg/mL
T_{max}	5 hours	4.79 hours	6.48 hours
$T_{1/2}$	21 hours	18.22 hours	20.14 hours

13. MED GUIDE/PATIENT INFORMATION LEAFLET: Watson stated in AF dated 8/11/06 that for each 1,000 count bottle, Watson will ship a tear-off pad of 50 Med Guides/Patient Information Leaflets per tear-off pad. Watson's 30 count containers have one Med Guide/Patient Information Leaflet affixed to the container.

Date of Review: 12/6/06 Dates of Submission: 10/11/06 and 11/13/2006

Primary Reviewer: Charlie Hoppes (for M.Dillahunt) Date:

Team Leader: Lillie Golson Date:

Redacted 7 page(s)

of trade secret and/or

confidential commercial

information from

LABELING REVIEW

DRAFT LABELING

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

/s/

Charles Hoppes
12/6/2006 11:22:32 AM
MEDICAL OFFICER

Lillie Golson
12/6/2006 02:11:55 PM
MEDICAL OFFICER

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

ANDA Number:	77-715
Date of Submissions:	August 11, 2005
Applicant's Name:	Watson Laboratories, Inc.
Established Name:	Bupropion Hydrochloride Extended-release Tablets (XL) 150 mg and 300 mg (Once Daily)

Labeling Deficiencies

1. CONTAINER (bottles of 30s, for the 150 mg strength, bottles of 30s and 1000s for the 300 mg strength)

   Principal display panel- revise the established name to read: "BuPROPion Hydrochloride Extended-Release Tablets (XL)" [delete USP].

2. INSERT

   a. GENERAL COMMENT

      Add "(XL)" to the established name wherever WELLBUTRIN XL is used, including the black box warning and medication guide.

   b. Add "Rx Only" directly below the title of the insert.

   c. Revise the established name in the title to "Bupropion Hydrochloride Extended-Release Tablets (XL)".

   d. DESCRIPTION

      i. First paragraph, revise to read; "Bupropion hydrochloride extended-release tablets (XL)..."

      ii. Second paragraph, first sentence, delete "USP".

      iii. Add "USP drug release test is pending" at the end of the second paragraph.

   e. CONTRAINDICATIONS

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

      ii. Start a new paragraph for "The concurrent administration of bupropion hydrochloride extended-release tablets (XL) and a monoamine oxidase...."

   f. WARNINGS

      Screening Patients for Bipolar Disorder, second paragraph, revise to " **Patients should be made aware that bupropion hydrochloride extended release tablets (XL) contain the same active ingredient found in ZYBAN®, used as an aid to smoking cessation treatment, and that bupropion hydrochloride extended release tablets (XL) should not be used in combination with ZYBAN®, or any other medications that contain bupropion, such as WELLBUTRIN SR® (bupropion hydrochloride extended release tablets (SR), the sustained-release formulation or WELLBUTRIN® (bupropion hydrochloride tablets), the immediate-release formulation."**

g. PRECAUTIONS

Clinical Worsening and Suicide Risk, second paragraph, revise to "Patients should be made aware that bupropion hydrochloride extended release tablets (XL) contain the same active ingredient found in ZYBAN®, used as an aid to smoking cessation treatment, and that bupropion hydrochloride extended release tablets (XL) should not be used in combination with ZYBAN®, or any other medications that contain bupropion, such as WELLBUTRIN SR® (bupropion hydrochloride extended-release tablets (SR), the sustained-release formulation, or WELLBUTRIN® (bupropion hydrochloride tablets), the immediate-release formulation."

h. ADVERSE EVENTS

i. Table 4, footnote *, add "bronchitis, dysmenorrhea, and dyspepsia".

ii. Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials, revise "Table 6" to "Table 4".

i. DOSAGE AND ADMINISTRATION

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

j. HOW SUPPLIED

Please add below the storage temperature statement "The following are registered trademarks of their respective manufacturers: Zyban®/GlaxoSmithKline, Wellbutrin®/GlaxoSmithKline, Wellbutrin SR®/GlaxoSmithKline."

3. MEDICATION GUIDE

a. Who should not take bupropion hydrochloride extended-release tablets (XL)? Do not take bupropion hydrochloride extended-release tablets if you:

Second bullet, revise to "...• **are taking ZYBAN® (used to help people stop smoking) or any other medicines that contain bupropion hydrochloride, such as WELLBUTRIN® (bupropion hydrochloride tablets) or WELLBUTRIN SR® (bupropion hydrochloride extended-release tablets (SR).** Bupropion is the same active ingredient that is in bupropion hydrochloride extended-release tablets (XL)."

b. What should I tell my doctor before using bupropion hydrochloride extended-release tablets (XL)? Second and third bullet, revise "bupropion hydrochloride extended-release tablets" to "bupropion".

c. Place "How should I store bupropion hydrochloride extended-release tablets (XL)?" on a separate paragraph.

d. Please add Zyban®, Wellbutrin® and Wellbutrin SR® in your list of registered trademarks and their manufacturers.

Please revise your label and labeling as described above and submit electronically. The immediate container labels and carton labeling may be submitted either electronically or in hard copy.

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

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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 29	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?			X
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?			X
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	

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

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

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

   - Per memo from Kim Dettelbach, [redacted] b(5)
   - S-014 provides for a larger and more prominent font to state the number of times a day that the bupropion formulation should be taken. S-018 was used for the text for the generics (revision of pregnancy category from a Category B to a Category C).

2. Bupropion extended release tablets for Wellbutrin XL will contain "(XL)" and "Once Daily" on the labeling to distinguish from the Wellbutrin SR generic products. Watson was instructed to use the Tall-Man lettering for the established name as recommended in the Name Differentiation Project.

Per Lillie Golson's email dated 9/11/06, the labeling should state Wellbutrin SR and Wellbutrin when referencing the immediate-release and sustained release formulations in the CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, DOSAGE AND ADMINSTRATION sections and the Med Guide. Wellbutrin SR and Wellbutrin were added because of safety/confusion issue when all three formulations are referenced in the same paragraph. I requested Watson to add the trademarks and corresponding manufacturer of Zyban, Wellbutrin and Wellbutrin SR.

3. USP ISSUE: There is a Bupropion Hydrochloride Extended-Release Tablets monograph in USP 29. However, according to the bio review (V:\firmsam\impax\ltrs&rev\77415D1104.doc), the monograph is not for Wellbutrin® XL:

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

   For this ANDA, D. Patel noted (V:\firmsam\watson\ltrs&rev\77715D0505.doc) that the firm conducted dissolution testing using the NDA 21-515 method. I emailed D. Patel on 4/25/06 to see if Watson needs to add "Drug Release Test and Dissolution Test pending" to their labeling. D. Patel replied on 4/27/06.

Ann,

Since there is no USP dissolution method for bupropion extended release tablet (Wellbutrin XL), Watson conducted dissolution testing using the RLD method. Dissolution method for this product may not be submitted to be placed in the USP. Therefore, I would think it may not be necessary to include the statement.

Thanks
Dev

From: Vu, Thuyanh (Ann)
Sent: Tuesday, April 25, 2006 11:50 AM
To: Patel, Devvrat
Subject: Question about USP and ANDA 77-715

Devvrat,

Could you advise me on the labeling for ANDA 77-715 (Watson's bupropion XL tabs). Your review stated that Watson followed the RLD's dissolution testing method. I realized that the USP 29 dissolution testing methods only pertains to bupropion IR and SR formulations. Should Watson put in the Labeling, the statement: "USP Drug Release Test is pending."? USP 29 also specified dissolution test in the labeling section. Do I also need to ask Watson to add in : "USP Dissolution Test is pending."?

Thanks
Ann

Latest email about USP issue from Lillie Golson and Nhan Tran dated 9/1/06:

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

From: Tran, Nhan L
Sent: Thursday, August 31, 2006 4:24 PM
To: Golson, Lillie D
Cc: Seo, Paul
Subject: RE: Wellbutrin XL

Lillie:

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

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

I hope I have answered your questions. If you need further clarifications, please let me know.

Thanks,

I asked Watson to delete "USP" from their labeling and labels. I will ask Watson to add "USP drug release test is pending" in their Description section since Watson could not currently meet USP specifications for test 1.

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

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

Exclusivity Data– NDA 21-515

Code	Reference	Expiration	Labeling Impact
I-497	Prevention of seasonal major depressive episodes in patients with seasonal affective disorder	June 12, 2009	None Carve Out- AF dated 8/11/06

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
Watson Laboratories, Inc.
1033 Stoneleigh Avenue
Carmel, NY 10512 [Vol 1.2, pg. 356]

6. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A3.1, pp. 56 & 57] **Component/ Function**
Bupropion Hydrochloride/API
Hydroxypropyl Cellulose/ [redacted]
Microcystalline Cellulose and colloidal silicon dioxide [redacted]
Stearic Acid/ [redacted]
[redacted]
Triethyl Citrate/ [redacted]
Methacrylic Acid Copolymer [redacted]
[redacted]
[redacted] Black Ink/Printing Ink

b(4)

7. CONTAINER/CLOSURE
30's: [redacted] bottle [redacted] [Vol 1.3, pg. 757]
1000's: [redacted] bottle [redacted] [Vol 3.2, pg 670]

b(4)

8. PACKAGING CONFIGURATIONS
RLD: 150 mg: Bottles of 30s and 90s 300 mg: Bottles of 30s
ANDA: 150 mg: Bottles of 30s 300 mg: Bottles of 30s and 1000s

9. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
RLD: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
ANDA: Store at 20-25°C (68-77°F). [See USP Controlled Room Temperature].

10. DISPENSING RECOMMENDATIONS:
NDA – Dispense in tight containers as defined in the USP.
ANDA –Dispense in a tight, light-resistant container as defined in the USP.

USP- Packaging and storage- Preserve in well-closed containers

11. TABLET IMPRINT (Vol 1.3, pg. 1110 for the 150 mg strength, Vol 3.2, pg. 798 for the 300 mg strength)
RLD: unscored
ANDA: The tablet descriptions are satisfactory as seen in the HOW SUPPLIED section.
- 150 mg: White to off-white, round, biconvex, film coated tablets with "WPI" over "3331" on one side and plain on the other side.
- 300 mg: White to off-white, round, biconvex, film coated tablets with "WPI" over "3332" on one side and plain on the other side.

12. BIOAVAILABILITY/BIOEQUIVALENCE: As of 8/22/06, the Division of Bioequivalence found that the firm's dissolution is inadequate and that the *in vivo* BE studies are pending. According to the labeling, food did not affect the AUC or C_{max}.

	Labeled	Sponsor Bio Study	
		Fasting	Fed
C_{max}	Not listed in RLD	68.93 mcg/mL	77.81 mcg/mL

	labeling		
T_{max}	5 hours	4.79 hours	6.48 hours
$T_{1/2}$	21 hours	18.22 hours	20.14 hours

13. MED GUIDE/PATIENT INFORMATION LEAFLET: Watson stated in AF dated 8/11/06 that for each 1,000 count bottle, Watson will ship a tear-off pad of 50 Med Guides/Patient Information Leaflets per tear-off pad. Watson's 30 count containers have one Med Guide/Patient Information Leaflet affixed to the container.

Date of Review: 8/22/06 Date of Submission: 8/11/06

Primary Reviewer: Thuyanh Vu (for M.Dillahunt) Date: 9/13/06

Team Leader: Lillie Golson Date: 9/13/06

---

cc:

ANDA: 77-715
DUP/DIVISION FILE
HFD-613/AVu for MDillahunt/LGolson (no cc)
V:\FIRMSNZ\WATSON\LTRS&REV\77715.na2.L.doc
Review

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

ANDA Number:	77-715
Date of Submissions:	5/19/05 (original submission); 7/28/05 (addition of 300 mg strength)
Applicant's Name:	Watson Laboratories, Inc.
Established Name:	Bupropion Hydrochloride Extended-release Tablets USP, (XL) 150 mg and 300 mg (Once Daily)

Labeling Deficiencies

1. CONTAINER (bottles of 30s, for the 150 mg strength, bottles of 30s and 1000s for the 300 mg strength)

   a. In order to ensure that safety information is provided with all antidepressant products, we encourage you to distribute the products only 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. However, if you choose to market your product in bulk packages, please describe how many medication guides and patient information leaflets will be provided and how you plan to ensure that the medication guides and patient information leaflets arrive at the pharmacy with your product.

   b. Principal display panel- revise the established name to read: "BuPROPion Hydrochloride Extended-Release Tablets USP (XL)" [add "(XL)"].

   c. Add the following statement to the container label, preferably on the principal display panel if space permits: "ATTENTION: Dispense with Medication Guide".

   d. Dosage: add "Take one tablet daily or as directed by physician."

   e. Revise "Each Tablet contains:" to "Each Extended-Release Tablet contains:".

   f. Add "Zyban® is a registered trademark of Glaxo SmithKline." to the side panel of the container label.

   g. Please ensure your labels comply with the bar code requirements prior to full approval.

   h. Please ensure that your container labels will print in color in both PDF and Word files. Currently, only the Word files print in color. You are reminded that your labels submitted in electronic formal must be actual size, color and clarity.

2. INSERT

   a. Update your labeling based on the attached approved labeling for the reference listed drug, Wellbutrin XL, approved February 28, 2006. Your package insert should be submitted in portable document formal (PDF).

   b. PRECAUTIONS:
   PREGNANCY: TERATOGENIC EFFECTS, delete all references to [redacted] b(4)

3. MEDICATION GUIDE

   a. HOW TO TRY TO PREVENT SUICIDAL THOUGHTS AND ACTIONS:
      i. Third paragraph, fifth bullet, change (see other side) to (see Section 3).
      ii. Fourth paragraph, delete the extra space between the "s" and "i" in "visits".

b. THERE ARE BENEFITS AND RISKS WHEN USING ANTIDEPRESSANTS: Replace the symbol ™ with ® for Prozac®, Zoloft® and Anafranil®.

c. IS THIS ALL I NEED TO KNOW IF MY CHILD IS BEING PRESCRIBED AN ANTIDEPRESSANT?: Add a new paragraph to this section to acknowledge the registered trademarks as follows: Prozac® is a registered trademark of Eli Lilly and Company, Zoloft® is a registered trademark of Pfizer Pharmaceuticals,and Anafranil® is a registered trademark of /Mallinckrodt Inc.

Please revise your label and labeling as described above and submit electronically. The immediate container labels and carton labeling may be submitted either electronically or in hard copy.

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

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

Attachment: RLD insert labeling

FOR THE RECORD:

1. MODEL LABELING
   This review was based on the labeling for Wellbutrin® XL (GlaxoSmithKline; Approved 2-28-06) NDA 21-515/S-012 with the following change:
   - Per memo from Kim Dettelbach [redacted] b(5)

   NDA 21-515/S-012 not posted on "Drugs at FDA" website. I received the RLD's PM (Renmeet Gujral) "okay" via email dated 4/21/06 to disseminate the RLD's FPL dated 12/2/05.

2. Bupropion extended release tablets for Wellbutrin XL will contain "(XL)" and "Once Daily" on the labeling to distinguish from the Wellbutrin SR generic products. Watson was instructed to use the Tall-Man lettering for the established name as recommended in the Name Differentiation Project.

3. USP ISSUE: There is a Bupropion Hydrochloride Extended-Release Tablets monograph in USP 29. However, according to the bio review (V:\firmsam\impax\ltrs&rev\77415D1104.doc), the monograph is not for Wellbutrin® XL:

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

   For this ANDA, D. Patel noted (V:\firmsam\watson\ltrs&rev\77715D0505.doc) that the firm conducted dissolution testing using the NDA 21-515 method. I emailed D. Patel on 4/25/06 to see if Watson needs to add "Drug Release Test and Dissolution Test pending" to their labeling. D. Patel replied on 4/27/06. He stated that the NDA dissolution testing method may not be submitted to be placed in the USP. Hence, it is not neccessary to include the statement "Drug Release Test and Dissolution Test pending".

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

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

   Exclusivity Data– NDA 21-515

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

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
   Watson Laboratories, Inc.
   1033 Stoneleigh Avenue
   Carmel, NY 10512 [Vol 1.2, pg. 356]

6. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A3.1, pp. 56 & 57] **Component/ Function**
Bupropion Hydrochloride/API
Hydroxypropyl Cellulose/ [redacted]
Microcystalline Cellulose and colloidal silicon dioxide/ [redacted]
Stearic Acid [redacted]

b(4)

[redacted]
Triethyl Citrate/ [redacted]
Methacrylic Acid Copolymer [redacted]
[redacted]
[redacted] Black Ink/Printing Ink

b(4)

7. CONTAINER/CLOSURE
   30's: [redacted] bottle [redacted], [Vol 1.3, pg. 757]
   1000's: [redacted] bottle [redacted] [Vol 3.2, pg 670]

b(4)

8. PACKAGING CONFIGURATIONS

RLD:	150 mg: Bottles of 30s and 90s	300 mg: Bottles of 30s
ANDA:	150 mg: Bottles of 30s	300 mg: Bottles of 30s and 1000s

9. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   RLD: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
   ANDA: Store at 20-25°C (68-77°F). [See USP Controlled Room Temperature].

10. DISPENSING RECOMMENDATIONS:
    NDA – Dispense in tight containers as defined in the USP.
    ANDA –Dispense in a tight, light-resistant container as defined in the USP.

11. TABLET IMPRINT (Vol 1.3, pg. 1110 for the 150 mg strength, Vol 3.2, pg. 798 for the 300 mg strength)
    RLD: unscored
    ANDA: The tablet descriptions are satisfactory as seen in the HOW SUPPLIED section.
    - 150 mg: White to off-white, round, biconvex, film coated tablets with "WPI" over "3331" on one side and plain on the other side.
    - 300 mg: White to off-white, round, biconvex, film coated tablets with "WPI" over "3332" on one side and plain on the other side.

12. BIOAVAILABILITY/BIOEQUIVALENCE: As of 4/21/06, the Division of Bioequivalence found that the firm's dissolution is inadequate and that the *in vivo* BE studies are pending. According to the labeling, food did not affect the AUC or C_{max}.

	Labeled	Sponsor Bio Study	
		Fasting	Fed
C_{max}	Not listed in RLD labeling	68.93 mcg/mL	77.81 mcg/mL
T_{max}	5 hours	4.79 hours	6.48 hours
$T_{1/2}$	21 hours	18.22 hours	20.14 hours

Date of Review: 4/25/06 Date of Submissions: 5/19/05 and 7/28/05

Primary Reviewer: Thuyanh Vu (for M.Dillahunt) Date: 5/1/06

Team Leader: Lillie Golson for L Golson Date: 5/1/06

cc:

ANDA: 77-715
DUP/DIVISION FILE
HFD-613/AVu for MDillahunt/LGolson (no cc)
V:\DIVISION\LABEL\Ann Vu\My Reviews\Bupropion XL (Wellbutrin XL)\77715.na1.L.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-715

CHEMISTRY REVIEWS

ANDA 77-715

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

Watson Laboratories, Inc.

Barbara O. Scott

OGD/DC2

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Chemistry Review Data Sheet

1. ANDA 77-715

2. REVIEW #: 2

3. REVIEW DATE: March 17, 2006; April 7, 2006; January 22, 2007, January 29, 2007

4. REVIEWER: Barbara O. Scott

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Application	May 19, 2005
Amendment	Dec. 6, 2006
Major Amendment (addition of 300 mg)	July 27, 2005 (magenta type)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Telephone Amendment	March 28, 2006 (Blue Type)
Response to information request	January 19, 2007 (Green Type)
Telephone Amendment	January 26, 2007 (Orange Type)

7. NAME & ADDRESS OF APPLICANT:

Watson Laboratories Inc.
311 Bonnie Circle
Corona, CA 92880
Attn: Christina M. Woods
Phone: 951.493.5452
FAX: 951.493.4581

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN):
Buproprion Hydrochloride USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for Watson Laboratories Inc.'s proposed ANDA for Bupropion Hydrochloride USP 150 mg and 300 mg is the approved reference listed drug, Wellbutrin XL® the subject of ANDA 21-515 held by SmithKine Beecham containing 150 mg and 300 mg Bupropion Hydrochloride.

Watson certifies that to the best of their knowledge, the following patents (unexpired) for this product in the Orange Book Database are invalid, unenforceable, or will not be infringed upon by the manufacture, use or sale of Bupropion Hydrochloride Extended Release Tablets (150 mg and 300 mg) for which this application is submitted: 6,096,341 and 6,143,327.

There is no unexpired exclusivity for this product.

10. PHARMACOL. CATEGORY:
Indicated for the treatment of major depressive disorder.

11. DOSAGE FORM:
Extended Release Tablet

12. STRENGTH/POTENCY:
150 mg and 300 mg (TDI = 450 mg/day)

13. ROUTE OF ADMINISTRATION:
Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

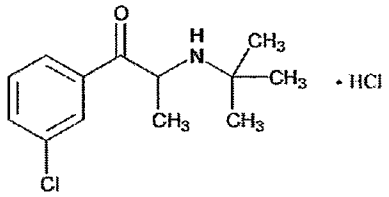
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

IUPAC Name: (±) -1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride
CAS Number: [31677-93-7]
Molecular Formula: $C_{13}H_{18}ClNO$ HCl
Molecular Weight: 276.21 g/mole (salt)
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]			Bupropion Hydrochloride	1	adequate	9 July 2005	A. Hahm
[redacted]				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		

b(4)

[redacted]	4	N/A		

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)
DMF Letters of Authorization and Technical data are provided on pp. 63-100, vol. 1.1

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	8/5/2005	
Methods Validation	N/A as per OGD policy		
Labeling	Acceptable	11/2/2006	P.Birch
Bioequivalence	Acceptable	12/6/2006	
EA	Acceptable		
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 77-715

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is approvable.

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

N/A

II. Summary of Chemistry Assessments

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

The drug substance and the drug product are compendial items.

The proposed drug product is Bupropion Hydrochloride Extended Release Tablets, USP 150 mg and 300 mg. The active ingredient is Bupropion Hydrochloride USP. The inactive ingredients are: Hydroxypropyl Cellulose, NF, Microcrystalline Cellulose, NF, Colloidal Silicon Dioxide, NF, Stearic Acid, NF, [redacted] Hydrochloric Acid, NF, [redacted] Methacrylic Acid Copolymer, NF, Triethyl Citrate, NF, [redacted] b(4)

Black Ink [redacted]

In a major amendment dated July 27, 2005 the firm submitted a request to add a 300 mg strength to the application.

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

Bupropion Hydrochloride Extended Release Tablets, USP 150 mg and 300 mg are intended for use in the treatment of major depressive disorder.

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable.

Redacted 36 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW # 2

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

/s/

Barbara O Scott
1/31/2007 08:41:44 AM
CHEMIST

Naiqi Ya
1/31/2007 09:16:55 AM
CHEMIST

Thomas Hinchliffe
1/31/2007 09:37:58 AM
CSO

ANDA 77-715

Bupropion Hydrochloride
Extended Release Tablets, USP
150 mg

Watson Laboratories, Inc.

Barbara O. Scott

OGD/DC2

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Chemistry Review Data Sheet

1. ANDA 77-715

2. REVIEW #: 1

3. REVIEW DATE: October 27, 2005

4. REVIEWER: Barbara O. Scott

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
none	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Application	May 19, 2005

7. NAME & ADDRESS OF APPLICANT:

Watson Laboratories Inc.
311 Bonnie Circle
Corona, CA 92880
Attn: Christina M. Woods
Phone: 951.493.5452
FAX: 951.493.4581

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN):
Buproprion Hydrochloride USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for Watson Laboratories Inc.'s proposed ANDA for Bupropion Hydrochloride USP 150 mg is the approved reference listed drug, Wellbutrin XL® the subject of ANDA 21-515 held by SmithKine Beecham containing 150 mg Bupropion Hydrochloride.

Watson certifies that to the best of their knowledge, the following patents (unexpired) for this product in the Orange Book Database are invalid, unenforceable, or will not be infringed upon by the manufacture, use or sale of Bupropion Hydrochloride Extended Release Tablets (150 mg) for which this application is submitted: 6,096,341 and 6,143,327.

There is no unexpired exclusivity for this product.

10. PHARMACOL. CATEGORY:
Indicated for the treatment of major depressive disorder.

11. DOSAGE FORM:
Extended Release Tablet

12. STRENGTH/POTENCY:
150 mg (450 mgTDI = mg/day)

13. ROUTE OF ADMINISTRATION:
Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

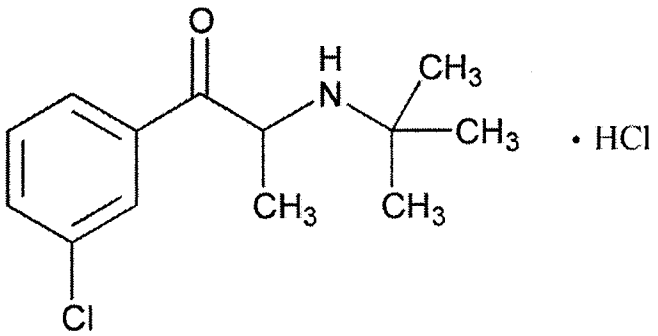
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

IUPAC Name: (±) -1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride
CAS Number: [31677-93-7]
Molecular Formula: $C_{13}H_{18}ClNO$ HCl
Molecular Weight: 276.21 g/mole (salt)
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]			Bupropion Hydrochloride	1	adequate	9 July 2005	A. Hahm
[redacted]				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		
				4	N/A		

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)
DMF Letters of Authorization and Technical data are provided on pp. 63-100, vol. 1.1

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	8/5/2005	
Methods Validation	N/A as per OGD policy		
Labeling	pending		D. Catterson
Bioequivalence	Dissolution-incomplete		
EA	Acceptable		
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 77-715

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is not approvable.

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

N/A

II. Summary of Chemistry Assessments

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

The drug substance and the drug product are compendial items.

The proposed drug product is Bupropion Hydrochloride Extended Release Tablets, USP 150 mg. The active ingredient is Bupropion Hydrochloride USP. The inactive ingredients are: Hydroxypropyl Cellulose, NF, Microcrystalline Cellulose, NF, Colloidal Silicon Dioxide, NF, Stearic Acid, NF, [redacted] Hydrochloric Acid, NF, [redacted] Methacrylic Acid Copolymer, NF, Triethyl Citrate, NF, [redacted] Black Ink, [redacted]

b(4)

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

Bupropion Hydrochloride Extended Release Tablets, USP 150 mg is intended for use in the treatment of major depressive disorder.

C. Basis for Approvability or Not-Approval Recommendation

This application is not approvable as per the deficiencies cited within this review.

III. Administrative

Executive Summary Section

A. Reviewer's Signature
Barbara O. Scott

B. Endorsement Block

HFD-640/Barbara O. Scott/10/27/05 B. Scott 01 Nov 05
HFD-640/N. Ya/10/27/05 11/2/05
HFD-640/T. Hinchliffe/10/27/05 11/3/05

C. CC Block

ANDA 77-715
ANDA DUP
DIV FILE
Field Copy

Redacted 24 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

cc: ANDA 77-715
DIV FILE
Field Copy

Endorsements
HFD-640/B. Scott/10/27/05 B. Scott 01 Nov 05

HFD-640/N. Ya/10/27/05 11/2/05

HFD-640/T. Hinchliffe/10/27/05 11/3/05

F/T by:rad10/28/05

V:\FIRMSNZ\Watson\LTRS&REV\77715cr1.DOC

TYPE OF LETTER: NOT APPROVABLE - MINOR

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-715

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-715
Drug Product Name	Bupropion Hydrochloride Extended-Release Tablets
Strength	150 mg and 300 mg
Applicant Name	Watson Laboratories, Inc.
Contact	Christine Woods
Phone	951-493-5452
Fax	951-493-4581
Submission Date(s)	05-19-05
Amendment Date(s)	07-27-05, 10-12-05, 03-28-05, 09-15-06
Reviewer	**Ethan M. Stier, Ph.D., R.Ph.**
First Generic	**No**

Addendum to a Review

I. Executive Summary

This is an addendum to the review of ANDA #77-715, submission data of 09-15-06 (DFS N077715 N 000 AB 15-Sep-2006). This addendum supersedes recommendation #4 of this review. DBE determined that Watson's Bupropion Hydrochloride Extended Release 300 mg tablet is bioequivalent to the GlaxoSmithKline's Wellbutrin XL® 300 mg tablet (RLD) under 320.24(b)(6). The fasting and non-fasting bioequivalence studies were conducted on the 150 mg strength tablet due to safety concerns (Control# 02-712 filed in V drive as V:\firmsam\Apotex\controls\02-712C1202 and 02-712md.doc).

CC: ANDA #77-715

BIOEQUIVALENCE – ACCEPTABLE

Submission Date: 05-19-05

1. **US Document** (Review Addendum)

Strengths: 300 mg
Outcome: AC

Outcome Decisions: AC

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
12/13/2006 04:06:37 PM
BIOPHARMACEUTICS

Xiaojian Jiang
12/13/2006 04:10:09 PM
BIOPHARMACEUTICS
on behalf of Shrinivas G. Nerurkar

Barbara Davit
12/13/2006 04:29:04 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-715
Drug Product Name	Bupropion XL Tablets
Strength	150 mg and 300 mg
Applicant Name	Watson Laboratories, Inc.
Contact	Christine Woods
Phone	951-493-5452
Fax	951-493-4581
Submission Date(s)	05-19-05
Amendment Date(s)	07-27-05, 10-12-05, 03-28-05, **09-15-06** (reviewed below)
Reviewer	**Ethan M. Stier, Ph.D., R.Ph.**
First Generic	**No**

I. Executive Summary:

Watson has previously submitted acceptable single-dose fasting and non-fasting bioequivalence studies comparing its test product, Bupropion Extended Release Tablets, 150 mg to the RLD product, Wellbutrin® XL tablets, 150 mg, from SKB in the original application, dated 05/19/05 (V:\firmsnz\watson\ltrs&rev\77715N0505.doc).

Due to concerns that this extended-release product could potentially dump its dose in vivo in patients who consume excessive amounts of alcohol, the Agency recently requested that the firm conduct additional dissolution testing using the FDA recommended dissolution medium of 0.1 N HCl with varying concentrations of ethanol (5% v/v, 20% v/v, and 40% v/v). Additionally, the firm was requested to accept the FDA recommended method and specification.

In the current amendment, 1) the firm submitted the requested in vitro alcohol dose dumping testing data and 2) and the firm acknowledged the FDA recommended method and specification. The Division of Bioequivalence (DBE) finds acceptable the results of Watson's in vitro dose dumping alcohol study.

The formulation of the 300 mg tablet of the test product is proportional to that of the 150 mg tablet, which underwent in vivo bioequivalence (BE) testing. A waiver of in vivo BE testing for the 300 mg strength tablet is granted. The application is complete.

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III. Background and References:

Related Reviews/Memos for Watson's Bupropion HCl XL Tablets:

1) Review of the original submission of the study V:\firmsnz\watson\ltrs&rev\77715N0505.doc.

2) Deputy Division Director Memo reviewing of Watson's submitted in vitro alcohol dose-dumping testing located on DFS as a memo to ANDA 77-715

Related Reviews/Memos for Impax's Bupropion HCl XL Tablets:

1) Review of the original submission of the study V:\FIRMSAM\IMPAX\LTRS&REV\77415N1104.doc

2) Review of Impax's submitted in vitro alcohol dose-dumping testing and review of clinical consult are located on DFS as a bioequivalence review of 08-04-06 and 08-08-06 submissions for ANDA 77415

IV. Current Submission:

DEFICIENCY COMMENT #1

1. *Based on the submitted dissolution results, your proposed dissolution specifications are not acceptable. Please acknowledge the acceptance of the following dissolution method and specifications for your test product:*

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

   2 hours: NMT —
   4 hours: —
   8 hours: —
   12 hours: NLT —

b(4)

FIRM'S RESPONSE: The firm accepted the FDA recommended dissolution method and specification.

REVIEWER'S COMMENT: The firm's response is acceptable.

DEFICIENCY COMMENT #2

Due to concern of dose dumping for the drug product, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

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

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

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

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

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

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

FIRM'S RESPONSE: The firm provided the dissolution testing data.

REVIEWER'S COMMENT: The data show that bupropion dissolution from Watson's product at 2 hrs in 5 and 20% ethanol was greater than in 0.1 N HCl without ethanol, and greater than from the RLD product. The **differences** between test and RLD product in 5% and 20% ethanol ranges from 6-12% for the 150 mg strength and from 14-17% for the 300 mg strength. However, in 40% ethanol, the test product and RLD product showed **comparable** dissolution at 2 hrs for both strengths.

The DBE concludes that the in vitro performance of Watson's product under the conditions of this test is acceptable based on comparing the alcohol dose-dumping testing results of Watson's test product to that of Impax's Bupropion HCl ER Tablet reviewed under ANDA 77-415. The DBE previously found acceptable the in vitro alcohol dose-dumping test results for Impax's product. The following is a summary of the findings:

1) Bupropion dissolution from Watson's product at 2 hrs in 5 and 20% ethanol was **not** more than dissolution from Impax's product. The average dissolution for Watson's product at 2 hrs in 5% and 20% ranges from **9-30%**, whereas the dissolution for Impax's product ranges from **30-35%**.

2) The DBE previously found Impax's in vitro alcohol dose-dumping study results acceptable based on the fact that there are **no** differences in drug dissolution **with** and **without** ethanol.

3) Impax's formulation released **39%** of the drug at 2 hours **without** ethanol for the 150 mg strength. The release rate was much faster than the corresponding RLD product (**1%** at 2 hrs without ethanol). The difference between **Impax's** product and the RLD product were much larger than that between **Watson's** product and the RLD product in 5 and 20% ethanol. The bioequivalence was demonstrated between Impax's product and the RLD product. Consistent with the in vitro results, an earlier Tmax than the RLD was observed in the in vivo study. However, OGD's clinical team has concluded that any differences in Tmax between Impax's Bupropion ER Tablets and Wellbutrin XL® do not impact the therapeutic equivalence of Impax's product. Thus, the faster release of Impax's product relative to the RLD in vitro and in vivo studies did not impact therapeutic equivalence.

Based on the above evidence, DBE concluded that since the level of drug release of Watson's product are comparable to that of Impax's product at 5% and 20% ethanol, Watson's Bupropion HCl ER Tablet gave acceptable results in the in vitro alcohol dose dumping study, as far as the safety and therapeutic equivalence were concerned.

Additionally, for a more comprehensive review of the in vitro alcohol dose-dumping testing please refer to the memo to ANDA 77-715 located on DFS.

Table I: Release of Bupropion HCl from 150 mg tablet at 2 hours in Varying Concentrations of Alcohol

TABLE 1: Percent Drug Release of 150 mg Bupropion HCl Extended-Release Tablets, USP in 0.1N HCl with various alcohol levels at 120 minutes (n=12 tablets per product).

Alcohol Level (% v/v)	Watson Bupropion HCl Extended-Release Tablets, USP, 150 mg (Lot #XT4L029, Mfg. Date: 12/04)			Wellbutrin® XL, 150 mg, (Lot #06E029P, Exp. Date: 08/07)		
	Mean (%)	Range (%)	% CV	Mean (%)	Range (%)	% CV
Test 1: 0%	2	0 to 5	87.4%	1	0 to 2	39.8%
Test 2: 5%	9	4 to 14	34.5%	3	1 to 7	78.6%
Test 3: 20%	23	17 to 29	17.2%	11	7 to 18	33.3%
Test 4: 40%	20	18 to 24	10.1%	16	13 to 18	8.5%

Table II: Release of Bupropion HCl from 300 mg tablet at 2 hours in Varying Concentrations of Alcohol

TABLE 2: Percent Drug Release of 300 mg Bupropion HCl Extended-Release Tablets, USP in 0.1N HCl with various alcohol levels at 120 minutes (n=12 tablets per product).

Alcohol Level (% v/v)	Watson Bupropion HCl Extended-Release Tablets, USP, 300 mg (Lot #XC5B013, Mfg. Date: 03/05)			Wellbutrin® XL, 300 mg, (Lot #06E002P, Exp. Date: 08/07)		
	Mean (%)	Range (%)	% CV	Mean (%)	Range (%)	% CV
Test 1: 0%	12	8 to 16	20.3%	4	2 to 11	68.6%
Test 2: 5%	20	12 to 28	22.0%	6	3 to 11	42.0%
Test 3: 20%	30	26 to 34	10.1%	13	10 to 17	17.3%
Test 4: 40%	22	18 to 36	22.5%	19	17 to 20	6.2%

Table III: Release of Bupropion HCl from 150 mg tablet in 0.1 N HCl-0% Alcohol

Manufacturer: Wellbutrin Lot# 06E029P Exp: 8/07
Date Completed: 7/27/2006 Reference: RD-P1313-25 & 26
Component: Bupropion HCl
Medium: 0.1N HCl
Vol (mL): 900
Apparatus: Basket @ 75 RPM

Sample/Time	0	15	30	45	60	75	90	105	120
1	0	0	0	0	0	0	0	0	1
2	0	0	0	0	0	0	0	1	1
3	0	0	0	0	0	0	0	1	1
4	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	1	1
6	0	0	0	0	0	0	0	0	1
7	0	0	0	0	0	0	0	0	1
8	0	0	0	0	0	0	0	0	1
9	0	0	0	0	0	0	0	1	1
10	0	0	0	0	0	0	1	1	2
11	0	0	0	0	0	0	0	0	1
12	0	0	0	0	0	0	1	1	2
avg %	0	0	0	0	0	0	0	1	1
min %	0	0	0	0	0	0	0	0	0
max %	0	0	0	0	0	0	1	1	2
SD	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.3	0.4
%CV	0.0	122.3	164.2	163.3	127.6	110.9	93.2	55.7	39.8

Manufacturer: Watson Lot# X34L023
Date Completed: 7/20/2006 Reference: RD-P1308-13, 22 & 27
Component: Bupropion HCl
Medium: 0.1N HCl
Vol (mL): 900
Apparatus: Basket @ 75 RPM

Sample/Time	0	15	30	45	60	75	90	105	120
1	0	0	0	0	0	0	0	1	4
2	0	0	0	0	0	0	0	0	1
3	0	0	0	0	0	0	0	1	2
4	0	0	0	0	0	0	0	0	1
5	0	0	0	0	0	0	1	1	3
6	0	0	0	0	0	0	0	1	2
7	0	0	0	0	0	0	0	0	1
8	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	1
10	0	0	0	0	0	0	0	0	1
11	0	0	0	0	0	0	1	2	5
12	0	0	0	0	0	0	0	0	1
avg %	0	0	0	0	0	0	0	1	2
min %	0	0	0	0	0	0	0	0	0
max %	0	0	0	0	0	0	1	2	5
SD	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.6	1.4
%CV	0.0	195.4	216.1	210.4	163.2	134.6	196.2	99.3	97.4

Table IV: Release of Bupropion HCl from 150 mg tablet in 0.1 N HCl-5% Alcohol

Product: Bupropion HCl ER Tablets, 150mg
Manufacturer: Wellbutrin Lot# 06E028P Exp: 8/07
Date Completed: 8/9/2006 Reference: RD-P1313-40 & 41
Component: Bupropion HCl
Medium: 0.1N HCl: Alcohol (95:5)
Vol (mL): 900
Apparatus: Basket @ 75 RPM

Sample/Time	0	15	30	45	60	75	90	105	120
1	0	0	0	0	0	0	0	0	1
2	0	0	0	0	0	0	0	1	2
3	0	0	0	0	0	0	0	1	2
4	0	0	0	0	0	1	1	4	7
5	0	0	0	0	0	0	1	1	2
6	0	0	0	0	0	0	1	1	2
7	0	0	0	0	0	1	1	3	5
8	0	0	0	0	0	1	1	2	4
9	0	0	0	0	0	0	0	1	1
10	0	0	0	0	0	0	0	1	1
11	0	0	0	0	0	0	0	1	1
12	0	0	0	0	0	0	0	1	1
avg %	0	0	0	0	0	0	1	1	3
min %	0	0	0	0	0	0	0	0	1
max %	0	0	0	0	0	1	1	4	7
SD	0.0	0.0	0.0	0.0	0.1	0.3	0.5	1.2	2.0
%CV	0.0	109.1	153.0	155.7	149.6	114.1	83.6	83.5	78.6

Product: Bupropion HCl ER Tablets, 150mg
Manufacturer: Watson Lot# XT4L029
Date Completed: 8/9/2006 Reference: RD-P1333-44 & 45
Component: Bupropion HCl
Medium: 0.1N HCl: Alcohol (95:5)
Vol (mL): 900
Apparatus: Basket @ 75 RPM

Sample/Time	0	15	30	45	60	75	90	105	120
1	0	0	0	0	1	2	5	9	14
2	0	0	0	0	0	1	2	5	9
3	0	0	0	0	0	1	2	3	7
4	0	0	0	0	0	1	1	3	10
5	0	0	0	0	0	1	3	6	13
6	0	0	0	0	0	1	2	4	9
7	0	0	0	0	0	1	3	6	12
8	0	0	0	0	0	1	3	5	9
9	0	0	0	0	0	1	1	3	8
10	0	0	0	0	0	0	1	2	4
11	0	0	0	0	0	0	1	2	5
12	0	0	0	0	0	1	2	3	6
avg %	0	0	0	0	0	1	2	5	9
min %	0	0	0	0	0	0	1	2	4
max %	0	0	0	0	0	1	2	6	14
SD	0.0	0.0	0.0	0.0	0.0	0.2	0.5	1.3	2.7	3.6
%CV	0.0	346.4	346.4	164.6	72.8	69.7	53.3	45.8	34.8

Table V: Release of Bupropion HCl from 150 mg tablet in 0.1 N HCl-20% Alcohol

Dissolution Profile Results

Product: Bupropion HCl ER Tablets, 150mg
Manufacturer: Wellbutrin Lot# 06E028P Exp: 8/07
Date Completed: 8/9/2006 Reference: RD-P1333-48 & 49
Component: Bupropion HCl
Medium: 0.1N HCl: Alcohol (80:20)
Vol (mL): 900
Apparatus: Basket @ 75 RPM

Sample/Time	0	15	30	45	60	75	90	105	120
1	0	0	0	0	1	3	5	7	11
2	0	0	0	0	1	2	4	6	8
3	0	0	0	0	1	2	4	7	10
4	0	0	0	1	2	5	6	12	15
5	0	0	0	0	1	2	3	5	8
6	0	0	0	1	2	5	8	12	16
7	0	0	0	0	1	2	3	5	7
8	0	0	0	0	1	3	5	8	11
9	0	0	0	0	1	2	3	5	7
10	0	0	0	1	3	6	10	14	18
11	0	0	0	0	1	2	4	6	9
12	0	0	0	1	2	4	6	11	15
avg %	0	0	0	0	1	3	5	8	11
min %	0	0	0	0	1	2	3	5	7
max %	0	0	0	1	3	6	10	14	18
SD	0.0	0.0	0.1	0.3	0.8	1.5	2.3	3.1	3.8
%CV	0.0	233.5	181.7	82.9	56.6	49.8	43.9	39.0	33.3

Comparative Dissolution Profile: Bupropion HCl

Product: Bupropion HCl ER Tablets, 150mg
Manufacturer: Watson Lot# XT4L029
Date Completed: 8/9/2006 Reference: RD-P1333-52 & 53
Component: Bupropion HCl
Medium: 0.1N HCl: Alcohol (80:20)
Vol (mL): 900
Apparatus: Basket @ 75 RPM

Sample/Time	0	15	30	45	60	75	90	105	120
1	0	0	0	2	5	8	15	22	29
2	0	0	0	2	5	9	14	21	28
3	0	0	0	3	5	9	13	19	25
4	0	0	0	1	4	7	10	13	17
5	0	0	0	2	5	9	13	19	25
6	0	0	0	1	3	6	10	13	18
7	0	0	0	2	5	8	12	16	22
8	0	0	0	2	5	9	14	20	26
9	0	0	0	2	4	7	10	15	21
10	0	0	1	3	5	9	17	23	29
11	0	0	0	2	5	8	13	19	26
12	0	0	0	2	4	7	10	14	19
avg %	0	0	0	2	5	8	13	18	23
min %	0	0	0	1	3	6	10	13	17
max %	0	0	1	3	5	9	17	23	29
SD	0.0	0.0	0.2	0.6	0.9	1.1	2.3	3.5	4.6
%CV	0.0	212.6	56.8	27.1	17.7	13.4	18.0	19.5	17.2

Table VI: Release of Bupropion HCl from 150 mg tablet in 0.1 N HCl-40% Alcohol

Dissolution Profile Results

Product: Bupropion HCl ER Tablets, 150mg
Manufacturer: Wellbutrin Lot# 8S0029P Exp. 8/07
Date Completed: 7/27/2006 Reference: RD-P1313-28 & 29
Component: Bupropion HCl
Medium: 0.1N HCl Alcohol (60:40)
Vol (mL): 900
Apparatus: Basket @ 75 RPM

Sample Time	0	15	30	45	60	75	90	105	120
1	0	0	0	2	4	7	11	15	18
2	0	0	0	2	5	9	11	14	17
3	0	0	0	2	4	8	10	13	16
4	0	0	0	2	4	5	10	13	17
5	0	0	0	2	3	6	10	13	16
6	0	0	1	2	3	6	9	12	15
7	0	0	1	3	5	8	10	13	17
8	0	0	1	3	6	9	12	15	18
9	0	0	1	3	5	8	10	13	16
10	0	0	1	2	4	7	9	12	15
11	0	0	1	3	5	8	11	14	17
12	0	0	0	2	4	6	8	11	13
avg %	0	0	1	2	4	7	10	13	16
min %	0	0	0	2	3	5	8	11	13
max %	0	0	1	3	6	9	12	15	18
SD	0.0	0.0	0.3	0.5	1.0	1.1	1.0	1.2	1.4
%CV	0.0	387.2	50.2	23.6	23.4	15.8	10.2	9.1	8.6

Product: Bupropion HCl ER Tablets, 150mg
Manufacturer: Watson Lot# XT41025
Date Completed: 8/1/2006 Reference: RD-P1313-28 & 29
Component: Bupropion HCl
Medium: 0.1N HCl Alcohol (60:40)
Vol (mL): 900
Apparatus: Basket @ 75 RPM

Sample Time	0	15	30	45	60	75	90	105	120
1	0	1	3	6	9	11	14	16	18
2	0	1	3	6	9	12	14	17	19
3	0	1	5	8	11	14	16	19	21
4	0	1	3	6	9	11	13	15	18
5	0	1	3	5	8	10	12	15	18
6	0	0	3	5	8	11	13	16	18
7	0	1	3	6	9	11	14	17	19
8	0	1	5	9	12	15	18	22	24
9	0	1	4	7	10	13	16	19	22
10	0	1	3	5	8	11	13	16	19
11	0	1	4	8	11	14	17	20	22
12	0	1	4	7	10	13	16	19	22
avg %	0	1	4	7	9	12	15	18	20
min %	0	0	3	5	8	10	12	15	18
max %	0	1	5	9	12	15	18	22	24
SD	0.0	0.3	0.8	1.2	1.4	1.6	1.8	1.9	2.0
%CV	0.0	38.0	22.5	17.6	14.8	12.6	12.0	10.9	10.1

Table VII: Release of Bupropion HCl from 300 mg tablet in 0.1 N HCl-0% Alcohol

Dissolution Profile Results

Product: Bupropion HCl ER Tablets, 300mg
Manufacturer: Wellbutrin Lot# 8S0032P Exp. 8/07
Date Completed: 7/27/2006 Reference: RD-P1313-27 & 31
Component: Bupropion HCl
Medium: 0.1N HCl
Vol (mL): 900
Apparatus: Basket @ 75 RPM

Sample Time	0	15	30	45	60	75	90	105	120
1	0	0	0	0	0	0	0	1	2
2	0	0	0	0	0	0	1	2	3
3	0	0	0	0	0	0	1	1	2
4	0	0	0	0	0	1	1	1	2
5	0	0	0	0	0	1	2	2	3
6	0	0	0	0	0	0	1	2	2
7	0	0	0	0	0	0	1	2	3
8	0	0	0	0	0	0	1	1	2
9	0	0	0	0	0	1	1	2	3
10	0	0	0	0	1	1	1	2	11
11	0	0	0	0	0	1	1	1	2
12	0	0	0	0	0	0	1	2	3
avg %	0	0	0	0	0	1	1	2	4
min %	0	0	0	0	0	0	0	1	2
max %	0	0	0	0	1	1	2	2	11
SD	0.0	0.0	0.0	0.0	0.2	0.3	1.0	1.0	2.6
%CV	0.0	52.0	120.3	95.3	95.0	65.1	91.0	77.7	66.6

Comparative Dissolution Profile: Bupropion HCl

Product: Bupropion HCl ER Tablets, 300mg
Manufacturer: Watson Lot# XT40840
Date Completed: 7/28/2006 Reference: RD-P1313-27 & 31
Component: Bupropion HCl
Medium: 0.1N HCl
Vol (mL): 900
Apparatus: Basket @ 75 RPM

Sample Time	0	15	30	45	60	75	90	105	120
1	0	0	1	3	6	9	11	13	15
2	0	0	0	2	5	8	10	12	14
3	0	0	0	2	4	7	9	11	13
4	0	0	0	2	4	6	8	10	12
5	0	0	0	1	3	5	7	9	11
6	0	0	0	1	3	5	7	9	11
7	0	0	0	2	5	8	10	12	14
8	0	0	0	2	4	7	9	11	13
9	0	0	0	2	4	6	8	10	12
10	0	0	0	2	4	6	8	10	12
11	0	0	0	1	3	5	7	9	11
12	0	0	0	1	3	5	7	9	11
avg %	0	0	0	2	4	6	8	10	12
min %	0	0	0	1	3	5	7	9	11
max %	0	0	0	3	6	9	11	13	15
SD	0.0	0.0	0.0	0.7	1.2	1.5	1.4	1.4	1.4
%CV	0.0	346.4	126.9	29.0	29.5	23.8	17.5	13.4	11.4

COPY

Table VIII: Release of Bupropion HCl from 300 mg tablet in 0.1 N HCl-5% Alcohol

Product: Bupropion HCl ER Tablets, 300mg
Manufacturer: Wellbutrin Lot#: 06E002P Exp: 8/07
Date Completed: 8/9/2006 Reference: RD-P1333-42 & 43
Component: Bupropion HCl
Medium: 0.1N HCl: Alcohol (95:5)
Vol (mL): 900
Apparatus: Basket @ 75 RPM

Sample/Time	0	15	30	45	60	75	90	105	120
1	0	0	0	0	0	1	2	3	4
2	0	0	0	0	0	0	1	2	3
3	0	0	0	0	0	1	2	3	4
4	0	0	0	0	0	1	2	2	3
5	0	0	0	0	1	2	3	5	7
6	0	0	0	0	0	1	2	3	4
7	0	0	0	0	1	1	3	4	7
8	0	0	0	0	1	2	3	4	7
9	0	0	0	0	1	1	2	5	8
10	0	0	0	0	1	2	5	8	11
11	0	0	0	0	0	1	2	3	6
12	0	0	0	0	0	1	2	3	5
avg %	0	0	0	0	0	1	2	4	6
min %	0	0	0	0	0	0	1	2	3
max %	0	0	0	0	1	2	5	8	11
SD	0.0	0.0	0.0	0.0	0.3	0.5	0.9	1.6	2.4
%CV	0.0	139.5	110.9	92.0	86.5	49.6	45.9	42.3	42.0

Product: Bupropion HCl ER Tablets, 300mg
Manufacturer: Watson Lot#: XC5B013
Date Completed: 8/9/2006 Reference: RD-P1333-46 & 47
Component: Bupropion HCl
Medium: 0.1N HCl: Alcohol (95:5)
Vol (mL): 900
Apparatus: Basket @ 75 RPM

Sample/Time	0	15	30	45	60	75	90	105	120
1	0	0	0	0	1	3	6	10	14
2	0	0	0	0	1	1	6	10	16
3	0	0	0	1	2	7	13	18	23
4	0	0	0	0	1	12	16	23	28
5	0	0	0	0	1	5	10	16	21
6	0	0	0	0	1	2	9	15	20
7	0	0	0	0	1	5	10	16	21
8	0	0	0	0	1	7	13	17	21
9	0	0	0	0	1	3	9	14	19
10	0	0	0	1	2	8	14	18	22
11	0	0	0	0	1	3	6	8	12
12	0	0	0	1	2	4	8	15	19
avg %	0	0	0	0	1	5	10	15	20
min %	0	0	0	0	1	1	6	8	12
max %	0	0	0	1	2	12	16	23	28
SD	0.0	0.0	0.1	0.2	0.3	3.1	3.5	4.1	4.5
%CV	0.0	346.4	128.1	39.6	26.3	62.0	36.6	27.1	22.0

Table VIII: Release of Bupropion HCl from 300 mg tablet in 0.1 N HCl-20% Alcohol

Dissolution Profile Results

Product: Bupropion HCl ER Tablets, 300mg
Manufacturer: Wellbutrin Lot#: 06E002P Exp: 8/07
Date Completed: 8/9/2006 Reference: RD-P1333-59 & 61
Component: Bupropion HCl
Medium: 0.1N HCl: Alcohol (80:20)
Vol (mL): 900
Apparatus: Basket @ 75 RPM

Sample/Time	0	15	30	45	60	75	90	105	120
1	0	0	0	1	2	3	5	7	10
2	0	0	0	1	3	5	7	10	14
3	0	0	0	1	2	4	7	9	13
4	0	0	0	2	3	6	9	13	17
5	0	0	0	1	3	5	7	10	13
6	0	0	0	1	3	4	7	10	13
7	0	0	0	2	4	6	8	11	14
8	0	0	0	2	3	6	9	13	17
9	0	0	0	1	2	4	5	8	10
10	0	0	0	1	2	4	6	9	10
11	0	0	0	1	2	4	6	10	13
12	0	0	0	1	3	4	6	9	12
avg %	0	0	0	1	3	5	7	10	13
min %	0	0	0	1	2	3	5	7	10
max %	0	0	0	2	4	6	9	13	17
SD	0.0	0.0	0.1	0.4	0.6	0.9	1.3	1.8	2.2
%CV	0.0	135.3	63.7	32.6	24.2	19.2	18.6	18.7	17.3

Product: Bupropion HCl ER Tablets, 300mg
Manufacturer: Watson Lot#: XC5B013
Date Completed: 8/9/2006 Reference: RD-P1333-64 & 65
Component: Bupropion HCl
Medium: 0.1N HCl: Alcohol (80:20)
Vol (mL): 900
Apparatus: Basket @ 75 RPM

Sample/Time	0	15	30	45	60	75	90	105	120
1	0	0	2	6	11	16	23	30	35
2	0	0	1	4	8	14	19	25	28
3	0	0	3	8	13	19	24	29	33
4	0	0	2	5	8	13	19	24	28
5	0	0	2	5	9	16	21	27	31
6	0	0	1	3	6	10	16	21	27
7	0	0	1	4	7	13	18	24	29
8	0	0	1	3	6	10	17	25	30
9	0	0	1	4	7	11	18	24	30
10	0	0	2	5	10	15	22	28	35
11	0	0	1	3	7	10	16	23	30
12	0	0	2	6	12	18	24	29	34
avg %	0	0	2	5	9	14	20	26	32
min %	0	0	1	3	6	10	16	21	28
max %	0	0	3	8	13	19	24	29	34
SD	0.0	0.0	0.7	1.2	2.4	3.6	3.5	3.2	3.0
%CV	0.0	109.2	42.1	24.5	27.3	26.1	17.5	12.5	10.5

Table X: Release of Bupropion HCl from 300 mg tablet in 0.1 N HCl-40% Alcohol

Dissolution Profile Results

Product: Bupropion HCl ER Tablets, 300mg
Manufacturer: Wellbutrin Lot# 95E002P Exp: 8/07
Date Completed: 7/27/2005 Reference: RD-P1313-31 & 32
Component: Bupropion HCl
Medium: 0.1N HCl: Alcohol (60:40)
Vol (mL): 900
Apparatus: Basket @ 75 RPM

Sample/Time	0	15	30	45	60	75	90	105	120
1	0	0	1	3	6	9	11	14	17
2	0	0	2	5	8	11	14	17	20
3	0	0	2	4	7	9	12	15	18
4	0	0	2	4	7	10	13	17	20
5	0	0	1	4	6	9	12	14	17
6	0	0	2	4	7	10	13	16	19
7	0	0	1	4	6	9	11	14	17
8	0	0	2	4	7	9	12	15	18
9	0	0	2	4	7	10	13	16	19
10	0	0	2	5	8	10	13	16	20
11	0	0	2	5	8	11	14	17	20
12	0	0	2	4	7	9	12	15	18
avg %	0	0	2	4	7	10	12	16	19
min %	0	0	1	3	6	9	11	14	17
max %	0	0	2	5	8	11	14	17	20
SD	0.0	0.1	0.3	0.5	0.6	0.7	0.8	1.0	1.2
%CV	0.0	39.4	17.4	11.6	8.6	7.3	6.7	6.4	6.2

Product: Bupropion HCl ER Tablets, 300mg
Manufacturer: Watson Lot# KC5B513
Date Completed: 8/2/2005 Reference: RD-P1504-33 & 36
Component: Bupropion HCl
Medium: 0.1N HCl: Alcohol (60:40)
Vol (mL): 900
Apparatus: Basket @ 75 RPM

Sample/Time	0	15	30	45	60	75	90	105	120
1	0	2	5	9	12	14	17	19	23
2	0	2	5	8	11	14	16	19	23
3	0	2	5	8	11	14	16	18	22
4	0	1	5	7	10	12	14	17	19
5	0	2	5	8	11	14	16	19	23
6	0	2	5	8	10	13	15	18	20
7	0	1	4	8	11	14	16	19	23
8	0	2	6	13	19	24	29	33	38
9	0	2	5	8	11	13	16	20	24
10	0	1	4	7	9	11	14	16	19
11	0	1	4	7	9	12	14	16	19
12	0	2	5	8	12	15	18	20	23
avg %	0	2	5	8	11	14	17	19	22
min %	0	1	4	7	9	11	14	16	19
max %	0	2	6	13	19	24	29	33	38
SD	0.0	0.3	0.7	1.6	2.5	3.3	4.0	4.6	6.0
%CV	0.0	21.0	14.0	19.8	22.3	23.5	24.0	25.0	27.5

A. Waiver Request

Strengths for which waivers requested	300 mg
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	Yes
Waivers granted (yes or no)	Yes

B. Deficiency Comments

None

C. Recommendations

1. The single-dose, fasting and non-fasting bioequivalence studies conducted by Watson Laboratories, Inc. on its Bupropion Hydrochloride Extended Release Tablets 150 mg comparing it to GlaxoSmithKline's Wellbutrin XL® (bupropion hydrochloride) Tablets, 150 mg are **acceptable**.

2. The in vitro dissolution testing conducted by Watson Laboratories, Inc. on its Bupropion Hydrochloride Extended Release Tablets, 150 mg, and 300 mg strengths respectively is **acceptable**. The firm has acknowledged the following dissolution method and specification:

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

   2 hours: NMT [redacted]
   4 hours: [redacted]
   8 hours: [redacted]
   12 hours: NLT [redacted]

   b(4)

3. Due to concern of dose dumping for the drug product, the Agency had previously requested that the firm conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium (see below). The firm conducted the requested dissolution (see data above). The in vitro testing is **acceptable**.

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

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

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

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

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

   As previously discussed in greater detail in the above review, the submitted in vitro alcohol dose dumping study is found to be acceptable for the following reasons: (1) Watson's test product and the RLD have comparable release at 40% v/v alcohol, (2) since Watson's product dissolved at a rate comparable to Impax's product at 5 and 20% ethanol; and (3) the DBE previously concluded that the rate of bupropion dissolution from Impax's product in 5 and 20% ethanol was acceptable. Therefore, the DBE concludes that Watson's Bupropion HCl ER Tablet gave acceptable results in the in vitro alcohol dose dumping study.

4. The formulation of the 300 mg strength is proportional to the 150 mg strength of the test product which underwent acceptable in vivo bioequivalence testing. The waiver of in vivo bioequivalence study requirements for the firm's Bupropion Hydrochloride Extended Release Tablets 300 mg is **granted.**

The application is complete.

D. Attachments

None

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-715 APPLICANT: WATSON

DRUG PRODUCT: Bupropion HCl Tablets
150 mg and 300 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the dissolution testing for the test products is conducted using the following method:

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

2 hours: NMT [redacted]
4 hours: [redacted]
8 hours: [redacted]
12 hours: NLT [redacted]

b(4)

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

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

ANDA 77-715

BIOEQUIVALENCE -COMPLETE Submission Date: 05-19-05, 07-27-05
10-12-05, 03-28-05, 09-15-06

1. **Study Amendment (STA)** **Strengths: 150 mg and 300 mg**
Outcome: AC

Outcome Decisions: **AC**

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
12/6/2006 04:52:00 PM
BIOPHARMACEUTICS

Xiaojian Jiang
12/6/2006 04:56:38 PM
BIOPHARMACEUTICS
on behalf of Shrinivas G. Nerurkar

Barbara Davit
12/6/2006 05:13:38 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-715
Drug Product Name	Bupropion Hydrochloride Extended Release Tablets
Strengths	150 mg and 300 mg
Applicant Name	Watson Laboratories, Inc.
Address	311 Bonnie Circle Corona, CA 92880-2882
Submission Date(s)	May 19, 2005
Amendment Date(s)	July 27, 2005, October 12, 2005, March 28, 2006
Reviewer	Chandra S. Chaurasia, Ph.D.
First Generic	No
File Location	V:\firmsnz\watson\ltrs&rev\77715N0505.doc

Executive Summary

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

The BE studies were conducted in a two-way crossover design in healthy volunteers. PK analyses were based on plasma bupropion and its active metabolite hydroxybupropion concentrations.

The fasting BE study was conducted in 47 healthy adult male and female subjects. The results (point estimate, 90% CI) of the study for bupropion are: LAUCt of 0.91, 86.7-94.7%; LAUCi of 0.91, 86.8-94.6% and LCmax of 0.94, 87.3-102.3%; and those for the hydroxybupropion are: LAUCt of 0.94, 88.8-98.4%; LAUCi of 0.93, 88.5-98.4% and LCmax of 0.93, 88.6-98.1%.

The fed BE study was conducted in 47 healthy adult male and female subjects. The results (point estimate, 90% CI) of the study for bupropion are: LAUCt of 0.93, 88.9-97.4%; LAUCi of 0.95, 89.6-97.6% and LCmax of 0.91, 85.3-97.2%; and those for the hydroxybupropion are: LAUCt of 0.97, 90.8-103.7%; LAUCi of 0.97, 90.1-103.4% and LCmax of 0.94, 93.6-107.6%.

The results of the fasting and fed studies are acceptable.

The formulation of the 300 mg tablet is proportionally similar to 150 mg tablet. The firm also conducted dissolution testing on its Bupropion Hydrochloride Extended Release Tablets, 150 mg and 300 mg. The dissolution testing is incomplete for the reasons given in the deficiency section. Therefore, the application is incomplete.

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III. Submission Summary

A. Drug Product Information

Test Product:	Bupropion Hydrochloride Tablets, USP 150 mg
Reference Product:	Wellbutrin XL® (Bupropion Hydrochloride) Tablets, 150 mg
RLD Manufacturer:	GlaxoSmithKline
NDA No.:	21-515
RLD Approval Date:	August 28, 2003
Indication:	For the treatment of major depressive disorders

B. PK/PD Information[1]

Bioavailability	Not yet determined
Food Effect	Food did not affect the Cmax or AUC of bupropion significantly.
Tmax	5 hours for bupropion; approximately 6 hours for the three active metabolites.
Metabolism	Bupropion is extensively metabolized in humans. There are three active metabolites: hydroxybupropion and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via hydroxylation of the tert -butyl group of bupropion and/or reduction of the carbonyl group. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized.
Excretion	Following oral administration of 200 mg of ^{14}C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. The fraction of the oral dose of bupropion excreted unchanged was only 0.5%.
Half-life	21 hours for bupropion; 20 hours for hydroxybupropion, 37 hours for threohydrobupropion, and 33 hours for erythrohydrobupropion
Relevant OGD or DBE History	**History On BE Study** 1. Prior to the issuance of the general BA/BE guidance in October 2000, the DBE had recommended the following for the drug product: a single-dose fasting BE study, a single-dose non-fasting BE study and a multiple-dose BE study. Bupropion, hydroxybupropion and a combination of threohydrobupropion and erythrobupropion were measured for the studies. The sampling schedule was generally up to 168 hours or 192 hours for single-dose studies. The practice was reflected in the reviews of the following documents: 2. Control Document #01-068 (——— 02/06/2001): The DBE had revised the recommendations concerning the BE requirements for the drug product based on the general BA/BE guidance (issued 10/2000). A single dose, replicate, fasting BE study on the highest strength, and a single dose, two way crossover, non-fasting BE study on the same strength were recommended. Measurement of bupropion and hydroxybupropion were requested but only

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	bupropion data were to be subject to the confidence interval criteria. 3 a). Control Document #02-695 ([redacted] 11/29/2002): • Based on the current general BA/BE guidance (March 2003), for bupropion drug products, plasma concentrations of bupropion, the parent drug, and hydroxybupropion, which is formed presystemically, should both be quantitated for the bioequivalence studies. Only the bupropion data should be analyzed using the confidence interval approach. For hydroxybupropion, the following data should be submitted: individual and mean plasma concentrations, individual and mean PK parameters, geometric means and ratios of means of Cmax, AUCt and AUC_{∞}. • With regard to the sampling schedule, per Part VI.C. Long Half-life Drugs of the general BA/BE guidance, which states that "Cmax and a suitably truncated AUC can be used to characterize peak and total drug exposure, respectively. For drugs that demonstrate low intrasubject variability in distribution and clearance, an AUC truncated at 72 hours (AUC0-72 hr) can be used in place of AUC0-t or AUC0-∞." Alternatively, the sampling schedule up to 168 hours or 192 hours postdose may be considered adequate 4. The RLD product, Wellbutrin XL® Tablet, 150 mg and 300 mg, (NDA 21-515) were approved on 08/28/03 to provide improved once-daily formulations for patients who have been treated with Wellbutrin SR® Tablet, which was approved (06/14/02). The two formulations and their release-controlling technologies are different. NDA 21-515 was approved based on a confirmatory bioequivalence study comparing this formulation with Wellbutrin® Tablets (immediate-release formulation). Since the 150 mg and 300 mg strengths are not formulation proportional, a steady-state bioequivalence study comparing the two strengths using 300 mg dosage was also submitted for NDA 21-515. It should be noted that Wellbutrin SR® Tablet product was approved based on a bioequivalence study comparing this formulation with Wellbutrin® Tablets (immediate-release formulation) also. The interchangeability of Wellbutrin® products is addressed in the labeling of Wellbutrin XL®. According to this labeling, "*When switching patients from WELLBUTRIN Tablets to WELLBUTRIN XL or from WELLBUTRIN SR Sustained-Release Tablets to WELLBUTRIN XL, give the same total daily dose when possible. Patients who are currently being treated with WELLBUTRIN Tablets at 300*

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	mg/day (for example, 100 mg 3 times a day) may be switched to WELLBUTRIN XL 300 mg once daily. Patients who are currently being treated with WELLBUTRIN SR Sustained-Release Tablets at 300 mg/day (for example, 150 mg twice daily) may be switched to WELLBUTRIN XL 300 mg once daily." The labeling of Wellbutrin XL® Tablets also recommends that "*The usual adult target dose for WELLBUTRIN XL Tablets is 300 mg/day, given once daily in the morning. Dosing with WELLBUTRIN XL Tablets should begin at 150 mg/day given as a single daily dose in the morning. If the 150-mg initial dose is adequately tolerated, an increase to the 300-mg/day target dose, given as once daily, may be made as early as day 4 of dosing. There should be an interval of at least 24 hours between successive doses.*" The 150 mg strength, therefore, is designated in the Orange Book as the RLD strength. Due to the safety concern, the 300 mg strength of the generic version can be waived of in vivo bioequivalence testing provided that the formulation of the higher strength is proportionally similar to that of the 150 mg strength, and the dissolution profiles of the two strengths are comparable. **History On Dissolution Methodology** 5. a). Control Document #02-695 ([redacted] 11/29/2002): b(4) Dissolution testing should be conducted in water and aqueous media of the following pH: 1.2, 4.5 and 6.8, using USP apparatus 2 (paddle) at 50, 75, and 100 rpm, and USP apparatus 1 (basket) at 100 rpm. In addition, dissolution testing should be conducted using the following method: USP Apparatus II (paddle) at 50 rpm using 900 mL of water at 37°C. Sampling times for this method should be 1, 2, 4, 6 and 12 hours or at least 80-85% dissolved. The comparative dissolution data should include mean, range, and %CV of percents dissolved at each time point. 5.b. ANDA 77-214 (Anchen Pharm, Submission dated 9/21/04) Review: Three different dissolution methods have been recommended for different ANDAs of bupropion HCl ER products. Method 1: USP Apparatus II (paddle) at 50 rpm, with 900 mL of water (recommended for ANDAs #75-913, 75-914, [redacted] Method 2: USP Apparatus II (paddle) at 50 rpm, with 900 mL of pH 1.5 SGF (without enzyme) (recommended for ANDA # [redacted] b(4) Method 3: USP Apparatus I (basket) at 50 rpm, with 900 mL of 0.1 N HCl, pH 1.5 (recommended for

	ANDA #75-932)
Agency Guidance:	None
Drug Specific Issues (if any):	Current DBE recommendations for demonstration of bioequivalence of Bupropion Hydrochloride Extended Release Tablets, 150 mg and 300 mg (with WELLBUTRIN XL® Tablets as the RLD) are as follows: 1. A single-dose, two-way crossover fasting in-vivo bioequivalence study comparing Bupropion Hydrochloride Extended Release Tablets, 150 mg, to the reference listed drug (RLD), Wellbutrin XL® (Bupropion Hydrochloride Extended Release) Tablets, 150 mg. Due to safety concerns, studies using the 300 mg dose are not recommended. 2. A single-dose, two-way crossover fed in-vivo bioequivalence study comparing Bupropion Hydrochloride Extended Release Tablets, 150 mg, to the RLD. 3. Measure plasma concentrations of the parent drug bupropion and metabolite hydroxybupropion; 4. Waiver of in vivo bioequivalence study requirements for the 300 mg strengths may be granted provide the conditions of 21 CFR§320.22(d)(2) are met. 5. Conduct comparative dissolution testing using 12 dosage units of the test and reference products using the following FDA method: Medium: 0.1 N HCl at 37°C ± 0.5°C Volume: 900 mL Apparatus: 1 (Basket) Rotational speed: 75 rpm Sampling time: 1, 2, 4, 6 and 8 hours and until at least 80% of the labeled content is dissolved.

[1]PDR® (Physician's desk reference) electronic version entry for WELLBUTRIN SR®

C. Contents of Submission

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

D. Pre-Study Bioanalytical Method Validation

FAST 40431 and FED 40432	DATA
Bioanalytical method validation report location	Volume 8, p. 2145
Analyte	Bupropion and Hydroxybupropion
Internal standard (IS)	Threohydroxybupropion-d_9
Method description	This method involves the extraction of bupropion, hydroxybupropion and the internal standard from human EDTA K_3 plasma by a liquid-liquid extraction procedure, then, injected into liquid chromatograph equipped with tandem mass spectrometry detector. Samples are kept frozen at -80°C prior to analysis and 0.100mL of plasma was used for analysis.
Limit of quantitation (ng/mL)	Bupropion: 1.00 Hydroxybupropion : 1.00
Average recovery of drug range (%)	Bupropion: 64.33 to 79.10 Hydroxybupropion : 52.59 to 68.01
Average recovery of IS (%)	70.82
Standard curve concentrations range (ng/mL)	Bupropion: 1.00 to 400.00 Hydroxybupropion: 1.00 to 398.80
QC concentration (ng/mL)	Bupropion: QC1: 3.00, QC2: 119.86, QC3: 279.66 Hydroxybupropion: QC1: 2.99, QC2: 119.66, QC3: 279.22
QC Intraday precision range (%)	Bupropion: 0.73 to 2.94 Hydroxybupropion : 1.87 to 4.28
QC Intraday accuracy range (%)	Bupropion: 98.75 to 104.17 Hydroxybupropion : 96.90 to 102.40
QC Interday precision range (%)	Bupropion: 2.51 to 7.20 Hydroxybupropion : 3.40 to 9.86
QC Interday accuracy range (%)	Bupropion: 95.03 to 100.11 Hydroxybupropion : 95.94 to 102.37
Bench-top stability (hrs)	Bupropion: 2 hours at room temperature Hydroxybupropion: 24 hours at room temperature Bupropion: 10 hours at 4°C Hydroxybupropion: 24 hours at 4°C

Pre-Study Bioanalytical Method Validation (continued)

FAST 40431 and FED 40432	DATA
Stock stability (days)	Analytes: 140 days at -80°C and 48 days at -20°C IS: 113 days at -80°C and 48 days at -20°C
Processed stability (hrs)	Bupropion: 91 hours at room temperature Hydroxybupropion: 91 hours at room temperature
Freeze-thaw stability (cycles)	Bupropion: 4 at -20°C Hydroxybupropion: 4 at -20°C Bupropion: 4 at -80°C Hydroxybupropion: 5 at -80°C
Long-term storage stability (days)	Bupropion: 616 days at -80°C Hydroxybupropion: 616 days at -80°C
Dilution integrity	Bupropion: QC3 diluted 2 fold: CV (%) 1.03 Nominal (%) 97.18 DQC diluted 20 fold: CV (%) 1.98 Nominal (%) 97.06 Hydroxybupropion: QC3 diluted 2 fold: CV (%) 3.27 Nominal (%) 97.67 DQC diluted 20 fold: CV (%) 3.75% Nominal (%) 97.09
Selectivity	Human plasma samples (EDTA K_3 as anti-coagulant) from 10 different individual human blank sources were tested for interfering peaks at the retention time of bupropion, hydroxybupropion and the internal standard. No significant interferences observed in 9 out of 10 tested matrices for bupropion and hydroxybupropion. None of the sources showed significant interference at the retention time of the internal standard.

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

E. In Vivo Studies

E.1. Single-dose Fasting Bioequivalence Study No. 40431

Study Summary	
Study No.	40431
Study Design	Randomized, 2-way crossover, single-dose, open-label, bioequivalence study in healthy subjects under fasting conditions
No. of subjects enrolled	48
No. of subjects completing	47*
No. of subjects analyzed	47
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 19 Female: 29
Test product	Bupropion Hydrochloride Extended Release Tablets, USP
Reference product	Wellbutrin-XL® Tablets
Strength tested	150 mg
Dose	1x150 mg, administered with 240 mL of water at room temperature

**Sub #44 elected to withdraw form the study for personal reasons prior to drug administration in Period 2*

Summary of Statistical Analysis for Bupropion As Reported by the Firm		
Fasting BE Study 40431 (N=47)		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	90.64	86.73%-94.72%
AUC∞	90.66	86.84%-94.64%
Cmax	94.51	87.28%-102.34%

Summary of Statistical Analysis for Hydroxybupropion As Reported by the Firm		
Fasting BE Study 40431 (N=47)		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	93.50	88.83%-98.41%
AUC∞	93.33	88.50%-98.42%
Cmax	93.24	88.63%-98.09%

**The reviewer's calculated values were same as reported by the firm.*

Reanalysis of Study Samples for Bupropion

Study No. 40431
Randomized, 2-Way Crossover, Bioequivalence Study of Bupropion 150 mg Extended-Release Tablet and Wellbutrin XL™ Following a 150 mg Dose in Healthy Subjects Under Fasting Conditions
Volume 7, p. 2038, 2059-2083

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	49	33	2.37	1.60	49	33	2.37	1.60
Unacceptable internal standard response	49	32	2.37	1.55	49	32	2.37	1.55
Incomplete analysis	0	1	0.0	0.05	0	1	0.0	0.05
Total	49	33	2.37	1.60	49	33	2.37	1.60

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table
[2] Bupropion 150 mg extended-release tablet, Lot No: XT4L029
[3] Bupropion 150 mg extended-release tablet (Wellbutrin XLTM), Lot No: 04D014P

Reanalysis of Study Samples for Hydroxybupropion

Study No. 40431
Randomized, 2-Way Crossover, Bioequivalence Study of Bupropion 150 mg Extended-Release Tablet and Wellbutrin XL™ Following a 150 mg Dose in Healthy Subjects Under Fasting Conditions
Volume 7, p. 2038, 2059-2083

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	63	56	3.05	2.71	59	53	2.86	2.56
Unacceptable internal standard response	48	34	2.32	1.64	48	34	2.32	1.64
Incomplete analysis	0	1	0.0	0.05	0	1	0.0	0.05
Sample concentration above upper limit of quantification	9	18	0.44	0.87	9	18	0.44	0.87
Sample reanalyzed to obtain confirming value	4	2	0.19	0.10	2	0	0.10	0.0
Sample repeated or reinjected by error	2	1	0.10	0.05	0	0	0.0	0.0
Total	63	56	3.05	2.71	59	53	2.86	2.56

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table
[2] Bupropion 150 mg extended-release tablet, Lot No: XT4L029
[3] Bupropion 150 mg extended-release tablet (Wellbutrin XLTM), Lot No: 04D014P

Total number of samples assayed for study 40431 = 2068

Did use of recalculated plasma concentration data change study outcome?
No, there were no pharmacokinetic repeats and no recalculations were performed for either the parent or the hydroxy metabolite in the fasting study 40431.

E.2. Single-dose Fed Bioequivalence Study No. 40432

Study Summary	
Study No.	40432
Study Design	Randomized, 2-way crossover, single-dose, open-label, bioequivalence study in healthy subjects under fed conditions
No. of subjects enrolled	48
No. of subjects completing	48
No. of subjects analyzed	48
No. of subjects included in the statistical analysis	47*
Subjects (Healthy or Patients?)	Healthy
Sex (es) included (how many?)	Male: 28 Female: 20
Test product	Bupropion Hydrochloride Extended Release Tablets, USP
Reference product	Wellbutrin-XL® Tablets
Strength tested	150 mg
Dose	1x150 mg, administered with 240 mL of water at room temperature

**Sub #3 took too much concomitant medication during the study period and was not included in the statistical analysis

Summary of Statistical Analysis for Bupropion As Reported by the Firm*		
Fed BE Study 40432 (N=47)		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	93.08	88.93%-97.43%
AUC_{∞}	93.55	89.61%-97.65%
C_{max}	91.07	85.34%-97.18%

Summary of Statistical Analysis for Hydroxybupropion As Reported by the Firm*		
Fed BE Study 40432 (N=47)		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	97.03	90.79%-103.69%
AUC_{∞}	96.52	90.12%-103.38%
C_{max}	93.63	93.63%-107.57%

**The reviewer's calculated values were same as reported by the firm.*

Reanalysis of Study Samples for Bupropion

Study No. 40432 Randomized, 2-Way Crossover, Bioequivalence Study of Bupropion 150 mg Extended-Release Tablet and Wellbutrin XL™ Following a 150 mg Dose in Healthy Subjects Under FED Conditions Volume 7, p. 2038, 2059-2083								
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	16	59	0.73	2.69	14	59	0.64	2.69
Unacceptable internal standard response	13	57	0.59	2.60	13	57	0.59	2.60
Incomplete analysis	0	2	0.0	0.09	0	2	0.0	0.09
Sample reanalyzed to obtain confirming value	2	0	0.09	0.0	1	0	0.05	0.0
Sample repeated or reinjected by error	1	0	0.05	0.0	0	0	0.0	0.0
Total	16	59	0.73	2.69	14	59	0.64	2.69

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table
[2] Bupropion 150 mg extended-release tablet, Lot No. XT4L029
[R] Bupropion 150 mg extended-release tablet (Wellbutrin XLTM), Lot No: 04D014P

Reanalysis of Study Samples for Hydroxybupropion

Study No. 40432 Randomized, 2-Way Crossover, Bioequivalence Study of Bupropion 150 mg Extended-Release Tablet and Wellbutrin XL™ Following a 150 mg Dose in Healthy Subjects Under FED Conditions Volume 7, p. 2038, 2059-2083								
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	49	96	2.24	4.38	47	96	2.15	4.38
Unacceptable internal standard response	12	55	0.55	2.51	12	55	0.55	2.51
Incomplete analysis	0	2	0.0	0.09	0	2	0.0	0.09
Sample concentration above upper limit of quantification	24	32	1.09	1.46	24	32	1.09	1.46
Sample reanalyzed to obtain confirming value	2	0	0.09	0.0	1	0	0.05	0.0
Rejected sample dilution	10	7	0.46	0.32	10	7	0.46	0.32
Sample repeated or reinjected by error	1	0	0.05	0.0	0	0	0.0	0.0
Total	49	96	2.24	4.38	47	96	2.15	4.38

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table
[2] Bupropion 150 mg extended-release tablet, Lot No: XT4L029
[R] Bupropion 150 mg extended-release tablet (Wellbutrin XLTM), Lot No: 04D014P

Total number of samples assayed for study 40432 = 2194

Did use of recalculated plasma concentration data change study outcome?
No, there were no pharmacokinetic repeats and no recalculations were performed for either the parent or the hydroxy metabolite in the fed study 40432.

F. Formulation

Location in appendix	Section B, Page 38
Are inactive ingredients within IIG limits?	**Yes**
If yes, 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?	**N/A: neither the test nor RLD are scored**
Is the formulation acceptable?	**Yes**
If not acceptable, why?	**N/A**

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	FDA (NDA method)
Medium	0.1N HCl
Volume (mL)	900 mL
USP Apparatus type	I (basket)
Rotation (rpm)	75 rpm
Sampling Times	120, 240, 480, and 960 minutes
Firm's proposed specifications	2 hours: [redacted] 4 hours: 8 hours: [redacted] 16 hours
FDA-recommended specifications*	2 hours: [redacted] 4 hours: 8 hours: [redacted] 12 hours
F2 metric calculated?	Yes
If no, reason why F2 not calculated	
Is method acceptable?	Yes
If not then why?	

b(4)

**Based on the submitted results under this ANDA*

H. Waiver Request(s)

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

I. Deficiency Comments

1. The firm's proposed dissolution specifications are not acceptable. The firm should acknowledge acceptance of the following FDA recommended dissolution method and specifications:

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

2 hours: [redacted]
4 hours:
8 hours: [redacted]
12 hours:

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

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

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

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

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

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

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

J. Recommendations

1. The single-dose, fasting and non-fasting bioequivalence studies conducted by Watson Laboratories, Inc. on its Bupropion Hydrochloride Extended Release Tablets, USP 150 mg (Lot # XT4L029) comparing it to GlaxoSmithKline's Wellbutrin XL® (bupropion hydrochloride) Tablets, 150 mg (Lot # 04D014P), are acceptable.

2. The in vitro dissolution testing conducted by Watson Laboratories, Inc. on its Bupropion Hydrochloride Extended Release Tablets, USP 150 mg, and 300 mg strengths, Lot Nos. XT4L029 and XC5B013, respectively is acceptable. However, the dissolution testing is incomplete for the reason given in deficiency section.

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

   2 hours: [redacted]
   4 hours: [redacted]
   8 hours: [redacted]
   12 hours

   b(4)

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

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

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

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

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

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

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

4. The formulation of the 300 mg strength is proportional to the 150 mg strength of the test product which underwent acceptable in vivo bioequivalence testing. The waiver of in vivo bioequivalence study requirements for the firm's Bupropion Hydrochloride Extended Release Tablets, USP 300 mg, cannot be granted at present for the reason given in deficiency section.

The application is incomplete pending the firm's acceptance of the FDA recommended dissolution method and specifications, and additional dissolution testing using various concentrations of ethanol in the dissolution medium.

The firm should be informed of the deficiency comments and recommendations.

Chandra S. Chaurasia 7/5/2006

Chandra S. Chaurasia, Ph.D., Reviewer, Branch 1 Date

Moheb H. Makary 7/5/06

Moheb H. Makary, Ph.D., Team Leader, Branch 1 Date

Barbara M. Davit 7/5/06

Dale P. Conner, Pharm. D. Date
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	40431
Study Title	Randomized, 2-way crossover, Bioequivalence Study of Bupropion 150 mg Extended-Release Tablet and Wellbutrin™ Following a 150 mg Dose in Healthy Subjects Under Fasting Conditions
Clinical Site	SFBC Anapharm Inc. 2050, Boul. Rene-Levesque Ouest Sainte-Foy, Quebec GIV 2K8 Canada
Principal Investigator	Dr. Benoit Girard
Study/Dosing Dates	Period I: 1/16/05 Period II: 1/30/05
Analytical Site	[redacted] b(4)
Analytical Director	[redacted]
Analysis Dates	3/04/05-4/04/05
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	78 days (First day of sample collection: January 16, 2005; last day of sample analysis: April 4, 2005)

Treatment ID	**A**	**B**
Test or Reference	Test	Reference
Product Name	Bupropion Hydrochloride Extended Release Tablets, USP	Wellbutrin-XL® (Bupropion Hydrochloride Extended Release) Tablets
Manufacturer	Watson	GlaxoSmithKline
Batch/Lot No.	XT4L029	04D014P
Manufacture Date	11/04	N/A
Expiration Date	TBE	8/2005
Strength	150 mg	150 mg
Dosage Form	Tablet	Tablet
Batch Size	[redacted]	N/A b(4)
Production Batch Size	[redacted]	N/A
Potency	103%	98.6%
Content Uniformity (mean, %CV)	101.5%, 1.2%	100.7%, 0.7%
Formulation	See Appendix Section B	
Dose Administered	1x150 mg with 240-mL of water at room temp.	1x150 mg with 240-mL of water at room temp.
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB: 3,4,5,6,9,14,15,16,19,22,23,24,26,29, 30,32,33,36,39,40, 41, 44*, 46,48 BA:1,2,7,8,10,11,12,13,17,18,20,21,25,27,28,31,34,35,37,38, 42, 43,45, 47
Blood Sampling Times	Pre dose (0),1.00, 2.00, 3.00, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 96.0, and 120 hours post-dose
Blood Volume Collected/Sample	3 mL
Blood Sample Processing/Storage	After collection, blood samples were placed in an ice water bath, and centrifuged under refrigeration. The plasma was then separated, transferred to polypropylene tubes, and immediately stored at -80°C ±15°C pending assay.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	At least 10 hours
Length of Confinement	At least 10 hours pre-dose until after the 24-hour after dosing for each study period.
Safety Monitoring	Seated blood pressure and heart rate measurements were performed prior to dosing and approximately 4, 6, 8, and 24 hours post-dose, in each period.

*Sub #44 elected to withdraw for personal reasons

Comments on Study Design: The study design is acceptable.

b) Clinical Results

Table 1. Demographic Profile for Subjects Completing Bupropion HCl Extended Release Tablets Bioequivalence Studies

Category		Project No. 40431			Project No. 40432		
		Treatment		Total	Treatment		Total
		AB	BA		AB	BA	
Age (years)	Mean ± SD	49 ± 10	42 ± 10	45 ± 11	43±12	47±14	45±13
	Range	32 – 65	26 – 60	26 – 65	21-62	25-65	21-65
	Median	51.5	40.5	43.5	43.5	53	49
	N	24	24	48	24	24	48
Age Groups	< 18	0	0	0	0	0	0
	18-40	6 (25.0%)	12 (50.0 %)	18 (37.5%)	10 (41.7%)	8 (33.3%)	18 (37.5%)
	41-64	17 (70.8%)	12 (50.0%)	29 (60.4%)	14 (58.3%)	15(62.5%)	29(60.4%)
	65-75	1 (4.2%)	0	1 (2.1%)	0	1 (4.2%)	1 (2.1%)
	> 75	0	0	0	0	0	0
Gender	Female	14 (58.3%)	15 (62.5%)	29 (60.4%)	13 (54.2%)	7 (29.2%)	20 (41.7%)
	Male	10 (41.7%)	9 (37.5%)	19 (39.6%)	11 (45.8%)	17 (70.8%)	28 (58.3%)
Race	Asian	0	0	0	0	0	0
	Black	0	0	0	2 (8.3%)	2 (8.3%)	4 (8.3%)
	Caucasian	23 (95.8%)	24 (100.0%)	47 (97.9%)	19 (79.2%)	20 (83.3%)	39 (81.3%)
	American Hispanic	1 (4.2%)	0	1 (2.1%)	3 (12.5%)	2 (8.3%)	5 (10.4%)
Height (cm)	Mean ± SD	167.3 ± 9.8	167.5 ± 7.5	167.4 ± 8.6	170.1±9.5	169.4±10.3	169.8±9.8
	Range	150.5 – 184.0	151.5-179.0	150.5 – 184.0	150.0-190.5	146.0-188.0	146.0-190.5
	Median	166.25	167.5	167.5	168.8	170.0	169.25
	N	24	24	48	24	24	48
Weight (kg)	Mean ± SD	70.9 ± 11.3	67.1 ± 9.9	69.0 ± 10.7	70.1±12.7	73.4±13.1	71.8±12.8
	Range	54.4 – 95.0	51.6 – 84.8	51.6 – 95.0	44.5-92.5	49.9-98.4	44.5-98.4
	Median	70.35	68.5	68.9	69.00	73.05	70.55
	N	24	24	48	24	24	48
BMI (kg/m^2)	Mean ± SD	25.2 ± 2.7	23.9 ± 2.7	24.6 ± 2.8	24.1±2.8	25.4±2.8	24.8±2.8
	Range	20.7 – 29.3	19.9 – 29.8	19.9 – 29.8	19.5-28.8	20.0-29.4	19.5-29.4
	Median	25.0	23.6	24.4	23.6	26.1	24.7
	N	24	24	48	24	24	48

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
44	Elected to withdraw for personal reasons prior to Period 2 dosing	Per 2	No

Table 3. Incidence of Adverse Events in Bupropion HCl Extended Release Tablets Bioequivalence Studies

System Class	Project No. 40431*		Project No. 40432*	
COSTART	A	B	A	B
Gastrointestinal disorders				
Constip	0	0	1 (1.4%)	0
Diarrhea	1 (2.0%)	0	0	0
Dry mouth	1 (2.0%)	0	1 (1.4%)	1 (1.4%)
Dyspepsia	1 (2.0%)	1 (2.0%)	0	1 (1.4%)
Pain	0	0	1 (1.4%)	0
Pain abdo	0	2 (4.1%)	4 (5.6%)	3 (4.2%)
Stool abnorm	0	0	1 (1.4%)	0
Vomit	0	0	1 (1.4%)	1 (1.4%)
General disorders and administration site conditions				
Asthenia	0	2 (4.1%)	1 (1.4%)	0
Chills	0	0	0	1 (1.4%)
Edema	0	0	0	1 (1.4%)
Injury, poisoning and procedural complications				
Asthenia	0	1 (2.0%)	0	0
Pain inject site	1 (2.0%)	0	2 (2.8%)	1 (1.4%)
Rash inject site	0	1 (2.0%)	1 (1.4%)	0
Investigations				
Hypertens	0	0	4 (5.6%)	1 (1.4%)
Tachycardia	0	1 (2.0%)	1 (1.4%)	2 (2.8%)
Metabolism and nutrition disorders				
Anorexia	0	0	1 (1.4%)	0
Musculoskeletal and connective tissue disorders				
Myalgia	0	0	2 (2.8%)	0
Pain	1 (2.0%)	1 (2.0%)	1 (1.4%)	
Nervous system disorders				
Dizziness	1 (2.0%)	2 (4.1%)	1 (1.4%)	0
Dream abnorm				1 (1.4%)
Dyspepsia	0	0	1 (1.4%)	0
Headache	5 (10.2%)	6 (12.2%)	5 (6.9%)	4 (5.6%)
Somnolence	1 (2.0%)	1 (2.0%)	1 (1.4%)	1 (1.4%)

Protocol Deviations

Thirty-four subjects in Period 1 and 31 subjects in Period 2 exhibited protocol deviations related to blood draw time – 1-9 minutes late except sub#20 period 1, 29 minute late for the 96 hr sampling time and sub#46 period 2, 13 minute late for the 36-hr sampling time (for details please see section 14.3 in Volume 1.2, pp 223-225). These deviations were minor and had no effect on the outcome of the study.

Comments on Dropouts/Adverse Events/Protocol Deviations:

- There were 38 adverse events experienced by 28 subjects – 17 with test and 21 with the reference drug. Twenty-nine AEs were listed mild in severity and nine were listed as moderate in severity. Seven AEs were listed as unrelated to study drug, 5 as remotely related, and 26 possibly related to study drugs.
- Subject #44 elected to withdraw from the study for personal reasons prior to Period 2 (reference) drug administration.

- All adverse events were resolved. There were no serious AE reported in this study.
- The adverse events and protocol deviations did not compromise the integrity of the study.

c) Bioanalytical Results

Table 4 Assay Quality Control – Within Study

	Bupropion							
QC Conc. (ng/mL)	3.02	30.21	60.42	140.98				
Inter day Precision (%CV)	4.28	3.49	4.36	9.15				
Inter day Accuracy (%)	100.66	103.51	99.39	100.43				
Cal. Standards Conc. (ng/mL)	1.00	2.00	20.04	40.07	80.14	120.22	160.29	200.36
Inter day Precision (%CV)	3.96	4.04	1.99	2.26	2.01	2.49	2.75	2.21
Inter day Accuracy (%)	101.00	99.00	90.47	101.37	102.85	101.89	101.94	101.65
Linearity Range (range of R^2)	0.9924-0.9980							

	Hydroxybupropion							
QC Conc. (ng/mL)	3.01	60.94	120.48	281.128				
Inter day Precision (%CV)	7.87	7.64	10.28	5.56				
Inter day Accuracy (%)	101.33	101.31	94.27	98.53				
Cal. Standards Conc. (ng/mL)	1.00	2.00	39.98	79.97	159.94	239.90	319.87	399.84
Inter day Precision (%CV)	6.00	4.02	3.95	3.05	2.71	3.79	3.44	4.02
Inter day Accuracy (%)	100.00	99.50	91.82	101.60	102.13	101.18	102.02	100.74
Linearity Range (range of R^2)	0.9916-0.9984							

Comments on Study Assay Quality Control:

Any interfering peaks in chromatograms?	None
Were 20% of chromatograms included?	YES
Were chromatograms serially or randomly selected?	Serially

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

Table 5 SOP dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
ANI 156.08 Vol. 1.6, pp 2381-2390	01/07/2003	Sample Re-assays and Reporting of Final Concentrations

Table 6 Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays:

- There were a total of 82 and 119 sample re-assays for bupropion and hydroxybupropion, respectively in the study, representing 3.97% and 5.76% of the total study assays. All re-assays were performed in accordance with the SOP.
- Analytical method and data are acceptable.

d) Pharmacokinetic Results

Mean plasma concentrations for bupropion and hydroxybupropion are presented in Tables below. The plasma-concentration time plots for each of the analytes are depicted in Figures 1 and 2 below.

Table 7 Arithmetic Mean Pharmacokinetic Parameters for Bupropion: Fasting Study #40431

PARAMETER		Test		Reference		
		Mean	%CV	Mean	%CV	T/R
LAUCT	Units	730.08	33.40	798.64	29.76	0.91
AUCI	ng•hr/mL	767.52	32.68	840.10	29.14	0.91
CMAX	ng/mL	68.93	33.94	73.48	35.75	0.94
TMAX	hr	4.79	16.83	4.69	13.44	1.02
KE	hr-1	0.04	36.34	0.04	40.48	1.07
THALF	hr	18.22	35.11	19.94	36.91	0.91
LAUCT	ng•hr/mL	691.89	0.05	764.23	0.04	0.91
LAUCI	ng•hr/mL	729.19	0.04	805.23	0.04	0.91
LCMAX	ng/mL	65.31	0.51	69.13	0.52	0.94

Table 8 Geometric Means and 90% Confidence Intervals Bupropion Fasting Study#40431

PARAMETER	Test	Reference	T/R	90% CI	
				Lower	Upper
AUCT	731.52	799.25	0.92	87.25	95.80
AUCI	769.03	840.81	0.91	87.30	95.63
CMAX	68.99	73.52	0.94	85.62	102.04
LAUCT	693.34	764.90	0.91	86.73	94.73
LAUCI	730.74	805.99	0.91	86.85	94.64
LCMAX	65.38	69.18	0.95	87.28	102.34

Table 9 Additional Study Information

Root mean square error, AUC	0.1273
Root mean square error, Cmax	0.2297
Ke and AUCi determined for how many subjects?	47
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as Cmax	None
Were the subjects dosed as more than one group?	No

Table 10 Mean Plasma Bupropion Concentrations, Single-Dose Fasting Bioequivalence Study#40431

Time	Test (n=47)		Reference (n=47)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	N/A	0.00	N/A	N/A
1	0.00	.	0.07	685.57	0.00
2	4.99	191.61	7.25	174.69	0.69
3	25.38	67.56	28.99	82.92	0.88
4	46.08	44.01	48.37	44.46	0.95
4.5	60.81	35.24	66.23	37.78	0.92
5	61.11	34.40	65.73	39.18	0.93
5.5	51.69	37.98	59.02	34.35	0.88
6	47.93	40.74	54.10	36.04	0.89
6.5	44.66	44.10	48.96	34.31	0.91
7	40.11	40.59	44.16	34.54	0.91
7.5	35.43	38.84	39.59	33.26	0.90
8	34.69	39.42	37.09	31.57	0.94
10	26.23	34.69	29.69	33.27	0.88
12	20.66	30.83	25.78	32.31	0.80
16	14.63	37.08	16.85	28.17	0.87
24	10.80	44.24	10.16	37.29	1.06
36	5.06	41.11	5.00	38.00	1.01
48	3.06	53.69	3.32	43.65	0.92
72	1.26	90.88	1.44	76.78	0.87
96	0.43	165.00	0.53	135.64	0.80
120	0.08	391.72	0.09	387.87	0.95

Figure 1 Mean Plasma Bupropion Concentration Time Plot, Single-Dose Fasting Bioequivalence Study #40431

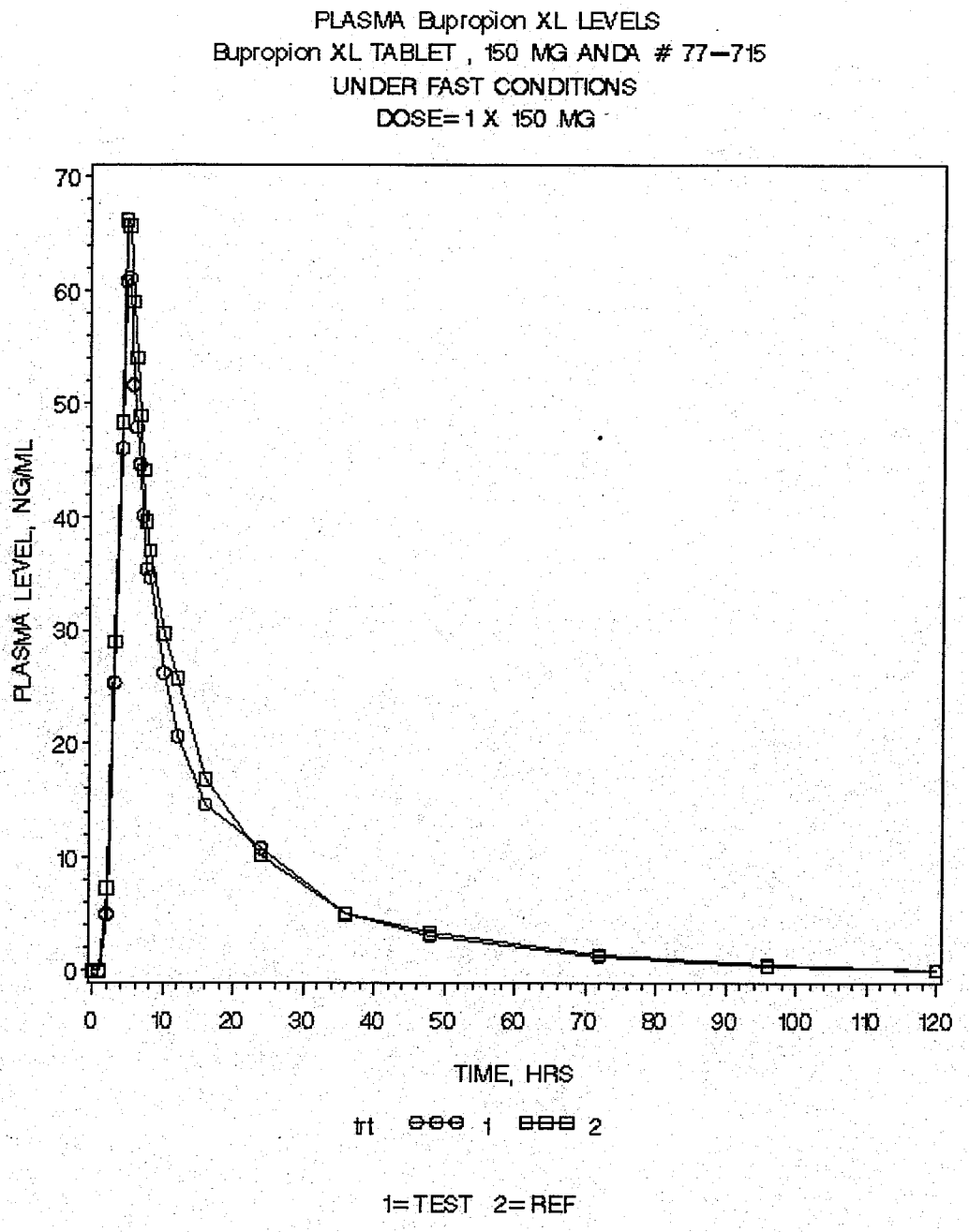


Table 11 Arithmetic Mean Pharmacokinetic Parameters for Hydroxybupropion: Fasting Study#40431

PARAMETER		Test		Reference		
		Mean	%CV	Mean	%CV	T/R
LAUCT	Units	12887.73	44.63	13632.08	40.51	0.95
AUCI	ng•hr/mL	13610.27	46.53	14391.28	41.71	0.95
CMAX	ng/mL	260.39	40.12	276.38	36.06	0.94
TMAX	hr	13.57	55.00	13.38	50.97	1.01
KE	hr-1	0.03	16.80	0.03	17.38	1.02
THALF	hr	24.52	16.95	25.01	17.40	0.98
LAUCT	ng•hr/mL	11639.98	0.00	12443.03	0.00	0.94
LAUCI	ng•hr/mL	12224.04	0.00	13089.65	0.00	0.93
LCMAX	ng/mL	237.77	0.20	254.99	0.17	0.93

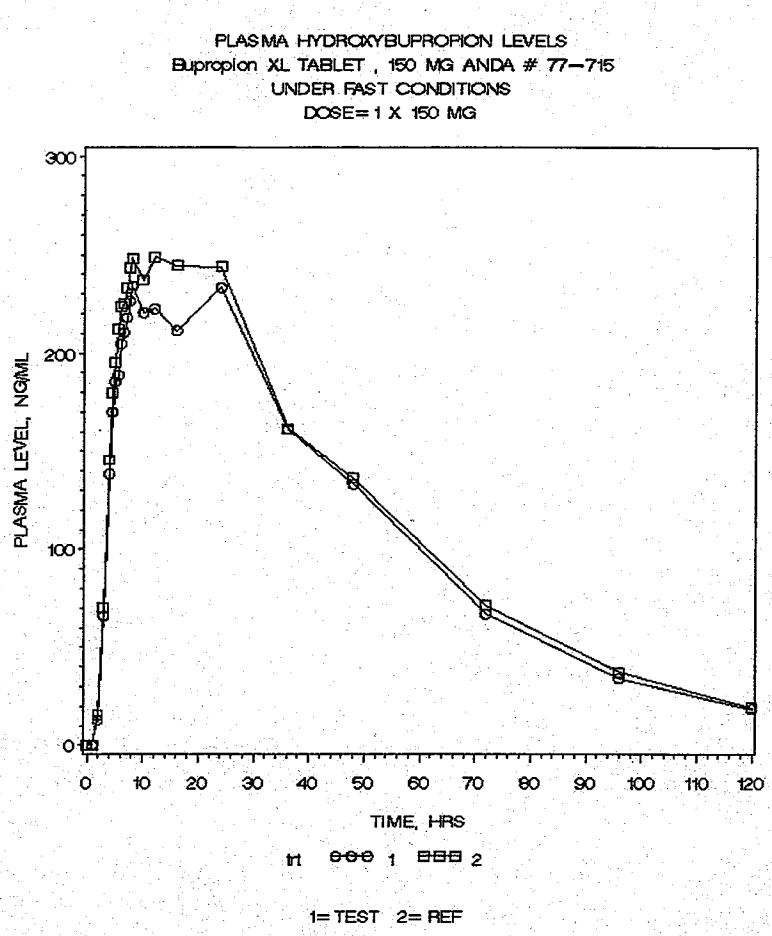
Table 12 Geometric Means and 90% Confidence Intervals for Hydroxybupropion: Fasting Study#40431

PARAMETER	Test	Reference	T/R	90% CI	
				Lower	Upper
AUCT	12890.95	13638.16	0.95	89.18	99.86
AUCI	13615.97	14400.97	0.95	88.99	100.10
CMAX	260.31	276.25	0.94	89.10	99.36
LAUCT	11639.92	12448.56	0.94	88.83	98.42
LAUCI	12225.37	13098.04	0.93	88.51	98.43
LCMAX	237.66	254.89	0.93	88.63	98.09

Table 12 Additional Study Information

Root mean square error, AUC	0.1478
Root mean square error, Cmax	0.1462
Ke and AUCi determined for how many subjects?	47
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as Cmax	None
Were the subjects dosed as more than one group?	No

Figure 2. Mean Plasma Hydroxybupropion Concentration Time Plot, Single-Dose Fasting Bioequivalence Study# 40431



Comments on Pharmacokinetic Analysis for the Fasting Study 340431:

1. Results (point estimate, 90% CI) of statistical data analyses from the study 40431 are:

   For bupropion: LAUCt of 0.91, 86.7-94.7%; LAUCi of 0.91, 86.8-94.6% and LCmax of 0.94, 87.3-102.3%; and

   For hydroxybupropion: LAUCt of 0.94, 88.8-98.4%; LAUCi of 0.93, 88.5-98.4% and LCmax of 0.93, 88.6-98.1%.

2. The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with the firm's calculations.

3. The 90% confidence intervals for ln-transformed AUCt, AUCinf, and Cmax for bupropion and hydroxybupropion are within the acceptable limits of 80-125%.

2. Single-dose Fed Bioequivalence Study

a) Study Design

Study Information	
Study Number	40432
Study Title	Randomized, 2-way crossover, Bioequivalence Study of Bupropion 150 mg Extended-Release Tablet and Wellbutrin™ Following a 150 mg Dose in Healthy Subjects Under Fed Conditions
Clinical Site	SFBC Anapharm Inc. 5160, Boul. Decarie, Suite 300 Montreal, Quebec H3X 2H9 Canada
Principal Investigator	Dr. Richard Larouche
Study/Dosing Dates	Period I: 01/12/05 Period II: 01/26/05
Analytical Site	[redacted]
Analytical Director	[redacted]
Analysis Dates	2/15/05-3/08/05
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	84 days (First day of sample collection: January 12, 2005; last day of sample analysis: March 8, 2005)

b(4)

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Bupropion Hydrochloride Extended Release Tablets, USP	Wellbutrin-XL® (Bupropion Hydrochloride Extended Release) Tablets
Manufacturer	Watson	GlaxoSmithKline
Batch/Lot No.	XT4L029	04D014P
Manufacture Date	11/04	N/A
Expiration Date	TBE	8/2005
Strength	150 mg	150 mg
Dosage Form	Tablet	Tablet
Batch Size	[redacted]	N/A
Production Batch Size	[redacted]	N/A
Potency	103%	98.6%
Content Uniformity (mean, %CV)	101.5%, 1.2%	100.7%, 0.7%
Formulation	See Appendix Section B	
Dose Administered	1x150 mg with 240-mL of water at room temp.	1x150 mg with 240-mL of water at room temp.
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: 1,4,7,8,9,10,15,16,18,19,20,24,26,27,29, 30,31,32,38,39, 41,42, 47,48 BA:2,3,5,6,11,12,13,14,17,21,22,23,25,28,33,34,35,36,37,40, 43,44,45, 46
Blood Sampling Times	Pre dose (0),1.00, 2.00, 3.00, 4.00, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 8.50, 9.00, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 96.0, and 120 hours post-dose
Blood Volume Collected/Sample	3 mL
Blood Sample Processing/Storage	After collection, blood samples were placed in an ice water bath, and centrifuged under refrigeration. The plasma was then separated, transferred to polypropylene tubes, and immediately stored at -80°C ±15°C pending assay.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	Following a supervised overnight fast of at least 10 hours, subjects received a standard high fat, high caloric breakfast which was completely consumed within 30 minutes prior to drug administration
FDA Diet	Yes
Length of Confinement	At least 11 hours pre-dose until after the 24-hour after dosing for each study period.
Safety Monitoring	Seated blood pressure and heart rate measurements were performed prior to dosing and approximately 4, 6, 8, and 24 hours post-dose, in each period.

*Sub #3 took too much concomitant medication during the study period and was not included in the statistical analysis

Comments on Study Design: The study design is acceptable.

b) Clinical Results

Table 13. Demographic Profile for Subjects Completing Bupropion HCl Extended Release Tablets Bioequivalence Studies

Category		Project No. 40431			Project No. 40432		
		Treatment		Total	Treatment		Total
		AB	BA		AB	BA	
Age (years)	Mean ± SD	49 ± 10	42 ± 10	45 ± 11	43±12	47±14	45±13
	Range	32 – 65	26 – 60	26 – 65	21-62	25-65	21-65
	Median	51.5	40.5	43.5	43.5	53	49
	N	24	24	48	24	24	48
Age Groups	< 18	0	0	0	0	0	0
	18-40	6 (25.0%)	12 (50.0 %)	18 (37.5%)	10 (41.7%)	8 (33.3%)	18 (37.5%)
	41-64	17 (70.8%)	12 (50.0%)	29 (60.4%)	14 (58.3%)	15(62.5%)	29(60.4%)
	65-75	1 (4.2%)	0	1 (2.1%)	0	1 (4.2%)	1 (2.1%)
	> 75	0	0	0	0	0	0
Gender	Female	14 (58.3%)	15 (62.5%)	29 (60.4%)	13 (54.2%)	7 (29.2%)	20 (41.7%)
	Male	10 (41.7%)	9 (37.5%)	19 (39.6%)	11 (45.8%)	17 (70.8%)	28 (58.3%)
Race	Asian	0	0	0	0	0	0
	Black	0	0	0	2 (8.3%)	2 (8.3%)	4 (8.3%)
	Caucasian	23 (95.8%)	24 (100.0%)	47 (97.9%)	19 (79.2%)	20 (83.3%)	39 (81.3%)
	American Hispanic	1 (4.2%)	0	1 (2.1%)	3 (12.5%)	2 (8.3%)	5 (10.4%)
Height (cm)	Mean ± SD	167.3 ± 9.8	167.5 ± 7.5	167.4 ± 8.6	170.1±9.5	169.4±10.3	169.8±9.8
	Range	150.5 – 184.0	151.5-179.0	150.5 – 184.0	150.0-190.5	146.0-188.0	146.0-190.5
	Median	166.25	167.5	167.5	168.8	170.0	169.25
	N	24	24	48	24	24	48
Weight (kg)	Mean ± SD	70.9 ± 11.3	67.1 ± 9.9	69.0 ± 10.7	70.1±12.7	73.4±13.1	71.8±12.8
	Range	54.4 – 95.0	51.6 – 84.8	51.6 – 95.0	44.5-92.5	49.9-98.4	44.5-98.4
	Median	70.35	68.5	68.9	69.00	73.05	70.55
	N	24	24	48	24	24	48
BMI (kg/m^2)	Mean ± SD	25.2 ± 2.7	23.9 ± 2.7	24.6 ± 2.8	24.1±2.8	25.4±2.8	24.8±2.8
	Range	20.7 – 29.3	19.9 – 29.8	19.9 – 29.8	19.5-28.8	20.0-29.4	19.5-29.4
	Median	25.0	23.6	24.4	23.6	26.1	24.7
	N	24	24	48	24	24	48

Dropout Information: No dropout was reported in this study. All 48 enrolled subjects completed the both periods of the study. However, Sub #3 took too much concomitant medications (10x500 mg tablets of acetaminophen, 8 caplets of Tylenol sinus during the study period between 17-hr and 80-hr post-dose in Period 1. The firm therefore decided to drop this subject in statistical analysis.

Table 14. Incidence of Adverse Events in Bupropion HCl Extended Release Tablets Bioequivalence Studies

System Class	Project No. 40431*		Project No. 40432*	
COSTART	A	B	A	B
Gastrointestinal disorders				
Constip	0	0	1 (1.4%)	0
Diarrhea	1 (2.0%)	0	0	0
Dry mouth	1 (2.0%)	0	1 (1.4%)	1 (1.4%)
Dyspepsia	1 (2.0%)	1 (2.0%)	0	1 (1.4%)
Pain	0	0	1 (1.4%)	0
Pain abdo	0	2 (4.1%)	4 (5.6%)	3 (4.2%)
Stool abnorm	0	0	1 (1.4%)	0
Vomit	0	0	1 (1.4%)	1 (1.4%)
General disorders and administration site conditions				
Asthenia	0	2 (4.1%)	1 (1.4%)	0
Chills	0	0	0	1 (1.4%)
Edema	0	0	0	1 (1.4%)
Injury, poisoning and procedural complications				
Asthenia	0	1 (2.0%)	0	0
Pain inject site	1 (2.0%)	0	2 (2.8%)	1 (1.4%)
Rash inject site	0	1 (2.0%)	1 (1.4%)	0
Investigations				
Hypertens	0	0	4 (5.6%)	1 (1.4%)
Tachycardia	0	1 (2.0%)	1 (1.4%)	2 (2.8%)
Metabolism and nutrition disorders				
Anorexia	0	0	1 (1.4%)	0
Musculoskeletal and connective tissue disorders				
Myalgia	0	0	2 (2.8%)	0
Pain	1 (2.0%)	1 (2.0%)	1 (1.4%)	
Nervous system disorders				
Dizziness	1 (2.0%)	2 (4.1%)	1 (1.4%)	0
Dream abnorm				1 (1.4%)
Dyspepsia	0	0	1 (1.4%)	0
Headache	5 (10.2%)	6 (12.2%)	5 (6.9%)	4 (5.6%)
Somnolence	1 (2.0%)	1 (2.0%)	1 (1.4%)	1 (1.4%)

Protocol Deviations

Thirty-five subjects in Period 1 and 34 subjects in Period 2 exhibited protocol deviations related to blood draw time – 1-20 minutes late except sub#20 period 1, 32 minute late for the 1 hr sampling time. In addition, there were 14 instances of samples not obtained Sub# 9 and 20 Period 1 at 6.5 hr, Sub#18 period 1 at 10 hr, Sub#19 Period 1 at 36 hr, Sub#14 period 1 at 96 hr, Sub#16 and 41 Period 1 at 120 hr, sub#28 period 2, at 6.5 hr, Sub#28 period 2 at 8.5 hr, Sub#30 Period 2 at 36 hr, Sub#14 period 2 at 48 hr, Sub#7 and 14 Period 2 at 72 hr and Sub# 42 in Period 2 at 120 hr post-dose (for details please see section 14.3 in Volume 1.11, pp 5017-5021). In this reviewer's opinion, considering the PK profile of each subject, these deviations were minor and had no effect on the outcome of the study.

Comments on Dropouts/Adverse Events/Protocol Deviations:

- There were 61 adverse events experienced by 31 subjects – 34 with test and 27 with the reference drug. Forty-five AEs were listed mild in severity, five were listed as moderate in severity and one AE was listed as severe in severity. Nine AEs were listed as unrelated to study drug, 14 as remotely related, 35 possibly related and three probably related to study drugs.
- There was one incidence of vomiting (severe AE) reported by subject #22 at 3 days 22 hour and 18 minutes post dose in Treatment B (reference) Period 1. The Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations (March 2003) stated that "In the case of modified-release products, the data from subjects who experience emesis any time during the labeled dosing interval can be deleted". Since, it is recommended that Wellbutrin-XL® tablets be administered orally once daily, therefore, subject #22 should not be excluded from the study analysis.
- There were no serious AE reported in this study.
- The adverse events and protocol deviations did not compromise the integrity of the study.

e) Bioanalytical Results

Table 15 Assay Quality Control – Within Study

	Bupropion							
QC Conc. (ng/mL)	3.02	30.21	60.42	140.98				
Inter day Precision (%CV)	3.62	2.54	2.58	3.86				
Inter day Accuracy (%)	100.66	104.07	99.27	101.53				
Cal. Standards Conc. (ng/mL)	1.00	2.00	20.04	40.07	80.14	120.22	160.29	200.36
Inter day Precision (%CV)	1.98	2.51	2.25	1.89	1.90	2.22	1.91	1.83
Inter day Accuracy (%)	101.00	99.50	90.97	101.60	102.60	101.46	101.74	101.66
Linearity Range (range of R^2)	0.9962-0.9988							

	Hydroxybupropion							
QC Conc. (ng/mL)	3.01	60.94	120.48	281.128				
Inter day Precision (%CV)	6.47	7.29	6.83	5.80				
Inter day Accuracy (%)	102.66	104.91	97.65	98.91				
Cal. Standards Conc. (ng/mL)	1.00	2.00	39.98	79.97	159.94	239.90	319.87	399.84
Inter day Precision (%CV)	4.04	3.43	2.90	3.11	3.16	3.05	3.20	3.55
Inter day Accuracy (%)	99.00	102.00	93.10	100.99	102.58	10.21	10.53	99.69
Linearity Range	0.9951-0.9991							

(range of R^2)	

Comments on Study Assay Quality Control:

Any interfering peaks in chromatograms?	None
Were 20% of chromatograms included?	YES
Were chromatograms serially or randomly selected?	Serially

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

c) Bioanalytical Results

Table 16. SOP dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
ANI 156.08 Vol. 1.6, pp 2381-2390	01/07/2003	Sample Re-assays and Reporting of Final Concentrations

Table 17 Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays:

- There were a total of 75 and 145 sample re-assays for bupropion and hydroxybupropion, respectively in the study, representing 3.4% and 6.6% of the total study assays. All re-assays were performed in accordance with the SOP.
- Analytical method and data are acceptable.

d) Pharmacokinetic Results

Mean plasma concentrations for bupropion and hydroxybupropion are presented in the Tables below. The plasma-concentration time plots for each of the analytes are depicted in Figures 3 and 4 below.

Table 17. Arithmetic Mean Pharmacokinetic Parameters for Bupropion: Fed Study #40432

PARAMETER		Test		Reference		
		Mean	%CV	Mean	%CV	T/R
LAUCT	Units	938.72	32.27	1003.36	31.57	0.94
AUCI	ng•hr/mL	980.77	31.26	1045.28	31.05	0.94
CMAX	ng/mL	77.81	36.12	83.94	29.61	0.93
TMAX	hr	6.47	21.47	7.01	25.56	0.92
KE	hr-1	0.04	36.27	0.04	43.56	1.00
THALF	hr	19.73	30.87	20.14	30.99	0.98
LAUCT	ng•hr/mL	891.25	0.04	956.94	0.03	0.93
LAUCI	ng•hr/mL	934.39	0.03	998.35	0.03	0.94
LCMAX	ng/mL	73.57	0.45	80.72	0.35	0.91

Table 18 Geometric Means and 90% Confidence Intervals for Bupropion: Fed Study #40432

PARAMETER	Test	Reference	T/R	90% CI	
				Lower	Upper
AUCT	938.09	1002.01	0.94	89.57	97.67
AUCI	980.14	1043.92	0.94	89.97	97.81
CMAX	77.70	83.89	0.93	86.49	98.74
LAUCT	890.66	955.65	0.93	89.25	97.32
LAUCI	933.79	997.05	0.94	89.84	97.63
LCMAX	73.49	80.69	0.91	85.34	97.18

Table 19 Additional Study Information for Bupropion: Fed Study #40432

Root mean square error, AUC	0.1249
Root mean square error, Cmax	0.1874
Ke and AUCi determined for how many subjects?	47
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as Cmax	None
Were the subjects dosed as more than one group?	No

Table 20 Mean Plasma Bupropion Concentrations, Single-Dose Fed Bioequivalence Study#40432

Time	Test (n=47)		Reference (n=47)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00	N/A	0.00	N/A	N/A
1	0.00	.	0.00	.	.
2	0.80	264.17	0.41	227.43	1.97
3	16.20	113.11	7.46	123.57	2.17
4	39.34	62.21	25.52	68.23	1.54
5	67.61	41.21	59.21	50.00	1.14
5.5	61.04	37.98	63.48	43.99	0.96
6	61.95	39.24	64.51	42.24	0.96
6.5	60.96	41.60	64.31	35.46	0.95
7	59.00	40.53	63.22	34.00	0.93
7.5	56.68	39.45	60.42	33.93	0.94
8	54.59	36.17	59.47	35.15	0.92
8.5	54.92	35.79	61.42	35.21	0.89
9	51.74	37.49	58.97	35.84	0.88
10	44.91	35.56	51.50	36.02	0.87
12	33.25	38.20	38.61	34.80	0.86
16	21.10	36.35	23.90	36.73	0.88
24	11.82	37.43	12.68	33.71	0.93
36	5.72	41.06	5.96	40.83	0.96
48	3.87	44.22	4.16	48.26	0.93
72	1.71	64.15	2.03	60.35	0.84
96	0.57	143.64	0.69	134.88	0.83
120	0.13	301.74	0.21	246.87	0.65

Figure 3 Mean Plasma Bupropion Concentrations-Time Plot, Single-Dose Fed Bioequivalence Study

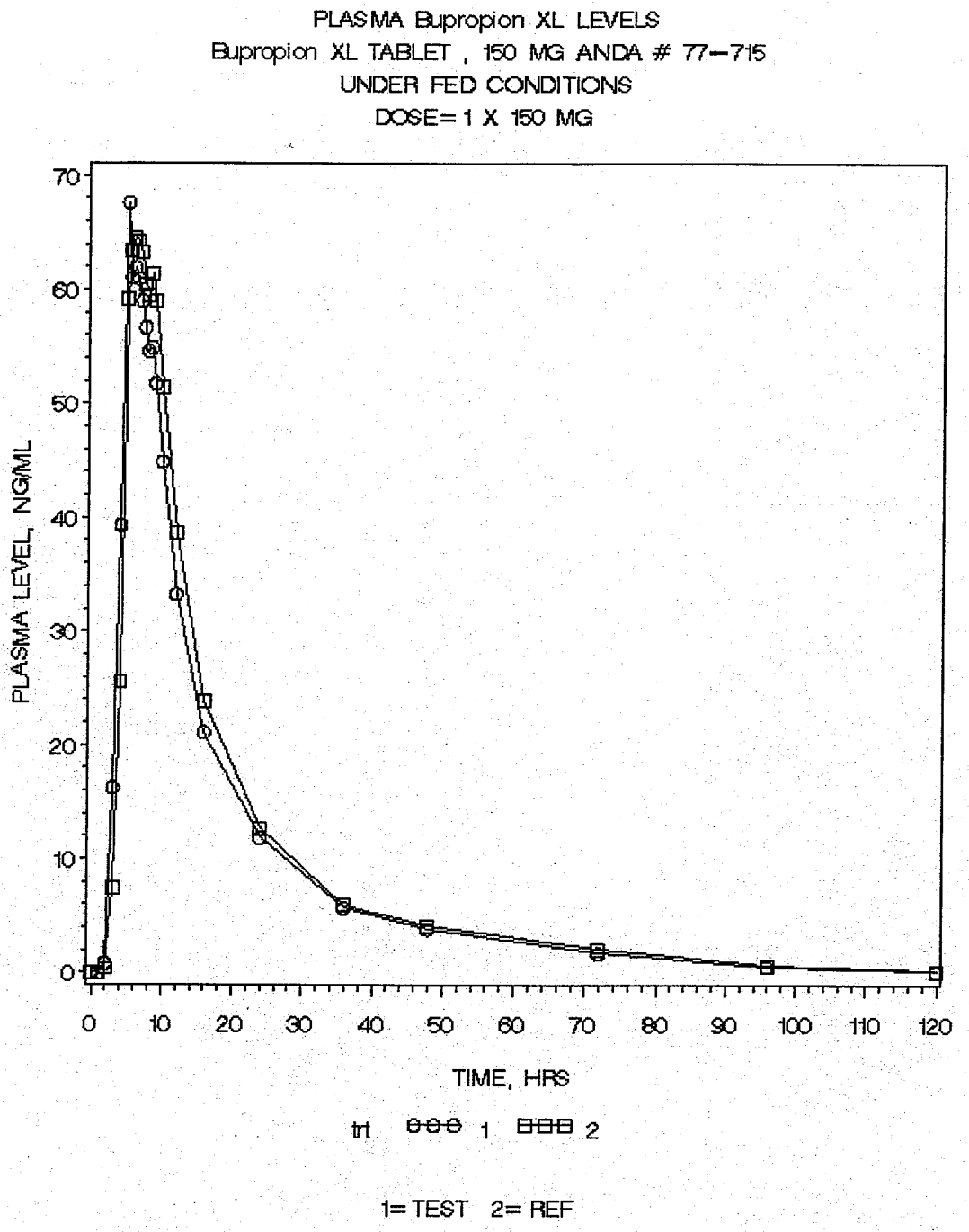


Table 21. Arithmetic Mean Pharmacokinetic Parameters for Hydroxybupropion: Fed Study #40432

PARAMETER		Test		Reference		
		Mean	%CV	Mean	%CV	T/R
LAUCT	Units	13546.48	42.17	13958.79	41.01	0.97
AUCI	ng•hr/mL	14534.58	43.92	14982.23	41.88	0.97
CMAX	ng/mL	287.06	36.36	290.18	38.94	0.99
TMAX	hr	14.76	37.43	17.46	37.86	0.85
KE	hr-1	0.03	23.09	0.03	25.83	1.02
THALF	hr	25.28	23.25	26.11	25.46	0.97
LAUCT	ng•hr/mL	12451.89	0.00	12847.01	0.00	0.97
LAUCI	ng•hr/mL	13248.42	0.00	13735.75	0.00	0.96
LCMAX	ng/mL	270.95	0.12	270.05	0.14	1.00

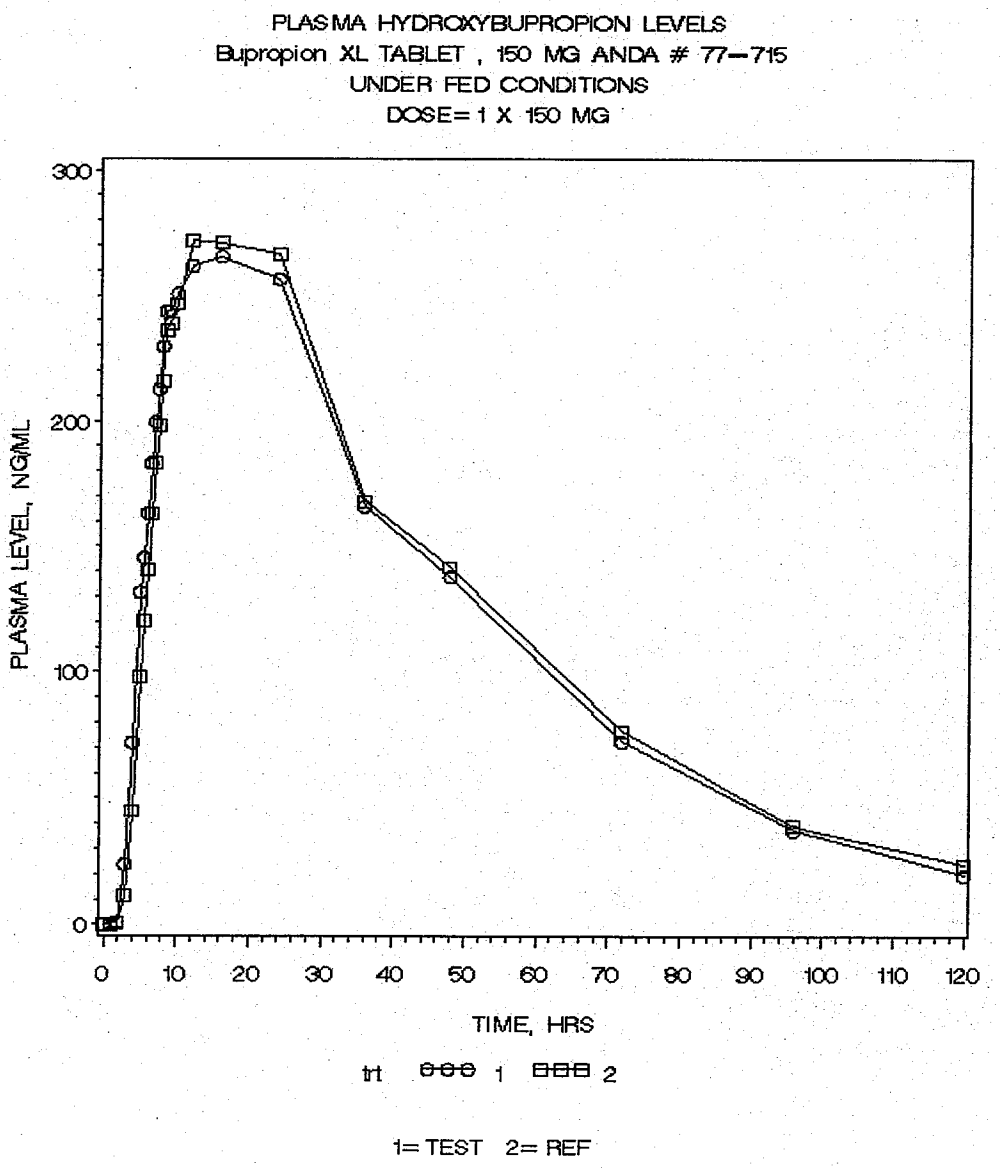
Table 22 Geometric Means and 90% Confidence Intervals for Hydroxybupropion: Fed Study #40432

PARAMETER	Test	Reference	T/R	90% CI	
				Lower	Upper
AUCT	13553.46	13950.85	0.97	90.20	104.10
AUCI	14537.11	14975.80	0.97	89.70	104.44
CMAX	287.13	290.20	0.99	91.78	106.11
LAUCT	12464.15	12845.59	0.97	90.80	103.69
LAUCI	13258.05	13735.60	0.97	90.12	103.38
LCMAX	271.08	270.12	1.00	93.63	107.57

Table 19 Additional Study Information Hydroxybupropion Fed Study340432

Root mean square error, AUC	0.1915
Root mean square error, Cmax	0.2003
Ke and AUCi determined for how many subjects?	47
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as Cmax	None
Were the subjects dosed as more than one group?	No

Figure 4 Mean Plasma Hydroxybupropion Concentrations-Time Plot, Single-Dose Fed Bioequivalence Study



Comments on Pharmacokinetic Analysis for the Fed Study 40432:

1. Sub #3 took too much concomitant medications (10x500 mg tablets of acetaminophen, 8 caplets of Tylenol sinus during the study period between 17-hr and 80-hr post-dose in Period 1. The firm therefore decided to drop this subject in statistical analysis. Inclusion of this subject in statistical data analyses did not change the PK study outcome to any significant effect.
2. Results (point estimate, 90% CI) of statistical data analyses from the study 40432 are:

   For Bupropion: LAUCt of 0.93, 88.9-97.4%; LAUCi of 0.95, 89.6-97.6% and LCmax of 0.91, 85.3-97.2%; and
   For Hydroxybupropion: LAUCt of 0.97, 90.8-103.7%; LAUCi of 0.97, 90.1-103.4% and LCmax of 0.94, 93.6-107.6%.

3. The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with the firm's calculations.
4. The 90% confidence intervals for ln-transformed AUCt, AUCinf, and Cmax for bupropion and hydroxybupropion are within the acceptable limits of 80-125%.

Summary/Conclusions, Single-Dose Fasting and Fed Bioequivalence Studies: The single-dose fasting and non-fasting BE studies are acceptable.

B. Formulation Data

Ingredients	Amount per Tablet	
	150 mg	300 mg

b(4)

C. Dissolution Data

Method 1: FDA Recommended method:

Source of Method:	NDA 21-515 (8/28/2003)[1a]
Medium:	0.1 N HCl
Volume:	900 mL, 37°C ± 0.5°C
Apparatus:	USP apparatus 1 (basket) at 75 rpm

Firm's proposed specifications[1a]:

2 hours:
4 hours:
8 hours:
16 hours

b(4)

FDA specifications[1b]: 2 hours: [redacted]
4 hours: [redacted]
8 hours: [redacted]
12 hours [redacted]

b(4)

[1a]*Dissolution review of ANDA 77-715 (V:\firmsnz\watson\ltrs&rev\77715D0505.doc (reviewed by Dr. Dev Patel).*
[1b]*Based on the submitted dissolution data ANDA 77-715 May 19, 2005.*

The firm's dissolution testing results using the FDA recommended methods are summarized in the Tables below.

Summary of In Vitro Dissolution Testing

Method: USP I (Basket) *Original ANDA 77-715 submission date May 19, 2005*
Medium: 0.1N HCl, 900 mL
Rotational Speed 75 RPM

Results of In Vitro Dissolution Testing (% dissolved)

Sampling Times (Min)	Test Product: Bupropion Hydrochloride E R Tablets, USP Lot No.: XT4L029 **Strength: 150 mg** No of Dosage Units: 12			Reference Product: Wellbutrin XL® Lot No.: 04D014P **Strength: 150 mg** No of Dosage Units: 12		
	Average	Range	% SD	Average	Range	% SD
120	4	1-14	4.4	1	0-2	0.6
240	34	28-43	4.4	21	11-27	4.9
380	55	50-63	3.8	48	39-55	5.1
480	71	67-77	3.1	72	62-80	5.2
600	82	79-87	2.3	87	83-91	2.7
720	89	87-92	1.7	93	89-95	1.9
840	93	90-95	1.7	95	92-96	1.8
960	94	92-97	1.7	97	93-99	1.7
1080	96	93-98	1.6	98	94-100	1.6
Sampling Times (Min)	Test Product: Bupropion[2] Hydrochloride E R Tablets, USP Lot No.: XC5B013 **Strength: 300 mg** No of Dosage Units: 12			Reference Product: Wellbutrin XL® Lot No.: 4ZP1099 **Strength: 300 mg** No of Dosage Units: 12		
	Average	Range	% RSD	Average	Range	% RSD
120	14	7-24	4.6	4	2-7	1.8
240	40	33-49	4.8	28	23-33	3.3
380	58	51-67	4.6	49	44-55	3.2
480	71	65-80	4.1	67	62-72	2.9
600	81	75-89	3.6	81	76-84	2.3
720	89	85-95	2.8	89	86-91	1.4
840	94	91-97	1.7	93	92-96	1.0
960	96	94-99	1.3	95	93-97	1.1
1080	98	95-100	1.1	96	96-98	1.1

[2]*Amendment to ANDA 77-715 submitted for the new 300 mg strength submission date July 27, 2005*

Method: USP I (Basket)
Medium: Water, 900 mL[3]
Rotational Speed 75 RPM

Results of In Vitro Dissolution Testing (% dissolved)

Sampling Times (Min)	Test Product: Bupropion Hydrochloride E R Tablets, USP Lot No.: XT4L029 **Strength: 150 mg** No of Dosage Units: 12			Reference Product: Wellbutrin XL® Lot No.: 04D014P **Strength: 150 mg** No of Dosage Units: 12		
	Average	Range	% SD	Average	Range	% SD
120	1	0-2	0.3	1	0-3	0.6
240	15	2-19	4.1	4	2.10	2.6
380	27	17-32	3.5	13	8-18	2.6
480	38	28-44	3.5	21	18-25	2.1
600	47	37-55	4.0	30	27-34	2.1
720	56	46-66	4.2	38	34-44	2.8
840	62	53-72	4.2	47	42-55	3.9
960	68	60-78	4.1	56	49-57	5.7
1080	72	66-83	4.1	64	55-80	6.8
Sampling Times (Min)	Test Product: Bupropion Hydrochloride E R Tablets, USP Lot No.: XC5B013 **Strength: 300 mg** No of Dosage Units: 12			Reference Product: Wellbutrin XL® Lot No.: 4ZP1099 **Strength: 300 mg** No of Dosage Units: 12		
	Average	Range	% RSD	Average	Range	% RSD
120	4	0-9	3.1	1	1-4	1.0
240	15	4-23	6.3	7	2-12	3.5
380	27	13-34	6.7	15	10-19	2.9
480	37	23-49	7.3	21	16-26	2.9
600	46	33-64	8.0	28	22-33	3.0
720	55	42-75	8.1	34	28-40	3.2
840	62	50-84	8.2	40	34-47	3.5
960	69	58-91	8.0	47	40-54	3.8
1080	74	64-95	7.5	53	47-60	4.1

Method: USP I (Basket)
Medium: pH4.5 Acetate Buffer, 900 mL[3]
Rotational Speed 75 RPM

Results of In Vitro Dissolution Testing (% dissolved)

Sampling Times (Min)	Test Product: Bupropion Hydrochloride E R Tablets, USP Lot No.: XT4L029 **Strength: 150 mg** No of Dosage Units: 12			Reference Product: Wellbutrin XL® Lot No.: 04D014P **Strength: 150 mg** No of Dosage Units: 12		
	Average	Range	% SD	Average	Range	% SD
120	0	0-1	0.1	0	0-0	0.1
240	14	9-20	3.1	1	1-4	0.8
380	31	28-35	2.2	6	2-11	3.4
480	43	40-46	2.1	14	7-21	4.3
600	52	49-56	2.3	22	15-30	4.6
720	60	56-63	2.4	31	22.40	5.3
840	67	63-70	2.4	40	30.50	6.4
960	73	69-76	2.2	49	37-60	7.7
1080	78	73-80	2.2	58	44-70	8.5
Sampling Times (Min)	Test Product: Bupropion Hydrochloride E R Tablets, USP Lot No.: XC5B013 **Strength: 300 mg** No of Dosage Units: 12			Reference Product: Wellbutrin XL® Lot No.: 4ZP1099 **Strength: 300 mg** No of Dosage Units: 12		
	Average	Range	% RSD	Average	Range	% RSD
120	1	0-5	1.3	1	0-2	0.6
240	15	8-22	4.2	3	1-9	2.8
380	26	20-33	4.0	6	2-12	3.3
480	36	32-42	3.1	11	2-18	3.9
600	45	40-50	2.9	17	9-23	4.1
720	53	47-57	2.9	23	15-29	4.6
840	60	54-65	3.1	29	22-38	5.2
960	66	60-71	3.3	35	27-46	6.0
1080	72	65-76	3.3	42	32-54	6.8

Method: USP I (Basket)
Medium: pH6.8 Phosphate Buffer, 900 mL[3]
Rotational Speed 75 RPM

Results of In Vitro Dissolution Testing (% dissolved)

Sampling Times (Min)	Test Product: Bupropion Hydrochloride E R Tablets, USP Lot No.: XT4L029 **Strength: 150 mg,** No of Dosage Units: 12			Reference Product: Wellbutrin XL® Lot No.: 04D014P **Strength: 150 mg** No of Dosage Units: 12		
	Average	Range	% SD	Average	Range	% SD
120	37	34-40	2.0	36	35-37	1.1
240	54	50-57	2.1	63	61-65	1.3
380	63	58-66	2.3	79	76-82	1.7
480	68	63-73	3.1	85	83-87	1.3
600	72	66-80	4.4	87	86-89	1.2
720	74	66-80	4.0	88	87-90	1.1
840	74	69-80	3.5	89	87-91	1.1
960	75	70-79	2.9	89	88-91	1.1
1080	74	71-79	2.5	89	88-91	1.1
Sampling Times (Min)	Test Product: Bupropion Hydrochloride E R Tablets, USP Lot No.: XC5B013 **Strength: 300 mg,** No of Dosage Units: 12			Reference Product: Wellbutrin XL® Lot No.: 4ZP1099 **Strength: 300 mg** No of Dosage Units: 12		
	Average	Range	% RSD	Average	Range	% RSD
120	35	32-43	2.7	35	33-38	1.6
240	57	51-70	4.6	59	56-62	1.7
380	70	63-81	4.5	74	71-77	1.9
480	79	70-88	4.5	84	80-87	2.1
600	84	75-87	3.4	90	85-93	2.0
720	85	79-87	2.3	92	87-95	2.1
840	85	81-87	1.7	93	88-96	2.1
960	84	81-86	1.6	93	89-96	2.0
1080	83	80-85	1.5	93	89-96	1.9

Table f_2 calculation (calculated by the reviewer):

Test Product	Reference Product	Dissolution Medium	f_2
Watson's Bupropion Hydrochloride E R Tablets, USP Lot No.: XT4L029 Strength: 150 mg	GSK's Wellbutrin XL® Lot No.: 04D014P Strength: 150 mg	0.1 N HCl	62.1
		Water	43.4
		Acetate buffer (pH 4.5)	43.4
		Phosphate Buffer (pH 6.8)	38.3

Test Product	Product	Dissolution Medium	f_2
Watson's Bupropion Hydrochloride E R Tablets, USP Lot No.: XC5B013 Strength: 300 mg	Watson's Bupropion Hydrochloride E R Tablets, USP Lot No.: XT4L029 Strength: 150 mg	0.1 N HCl	68.4
		Water	88.5
		Acetate buffer (pH 4.5)	61.3
		Phosphate Buffer (pH 6.8)	52.1
	GSK's WELLBUTRIN® XL, 300 mg Lot No.: 4ZP1099	0.1 N HCl	60.1
		Water	38.2
		Acetate buffer (pH 4.5)	30.0
		Phosphate Buffer (pH 6.8)	40.8

Comments on Dissolution Testing:

1. The firm has conducted comparative dissolution testing using the following method specified in the approval letter for Wellbutrin XL® (NDA 21-515, 8/28/2003):
   Medium: 0.1 N HCl at 37°C ± 0.5°C
   Volume: 900 mL
   Apparatus: 1 (Basket)
   Rotational speed: 75 rpm
   Sampling time: 2, 4, 8 and 16 hours

2. In addition to the above dissolution testing, the firm has also conducted dissolution profile testing in each of the following media using USP apparatus 1 (basket) at 75 rpm and 900 mL.
   Water
   pH 4.5 buffer
   pH 6.8 buffer

3. The f2 value between the test 150 mg and RLD 150 mg is > 50. However, the f2 values between test 150 mg vs. test 300 mg are >50 in each of the additional 3 media, these values are <50 between the test 150 mg vs RLD 150 mg and the test 300 mg vs the reference 300 mg.

4. With regards to dissolution specifications for stability and quality control program, the Firm has proposed the following specifications:
   2 hours: [redacted]
   4 hours
   8 hours:
   16 hour

b(4)

However, based on the submitted dissolution results, the DBE recommends the following specifications:
   2 hours: [redacted]
   4 hours:
   8 hours:
   12 hours

b(4)

It is noted that the firm has committed to updating the drug product specifications to incorporate the drug release testing requirements as specified by the DBE when it is requested by DBE (response submitted on March 28, 2006 in response to Telephone CMC Amendment dated March 20, 2006).

Additional Comments on Dissolution Testing:

Due to concern of dose dumping for the drug product, the Agency currently requests that additional multi point dissolution testing be conducted on each strength of the test and reference products (12 units each) using the proposed method (i.e., 900 mL, 0.1 N HCl, Apparatus 1, 75 rpm) with and without alcohol as described below:

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

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

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

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

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

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

D. Consult Reviews: None

E. SAS Output

STUDY	DATA	SAS PROGRAM	SAS OUTPUT
Fasting Study 40431	BUPROP FAST CONC Data.txt BUPROP FAST PK Data.txt HYDROXYBU FAST CONC Data.txt HYDROXYBU FAST PK Data.txt	Bupropion Fast SAS Prog.txt HYDROXYBUPROP fast SASProg.txt	BUPROP FAST SAS OUTPUT.txt HYDROXYBU FAST SAS OUTPUT.txt
Fed Study 40432	BUPROP FED CONC Data.txt BUPROP FED PK Data.txt HYDROXYBU FED CONC Data.txt HYDROXYBU FED PK Data.txt	Bupropion FED SAS Prog.txt HYDROXYBUPROP FED SAS Prog.txt	BUPROP FED SAS OUTPUT.txt HYDROXYBU FED SAS OUTPUT.txt

F. Additional Attachments

None

CC: ANDA 77-715
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ Reviewer C. Chaurasia
HFD-650/ Project manager A. Sigler
HFD-650/ Team Leader M. Makary

V:\firmsnz\watson\ltrs&rev\77715N0505.doc

Endorsements: (Final with Dates)
HFD-650/C. Chaurasia CSC 7/5/06
HFD-650/M. Makary MHM 7/5/06
HFD-650/D.P. Conner BMD 7/5/06

BIOEQUIVALENCE -- DEFICIENCIES

Submission date(s): May 19, 2005, July 29, 2005, October 12, 2005 and March 28, 2006

1. Fasting Bioequivalent STUDY (STF)
Clinical: SFBC Anapharm Inc.
2050, Boul. Rene-Levesque Ouest
Sainte-Foy, Quebec GIV 2K8
Canada

Strengths: 150 mg
Outcome: AC

7/27/06

b(4)

2. Fed Bioequivalent STUDY (STP)
Clinical: SFBC Anapharm Inc.
2050, Boul. Rene-Levesque Ouest
Sainte-Foy, Quebec GIV 2K8
Canada

Strengths: 150 mg
Outcome: AC

b(4)

3. DISSOLUTION (Dissolution Data)

Strengths: 150 mg and 300 mg
Outcome: IC

Outcome Decisions: IC – Incomplete

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	77-715
Drug Product Name	Bupropion HCl Extended Release Tablet, USP
Strength	150 mg
Applicant Name	Watson Laboratories, Inc.
Submission Date(s)	May 19, 2005
First Generic	No
Reviewer	Devvrat Patel, Pharm.D.
File Location	V:\firmsnz\watson\ltrs&rev\77715D0505.doc
Clinical Site	SFBC Anapharm Inc. 2050 Boul. Rene-Levesque Ouest, Sainte-Foy, Quebec, Canada
Analytical Site	b(4)

EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

USP 28 lists three dissolution methods for bupropion extended release tablets. However, NDA 21-515 (Wellbutrin XL®) dissolution method is not listed in the USP 28. It is noted that there are three RLDs for bupropion extended release tablets (NDA 20-711, Zyban®; NDA 20-358, Wellbutrin SR®; NDA 21-515, Wellbutrin XL®) listed in the Orange Book.

The firm conducted dissolution testing using the NDA 21-515 method. The dissolution testing is incomplete because the firm did not submit dissolution data in three additional media. The firm should conduct additional dissolution testing in three other dissolution media (water, USP buffer media at pH 4.5, and 6.8) using USP Apparatus 1 (Basket) at 75 rpm.

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

RLD METHOD

There are three USP Dissolution tests:

TEST-1

Medium	**Water**
Volume	900 mL
Temperature	Not indicated
Apparatus	**II (Paddle)**
Rotational Speed	50 rpm
Specifications	1 hr: 25-45%, 4 hrs: 60-85%, 8 hrs: NLT 80%
Sampling Times	1, 4 and 8 hours
Detection	**UV absorbance at 298 nm wavelength**

TEST-2

Medium	**0.1 N HCl, pH 1.5**
Volume	900 mL
Temperature	Not indicated
Apparatus	**I (Basket)**
Rotational Speed	50 rpm
Specifications	1 hr: 25-50%, 2 hrs: 40-65%, 4 hrs: 65-90%, 6 Hrs.: NLT 80%
Sampling Times	1, 2, 4 and 6 hours
Detection	**HPLC**

TEST-3

Medium	**Water**
Volume	900 mL
Temperature	Not indicated
Apparatus	**II (Paddle)**
Rotational Speed	50 rpm
Specifications	1 hr: 30-55%, 2 hrs: 50-75%, 4 hrs: 70-90%, 6 hrs: NLT 80%
Sampling Times	1, 2, 4 and 6 hours
Detection	**UV absorbance at 250 nm wavelength**

Source of Method: USP 28

NDA Method (21-515, 7/3/2003)

Medium	**0.1 N HCl**
Volume	900 mL
Apparatus	**I (Basket)**
Rotational Speed	75 rpm
Specifications	2 hrs: NMT [redacted]%; 4 hrs: [redacted]%; 8 hrs: [redacted]%; 16 hrs: NLT [redacted]

b(4)

SAS Transport Files

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

Table 1. Summary of In Vitro Dissolution Data

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	360 min	480 min	600 min	720 min	
Diss. Study report # RD-P0523, p. 33 & 39	Test Bupropion Hydrochloride [Lot # XT4L029]	150 mg Tablet	Dissolution: Apparatus: USP Type I Speed of Rotation: 75 rpm Medium: 0.1N JC; Volume: 900 mL Temperature: 37°C ± 5°C	12	4 (1-14)	34 (28-43)	55 (50-63)	71 (67-77)	82 (79-87)	89 (87-92)	Vol. 1, Sect. VI, p. 41
					840 min	960 min	1080 min				
					93 (90-95)	94 (92-97)	95 (93-98)				
Diss. Study report # RD-P0523, p. 21 & 42	Reference Wellbutrin XL® [Lot # 04D014P]	150 mg Tablet		12	120 min	240 min	360 min	480 min	600 min	720 min	Vol. 1, Sect. VI, p. 41
					1 (0-2)	21 (11-27)	48 (39-55)	72 (62-80)	87 (83-91)	93 (89-95)	
					840 min	960 min	1080 min				
					95 (92-98)	97 (93-99)	98 (94-100)				

The firm proposes the following specifications:

2 hours: [redacted]
4 hours: [redacted]
8 hours: [redacted]
16 hours. [redacted]

COMMENTS:

1. The firm has provided the in-vivo study data summary, dissolution data and formulation data in the electronic format recommended by the DBE.

2. USP 28 lists three dissolution methods for bupropion extended release tablets. However, NDA 21-515 (Wellbutrin XL®) dissolution method is not listed in the USP 28. It is noted that there are three RLDs for bupropion extended release tablets (NDA 20-711, Zyban®; NDA 20-358, Wellbutrin SR®; NDA 21-515, Wellbutrin XL®) listed in the Orange Book.

3. The firm conducted dissolution testing using the method specified in the approval letter for Wellbutrin XL® (NDA 21-515, 8/28/2003).

DEFICIENCY COMMENTS:

In addition to the NDA method, the firm is advised to conduct dissolution testing in three other dissolution media (water, USP buffer media at pH 4.5, and 6.8) using USP Apparatus 1 (Basket) at 75 rpm. Sufficient sampling times are recommended to provide assurance against premature release of the drug (dose dumping) from the formulation.

RECOMMENDATIONS:

The firm should conduct additional dissolution testing in three other dissolution media (water, USP buffer media at pH 4.5, and 6.8) using USP Apparatus 1 (Basket) at 75 rpm. Sufficient sampling times are recommended to provide assurance against premature release of the drug (dose dumping) from the formulation.

Devvrat Patel 9/22/2005

Devvrat Patel, Pharm.D. Date
Division of Bioequivalence, Branch V
Office of Generic Drugs

Moheb H. Makary 9/22/05

Moheb H. Makary, Ph.D. Date
Acting Team Leader, Division of Bioequivalence, Branch V
Office of Generic Drugs

Dale P. Conner 9/29/05

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

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-715 APPLICANT: Watson Laboratories, Inc.

DRUG PRODUCT: Bupropion HCl Extended Release Tablet, USP 150 mg

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 deficiency has been identified:

Please conduct comparative dissolution testing using 12 units of each test and reference product in three other dissolution media (water, USP buffer media at pH 4.5, and 6.8) using USP Apparatus 1 (Basket) at 75 rpm. Sufficient sampling times are recommended to provide assurance against premature release of the drug (dose dumping) from the formulation.

We acknowledge that you have provided in-vivo study data, dissolution data, and formulation data in the electronic format recommended by the Division of Bioequivalence.

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

CC: 77-715
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ Patel
HFD-650/ Project Manager

Endorsements: (Final with Dates)
HFD-650/Patel 9/22/05
HFD-650/Makary 9/22/05
HFD-650/Thompson
HFD-650/D.P. Conner 9/29/05

BIOEQUIVALENCE - INCOMPLETE Submission date: May 19, 2005

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

1. DISSOLUTION (Dissolution Data) Strength: 150 mg
Outcome: IC

Outcome Decisions: IC – Incomplete
WinBio Comments: IC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-715

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Paragraph IV Patent Certification

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

In accordance with Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355), 21 CFR § 314.94(a)(12) and based on the patent data listed in the Electronic Orange Book "Approved Drug Products with Therapeutic Equivalence Evaluations" current through July 26, 2005, Watson Laboratories Inc. certifies that, in its opinion and to the best of its knowledge, the following mentioned patents are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of Bupropion Hydrochloride Extended-Release Tablets, USP (150 mg and 300 mg), for which this application is submitted:

U.S. PATENT #	EXPIRATION DATE	STRENGTH COVERED BY PATENTS
6,096,341	October 30, 2018	150 mg and 300 mg
6,143,327	October 30, 2018	

In accordance with 21 CFR § 314.95(a) and Section 505(j)(2)(B)(i), Watson Laboratories, Inc. further states that, upon receipt of acknowledgment from the FDA concerning acceptance for review of this submission, appropriate notice regarding this Paragraph IV certification, as required under 21 CFR § 314.95(c) and Sections 505(j)(2)(B)(ii)-(iv), will be provided to:

(I) each owner of the patent which is the subject of the certification or the representative designated by the owner to receive such notice, and

(II) the holder of the approved application under section 505(b) of the Act for the listed drug that is claimed by the patent or the representative of such holder designated to receive such notice; for which the applicant is seeking approval.

At such time, this application will be amended to certify that such notice requirements have been met as required under 21 CFR § 314.95(b).

Christine M. Woods
Associate Director, Regulatory Affairs
Watson Laboratories, Inc.

26 July 2005
Date

Paragraph IV Patent Certification

Bupropion Hydrochloride Extended-Release Tablets, USP
150 mg

In accordance with Section 505 (j) (2) (A) (vii) (IV) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355), 21 CFR § 314.94 (a) (12) and based on the patent data listed in the Electronic Orange Book "Approved Drug Products with Therapeutic Equivalence Evaluations" current through March 2005, Watson Laboratories Inc. certifies that, in its opinion and to the best of its knowledge, the following mentioned patents are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of Bupropion Hydrochloride Extended-Release Tablets, USP (150 mg), for which this application is submitted:

U.S. PATENT #	EXPIRATION DATE	STRENGTH COVERED BY PATENTS
6,096,341	October 30, 2018	150 mg
6,143,327	October 30, 2018	

In accordance with 21 CFR § 314.95 (a) and Section 505 (j) (2) (B) (i), Watson Laboratories, Inc. further states that, upon receipt of acknowledgment from the FDA concerning acceptance for review of this submission, appropriate notice regarding this Paragraph IV certification, as required under 21 CFR § 314.95 (c) and Sections 505 (j) (2) (B) (ii)-(iv), will be provided to:

(I) each owner of the patent which is the subject of the certification or the representative designated by the owner to receive such notice, and

(II) the holder of the approved application under section 505 (b) of the Act for the listed drug that is claimed by the patent or the representative of such holder designated to receive such notice; for which the applicant is seeking approval.

At such time, this application will be amended to certify that such notice requirements have been met as required under 21 CFR § 314.95 (b).

Christine M. Woods
Associate Director, Regulatory Affairs
Watson Laboratories, Inc.

19MAY2005
Date

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

Exclusivity Statement

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

Watson Laboratories, Inc. acknowledges the following exclusivity:

- Exclusivity for Prevention of Seasonal Major Depressive Episodes in Patients with Seasonal Affective Disorder (I-497), for Wellbutrin XL®, Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg, set to expire on June 12, 2009.

Information related to the above-listed exclusivity (I-497) will not be included in any Watson labeling until such exclusivity has expired.

Janie M. Gwinn
Director, Regulatory Affairs
Watson Laboratories, Inc.

8/9/06
Date

Exclusivity Statement

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

Watson Laboratories, Inc. acknowledges that, in its opinion and the best of its knowledge, there are no unexpired exclusivities applicable to Wellbutrin XL®, Bupropion Hydrochloride Extended-Release Tablets, 150 mg and 300 mg, manufactured for GlaxoSmithKline.

Christine M. Woods
Associate Director, Regulatory Affairs
Watson Laboratories, Inc.

26 July 2005
Date

Exclusivity Statement

Bupropion Hydrochloride Extended-Release Tablets, USP
150 mg

Watson Laboratories, Inc. acknowledges that, in its opinion and the best of its knowledge, there are no unexpired exclusivities applicable to Wellbutrin XL®, Bupropion Hydrochloride Extended-Release Tablets, 150 mg, manufactured for GlaxoSmithKline.

Christine M. Woods
Associate Director, Regulatory Affairs
Watson Laboratories, Inc.

9 MAY 2005
Date

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-715 Applicant Watson Laboratories, Inc.
Drug Bupropion Hydrochloride Extended-release Tablets Strength(s) 150 mg and 300 mg (once daily)

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

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. **Martin Shimer** Chief, Reg. Support Branch	Date 6/11/07 Initials IM	Date 6/13/07 Initials rlw/for

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
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 ☐
Is applicant eligible for 180 day NO
Generic Drugs Exclusivity for each strength: Yes ☒ No ☐
Date of latest Labeling Review/Approval Summary 5/21/07
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: PIV

Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = _____ NDA# 21-515
Date Checked 6/13/07
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐
Date settled: 2/26/07

Comments: Original application submitted 5/20/05 for 150 mg strength with PIV certs to '341 and '327 patents. 300 mg amendment added 7/28/05 with PIV certs to same patents. PIV notices sent 7/21/05 and 7/28/05 to appropriate parties. Litigation filed 9/6/05 against '341 and '327 patents. Litigation dismissed with prejudice on '341 and '327 patents 2/26/07. Watson is eligible for Full Approval 6/12/07 on the 300 mg strength only as 180 day exclusivity for Impax product ends. Anchen still holds 180 exclusivity on the 150 mg strength and has not yet gone to market, so Watson is eligible for Tentative Approval on the 150 mg strength.

2. Project Manager, Thomas Hinchliffe Team 10 Review Support Branch	Date 6/4/07 Initials TOH	Date 6/11/07 Initials stoh

Original Rec'd date May 20, 2005
Date Acceptable for Filing May 20, 2005
Patent Certification (type) IV
Date Patent/Exclus.expires Oct 30, 2018

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 ☐
Previously reviewed and tentatively approved ☒ Date JANUARY 31, 2007
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments: _____

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 4/18/2007
Date of Office Bio Review 12/6/2006
Date of Labeling Approv. Sum 5/21/07 -150mg
6/4/07 -300 mg
Labeling Acceptable Email Rec'd Yes ☐ No ☐
Labeling Acceptable Email filed Yes ☐ No ☐
Date of Sterility Assur. App. NA
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 ☐

From: Shimer, Martin
Sent: Wednesday, May 16, 2007 12:01 PM
To: Hinchliffe, Thomas; West, Robert L
Subject: RE: Wellbutrin XL

I just spoke with Margaret Choy. Anchen has not yet launched their 150 mg product. Therefore, all subsequent applicants will only be eligible for TA.

Marty

From: Hinchliffe, Thomas

Sent: Wednesday, May 16, 2007 8:53 AM
To: Shimer, Martin; West, Robert L
Subject: RE: Wellbutrin XL

Oh Yes...
Margaret Choy : 949-639-8127

Thomas Hinchliffe, PharmD
LCDR, U.S. Public Health Service
Project Manager
Office of Generic Drugs
Food and Drug Administration
HFD-617, Rm E230, MPN2
301-827-5771

From: Shimer, Martin
Sent: Wednesday, May 16, 2007 8:48 AM
To: West, Robert L; Hinchliffe, Thomas
Subject: RE: Wellbutrin XL

Tom,

Since Anchen was approved for both the 150 mg and 300 mg strengths it is possible that they began to market both products triggering their exclusivity for the 150 mg as well. Do you have contact information for someone at Anchen? I'll call them and verify whether they ever began to market their 150 mg product.

Marty

From: West, Robert L
Sent: Wednesday, May 16, 2007 7:00 AM
To: Hinchliffe, Thomas; Shimer, Martin
Subject: RE: Wellbutrin XL

I think it is only the 300 mg strength. The 150 mg strength should remain tentatively approved.

Bob

From: Hinchliffe, Thomas
Sent: Tuesday, May 15, 2007 1:57 PM
To: Shimer, Martin
Cc: West, Robert L
Subject: Wellbutrin XL

Hey Marty,

On June 18, 2007 a 180 day exclusivity expires which anchen is holding for the bupropion xl generic. I've received some requests for final approval. So I know when preparing these AP packages is it both strengths that are eligible for full approval after the 180 days expires or just the 300 mg. One firm made mention about only the 300 mg. Let me know

Thanks,
tom

Thomas Hinchliffe, PharmD
LCDR, U.S. Public Health Service
Project Manager
Office of Generic Drugs
Food and Drug Administration
HFD-617, Rm E230, MPN2
301-827-5771

3. Labeling Endorsement

Reviewer: Labeling Team Leader:

Date6/4/07 Date6/4/07

Name/InitialsLG Name/InitialsLG

Comments:

From: Golson, Lillie D
Sent: Monday, June 04, 2007 2:20 PM
To: Hinchliffe, Thomas; Golson, Lillie D
Subject: FW: 77-715, Needs your AP/TA Endorsement

From a labeling standpoint, labeling is acceptable for the 300 mg product. Please endorse on behalf of Michelle and me.

Thanks

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 6/13/07
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initialsrlw/for
Comments: Form template utilized.

5. Div. Dir./Deputy Dir. Date6/12/07
Chemistry Div. II Initials FF

Comments:TA 1/31/07
Curent letter for AP of 300 mg and TA for 150 mg
Dose dumping studies ok
Minor CMC changes ok for AP

6. Frank Holcombe **First Generics Only** Date6/13/07
Assoc. Dir. For Chemistry Initialsrlw/for
Comments: (First generic drug review)
N/A. Anchen's ANDA 77-284 for this drug product (150 mg and 300 mg) was approved on 12/14/06. IMPAX's ANDA 77-415 for this drug product (300 mg strength only) was approved on 12/15/06.

7. Vacant Date_____
Deputy Dir., DLPS Initials_____
RLD = Wellbutrin XL Tablets 150 mg and 300 mg (Once-A-Day)
GlaxoSmithKline NDA 21-515 (001, 002)

8. Peter Rickman Date6/13/07
Director, DLPS Initialsrlw/for
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments:This ANDA was tentatively approved on January 31, 2007. Refer to the administrative sign-off form completed at that time. Final approval was blocked at that time by ongoing patent litigation on both the '341 and '327 patents as well as by Anchen/IMPAX's eligibility for 180-day generic exclusivity for both strengths.

On March 15, 2007, Watson submitted a minor amendment to request final approval for their 300 mg tablet strength based upon the dismissal on February 26, 2007, of the patent infringement lawsuit (copy of court's dismissal order provided). Watson requested that final approval for their 300 mg tablet strength be granted upon the expiration of Anchen's/IMPAX's 180-day exclusivity for the 300 mg tablet strength on June 18, 2007. Note: The agency has concluded that Anchen's/IMPAX's exclusivity for the 300 mg tablet strength expired on 6/12/07. The agency is not aware that Anchen/IMPAX have triggered their exclusivity for the 150 mg tablet strength.

FPL found acceptable for final approval (300 mg strength) 6/4/07 (in DFS). GSK's I-497 exclusivity has been "carved-out" of the package insert labeling. This is

acceptable.

CMC found acceptable for approval of the 300 mg tablet atrength (and continued tentative approval of Watson's 150 mg tablet strength) - Chemistry Review #3 dated 4/24/07. Methods validation was not requested.

OR

8. Robert L. West — Date 6/13/07
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 4/18/07 (Verified 6/13/07). No "OAI" Alerts noted.

Refer to explanation provided by M.Shimer for regulatory basis for approval of Watson's 300 mg tablet strength and the continued tentatative approval of Watson's 150 mg tablet strength.

Ethanol/dose-dumping "pre-mature release" in vitro data submitted prior to tentative approval.

Recommendation: Approve Watson's 300 mg tablet strength;
Tentative Approval (continued) for Watson's 150 mg tablet strength.

9. Gary Buehler — Date 6/13/07
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 — Date_____
Review Support Branch — Initials _____
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
6/13/07Time notified of approval by phone 6/13/07Time approval letter faxed

FDA Notification:
6/13/07Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
6/13/07Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

EES Data for: 077715

*** Compliance Recommendations ***

App No	Doc Seq No	Date	OC Recommendation
077715	000	4/18/2007	ACCEPTABLE
077715	000	8/5/2005	ACCEPTABLE

*** EER Table ***

CFN	Name	Profile Code	Last Milestone Name	Last Milestone Date	Last Status	Last Status Date	OAI Alert
[redacted]		CTL	OC RECOMMENDATION	4/18/2007	AC	4/18/2007	
1318933	WATSON LABORATORIES INC	TCM	OC RECOMMENDATION	8/5/2005	AC	8/5/2005	
[redacted]		CSN	OC RECOMMENDATION	7/19/2005	AC	7/19/2005	
		CTL	OC RECOMMENDATION	7/19/2005	AC	7/19/2005	

b(4)

COMIS TABLE:

Comis Application Table Data for Application No: 077715  ***COMIS Application Table Search***  ***COMIS Assignment Data***

Drug Name: BUPROPION HYDROCHLORIDE

Potency: 150 MG AND 300 MG NS Dosage Form: EXT APPL Type: N

Applicant: WATSON LABS

Status Code: PN 600 Status Date: 3/16/2007 Clock Date: 5/20/2005 USP: Y Org:

Therapeutic Drug Class: ANTIDEPRESSANTS

Patent Certification: 4 Patent Expiration Date: PEPFAR:

Incom Doc Type	Seq No	Supp Mod Type	Letter Date	Stamp Date	Decision Code	Decision_Date	Status code	Status Date	Priority Flag	Document ID-Click to see Assignment	Priority Date
N Volume Locator	000		5/19/2005	5/20/2005	NA	11/3/2005	PN	3/16/2007	-1	2707877	3/16/2007
N Volume Locator	000	MC	7/15/2005	7/18/2005	CL	7/18/2005				2729969	
N Volume Locator	000	AC	7/27/2005	7/28/2005	TA	1/31/2007				2735213	
N Volume Locator	000	AF	7/28/2005	7/29/2005	TA	1/31/2007				2735257	
N Volume Locator	000	MC	9/27/2005	9/28/2005	CL	9/28/2005				2757355	
N Volume Locator	000	AB	10/12/2005	10/13/2005	OP	10/13/2005				2762523	

N ➧ *Volume Locator*	000	AC	12/6/2005	12/7/2005	TA	1/31/2007				2781479		
N ➧ *Volume Locator*	000	XP	3/23/2006	3/24/2006	CL	3/24/2006				2916034		
N ➧ *Volume Locator*	000	AC	3/28/2006	3/29/2006	TA	1/31/2007				2917888		
N ➧ *Volume Locator*	000	AX	4/28/2006	4/28/2006	GR	4/28/2006				2929985		
N ➧ *Volume Locator*	000	AF	8/11/2006	8/14/2006	TA	1/31/2007				2977187		
N ➧ *Volume Locator*	000	AB	9/15/2006	9/18/2006	OP	9/18/2006				2991346		
N ➧ *Volume Locator*	000	AF	10/11/2006	10/12/2006	TA	1/31/2007				3001405		
N ➧ *Volume Locator*	000	AF	11/13/2006	11/14/2006	TA	1/31/2007				3016459		
N ➧ *Volume Locator*	000	AC	1/19/2007	1/22/2007	TA	1/31/2007				3045754		
N ➧ *Volume Locator*	000	AM	1/26/2007	1/29/2007	TA	1/31/2007				3048709		
N ➧ *Volume Locator*	000	AM	3/15/2007	3/16/2007	OP	3/16/2007				3070798		
N ➧ *Volume Locator*	000	AF	5/21/2007	5/22/2007	OP	5/22/2007				3103045	***Comis Document Table Data***	

ORANGE BOOK PRINT OFF:

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
021515	002	6096341	OCT 30,2018			
021515	002	6143327	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 submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. 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
4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.
5. U.S. Patent Nos. RE 36481 and RE 36520 were relisted for Zocor (NDA 19-766) pursuant to the decision and related order in Ranbaxy Labs. v.Leavitt, No. 05-1838 (D.D.C. April 30, 2006). The '481 and '520 patents remained listed in Approved Drug Products with Therapeutic Equivalence Evaluations until any applicable periods of exclusivity pursuant to section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act were triggered and run. For additional information on this matter, please refer to Docket Nos. 2005P-0008 and 2005P-0046. Patents were subsequently delisted in the December 2006 Orange Book update as the exclusivity periods have triggered and run to expiration.

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 May, 2007
Patent and Generic Drug Product Data Last Updated: June 12, 2007

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
6/13/2007 11:16:32 AM

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

May 21, 2007

ORIG AMENDMENT
N/AF

Gary Buehler, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Labeling Amendment

RE: Abbreviated New Drug Application #77-715
Bupropion Hydrochloride Extended-Release Tablets (XL)
150 mg & 300 mg (Once Daily)

**** ELECTRONIC FINAL PRINTED LABELING INCLUDED****

Dear Mr. Buehler:

Watson Laboratories, Inc. (Watson) is submitting this Labeling Amendment in reference to the e-mail from OGD titled, "New Warnings for Antidepressant Medications," dated May 3, 2007 (attached) in which Watson was requested to submit revisions to the product labeling and Medication Guide for Bupropion Hydrochloride Extended-Release Tablets (XL), ANDA #77-715, within 30 days from the date of the e-mail.

FDA's comment appears in bold and italic font below with Watson's response immediately following the comment.

...Therefore, we are requesting revisions to your labeling and the antidepressant medication guides to incorporate the committee's recommendations. Specifically, we are requesting the changes found in the link below for the product labeling and the Medication Guide,

http://www.fda.gov/cder/drug/antidepressants/default.htm

These labeling revisions should be submitted in the form of a "Supplement - Changes Being Effected" within 30 days from the date of this email. Please submit the insert labeling in FPL electronically.

- ***You are reminded that final printed labels submitted in electronic format must be actual size, color and clarity.***
- ***The FPL submitted in pdf should be text-based (not image based).***
- ***To assist in our review, we request that labeling also be submitted in MS Word format.***

- ***Please provide a side-by-side comparison of your proposed labeling with your previously approved labeling with all differences annotated and explained.***

Please submit the stand-alone Medication Guide that will be dispensed to the patients for our review.

Ensure the Medication Guide is formatted according to 21 CFR 208.20.

Watson has revised its labeling as requested. Additionally, as discussed between Ernest Lengle, Ph.D. of Watson and Peter Rickman of OGD on 21 May 2007, Watson removed the reference to the 150 mg strength. In accordance with 21 CFR §314.94(d)(ii) as effected June 8, 2004, which required the submission of electronic labeling, Watson provides one (1) computer CD ROM containing Watson's proposed labeling in MS Word, Adobe PDF and XML formats. The CD ROM is located at the front of the blue Archival Copy of this submission. Please refer to the Table of Contents contained on the enclosed CD ROM for access to the files and directory pathways. Watson's Medication Guide is formatted according to 21 CFR § 208.20; 12 hard copies of the revised Final Printed Medication Guide are provided in **EXHIBIT 1**.

As required by 21 CFR §314.94(a)(8)(iv), Watson has included the side-by-side comparison of its proposed final printed Package Insert, and Medication Guide with the previously submitted versions of Watson's labeling (Package Insert and Medication Guide dated September 2006), with all differences annotated and explained.

Watson encloses one volume each of one (1) Archival and one (1) Review Copy. An MS Word file of this cover letter is provided on the CD ROM for the reviewer's convenience.

Finally, it is Watson's view that this Labeling Amendment adequately addresses the cited request. Please contact me by telephone at 951-493-5452 or via facsimile at 951-493-4581 if you have any questions.

Sincerely,

Christine M. Woods
Associate Director
R&D Regulatory Affairs

"Dillahunt, Michelle"
<michelle.dillahunt@fda.hhs.gov>
05/03/2007 12:33 PM

To "Dillahunt, Michelle" <michelle.dillahunt@fda.hhs.gov>
cc "Dillahunt, Michelle" <michelle.dillahunt@fda.hhs.gov>
Subject New Warnings for Antidepressant Medications

Dear: ANDA Applicant:

Please refer to your abbreviated new drug applications submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for your antidepressant drug product.

We additionally refer to the December 13, 2006 meeting of the Psychopharmacologic Drugs Advisory Committee to discuss FDA's meta-analysis of suicidality data derived from placebo-controlled trials of antidepressants in adult patients with major depressive disorder and other psychiatric disorders.

Based upon the recommendations made by the committee, additional changes are needed in antidepressant labeling and medication guides to alert practitioners, patients, family members and caregivers about an increased risk of suicidal thinking and behavior (suicidality) in young adults with major depressive disorder (MDD) and other psychiatric disorders who are taking antidepressant medications. Changes are also needed to inform practitioners about an apparent favorable effect of antidepressants on suicidality in older adults and to remind them that the disorders being treated with antidepressants are themselves associated with an increased risk of suicidality.

Therefore, we are requesting revisions to your labeling and the antidepressant medication guides to incorporate the committee's recommendations. Specifically, we are requesting the changes found in the link below for the product labeling and the Medication Guide,

http://www.fda.gov/cder/drug/antidepressants/default.htm

Simultaneous with this supplement request, FDA has issued a Press Release as well as updated our Internet site with the revised Medication Guides to alert the community to this action. Since there are so many MDD products, we feel that

these actions are a better way to alert the community than individual Dear Health Care Professional (DHCP) letters for each of these products. Thus, we are not requesting individual DHCP letters.

These labeling revisions should be submitted in the form of a "Supplement - Changes Being Effected" within

30 days from the date of this email. Please submit the insert labeling in FPL electronically.

- You are reminded that final printed labels submitted in electronic format must be actual size, color and clarity.
- The FPL submitted in pdf should be text-based (not image based).
- To assist in our review, we request that labeling also be submitted in MS Word format.
- Please provide a side-by-side comparison of your proposed labeling with your previously approved labeling with all differences annotated and explained.

Please submit the stand-alone Medication Guide that will be dispensed to the patients for our review.

Ensure the Medication Guide is formatted according to 21 CFR 208.20.

Sincerely,
Michelle Dillahunt, PharmD

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

ARCHIVAL COPY

ORIG AMENDMENT

N/A

March 15, 2007

Gary Buehler, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Minor Amendment
Final Approval Requested

RE: ANDA #77-715
Bupropion Hydrochloride Extended-Release Tablets (XL)
150 mg and 300 mg (Once Daily)

RECEIVED
MAR 16 2007
OGD-OTER

Dear Mr. Buehler:

Watson Laboratories, Inc. "Watson" is submitting this *Minor Amendment, Final Approval Requested* in reference to the letter from OGD, dated January 31, 2007 granting Watson Tentative Approval for the above product (ANDA #77-715).

Watson's ANDA contains paragraph IV certifications to each of the U.S. Patent Nos. 6,096,341 (the '341 patent) and 6,143,327 (the '327 patent) under section 505 (j) (2) (A) (vii) (IV) of the Act stating that the patents are invalid, unenforceable, or will not be infringed by Watson's manufacture, use, or sale of Bupropion Hydrochloride Extended-Release Tablets, 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 Watson Laboratories, Inc. for infringement of one or more of these patents that were the subject of the paragraph IV certifications. This action was brought against Watson prior to the expiration of 45 days from the date the notice Watson provided under section 505 (j) (2) (B) (i) was received by the NDA/patent holders. Watson notified the agency that Watson had complied with the requirements of section 505 (j) (2) (B) of the Act, and litigation for infringement of the '341 and '327 patents was brought against Watson in the United States District Court for the Southern District of New York Biovail Laboratories International SRL v. Watson Laboratories, Inc., Civil Action No. 05CV7991.

In the Tentative Approval it was stated "Therefore, final approval cannot be granted until:

1. a. The expiration of the 30-month period provided for in section 505 (j)(5)(B)(iii), currently February 2, 2008,

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

c. the listed patents has expired, and

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

On February 26, 2007 the lawsuit filed by Biovail Laboratories International, SRL against Watson Laboratories, Inc. and all subsequent counter suits was dismissed by the U.S. District Court for the Southern District of New York. A copy of the Dismissal Order is provided in **EXHIBIT 1**.

Based on the dismissal of the lawsuit and in accordance to 21 U.S.C. 355(j)(5)(B)(ii) of the Act, Watson believes that our drug product, Bupropion Hydrochloride Extended-Release Tablets (XL), 300 mg (Once Daily) will be eligible for Final Approval as of June 18, 2007 (the date Anchen Pharmaceuticals 180-Day Exclusivity is scheduled to expire).

With this amendment Watson is requesting a change in ANDA status from Tentative Approval to Final Approval for Bupropion Hydrochloride Extended-Release Tablets (XL), 300 mg (Daily).

Watson certifies that except for *minor changes* noted below, there has been no change in the CMC section since Tentative Approval was granted to this application.

1. Watson wants to clarify and update previously submitted information. In the original application, Watson provided contract testing laboratory information for [redacted] located in [redacted]. However, the actual testing done by [redacted] was performed at their [redacted] facility. In addition, since the time the application was filed, [redacted] located in [redacted] has changed its name to [redacted] b(4)

   Provided below is the full address and contact information for [redacted] formerly [redacted] Provided in **EXHIBIT 2** are [redacted] cGMP Statement, Debarment Certification, FDA Establishment Inspection information and a press release from their website regarding the name change.

[redacted] b(4)

[redacted]

2. Watson hereby withdraws Watson's test method, RNOT-00013-00, Test Method for Hydroxypropyl Cellulose, NF ([redacted] , filed in the Addition of 300 mg Product Strength Major Amendment submitted July 27, 2005, on pages 159-170. The test method RNOT-00013-00 has not been and will not be used to test Hydroxypropyl Cellulose, NF. Testing for the Inactive Ingredient, Hydroxypropyl Cellulose, NF, for submission batches was conducted by [redacted] using USP/NF tests and specifications (Certificate of Analysis from [redacted] is on pages 110-112 of the Original Application submitted May 19, 2005 and is provided for the ease of the reviewer in **EXHIBIT 3**). Because [redacted] will be used for testing of future lots of Hydroxypropyl Cellulose, NF used in the manufacture of commercial batches, withdrawal of test method RNOT-00013-00 will have no impact. Watson commits to maintain current test procedures and specifications for all ingredients used in the manufacture of the drug product to the most current official USP/NF monographs, whenever applicable.

b(4)

Watson acknowledges its commitment in the Telephone Amendment dated January 19, 2007 to submit revised Master Batch Records with target ranges for upper limits for each functional coating of the 300 mg strength product in a Post Approval Supplement.

We have enclosed one (1) Archival and one (1) Review Copy. In accordance with 21 CFR §314.96(b), one (1) Field Copy of the Amendment will be forwarded to the manufacturing facility's District Office, in Jamaica, NY. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the Archival and Review Copies of this Amendment.

Watson trusts this information submitted is sufficient for this amendment to be evaluated and our application approved. If I can assist with the review of this amendment, please contact me by telephone at (951) 493-5446, or by facsimile at (951) 493-4581.

Sincerely,

Ernest Lengle, Ph.D.

Ernest Lengle, Ph.D
Executive Director
Regulatory Affairs

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-715 Applicant Watson Laboratories, Inc.
Drug Bupropion Hydrochloride Extended Release Tablets, USP Strength(s) 150 mg and 300 mg

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

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. Martin Shimer Chief, Reg. Support Branch	Date 28 Apr 2006 Initials MS	Date _____ Initials _____

Contains GDEA certification: Yes ☑ No ☐ **Determ. of Involvement?** Yes ☐ No ☐
(required if sub after 6/1/92)
Pediatric Exclusivity System
RLD = **NDA#** _____
Patent/Exclusivity Certification: Yes ☑ No ☐ **Date Checked** _____
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☑ No ☐ **Nothing Submitted** ☐
Was applicant sued w/in 45 days: Yes ☑ No ☐ **Written request issued** ☐
Has case been settled: Yes ☐ No ☑ **Date settled:** **Study Submitted** ☐
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☑
Date of latest Labeling Review/Approval Summary pending
Any filing status changes requiring addition Labeling Review Yes ☐ No ☑
Type of Letter: OPE to 3418 & 327 → sued on both patents w/in 45 DAYS
Comments: CA# 05 CV 7799 filed in Southern District of NY on 9/6/05 30 month = 2/2/08

Eligible for 180 day

2. Project Manager, Thomas Hinchliffe Team 10 — Date 4/2/06 — Date _____
Review Support Branch — Initials TOH — Initials _____

Original Rec'd date May 20, 2005
Date Acceptable for Filing May 20, 2005
Patent Certification (type) IV
Date Patent/Exclus.expires Oct 30, 2018
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
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 8/5/2005
Date of Office Bio Review 12/6/2006
Date of Labeling Approv. Sum 12/6/2006
Labeling Acceptable Email Rec'd Yes ☐ No ☒
Labeling Acceptable Email filed Yes ☐ No ☒
Date of Sterility Assur. App. NA
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 ☒

3. Labeling Endorsement

Reviewer:	Labeling Team Leader:
Date 12/13/2006	Date 12/13/2006
Name/Initials Charlie Hoppes/CVH	Name/Initials Lillie Golson/lg

Comments:
AP summary drafted 12/6//2006 remains acceptable…no new labeling approvals for the RLD.

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 12/13/06
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials DTR
Comments: changes saved to v drive

5. Div. Dir./Deputy Dir. Date 1/29/07
Chemistry Div. II Initials FF

Comments: Composition statement has been revised to delineate correctly both the ER and DR coating levels. (Amendments dated 1/19 and 1/26/07)
CMC ok

6. Frank Holcombe **First Generics Only** Date 1/31/07
Assoc. Dir. For Chemistry Initials rlw/for
Comments: (First generic drug review)
N/A. Anchen's ANDA 77-284 for this drug product (150 mg and 300 mg) was approved on 12/14/06. IMPAX's ANDA 77-415 for this drug product (300 mg) was approved on 12/15/06.

7. Vacant Date 1/31/07
Deputy Dir., DLPS Initials rlw/for
RLD = Wellbutrin XL Tablets 150 mg and 300 mg (Once-a-Day)
GlaxoSmithKline NDA 21-515 (001, 002).

8. Peter Rickman Date 1/31/07
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 7/5/06. Dissolution studies on both strengths found acceptable upon submission and review of additional dissolution studies related to dose-dumping in alcoholic media. Waiver granted to the 300 mg tablet strength under 21 CFR 320.22(d)(2). Bio study sites have acceptable DSI inspection histories. Review entered into DFS 12/6/06 B.Davit, Ph.D.

Labeling found acceptable for approval 12/6/06.

CMC found acceptable (Chemistry Review #2) 12/13/06. Methods validation was not requested.

OR

8. Robert L. West Date 1/31/07
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 8/5/05 (Verified 1/31/07). No "OAI" Alerts noted.

When this ANDA was submitted on May 19, 2005, it only provided for the 150 mg strength tablet. The 300 mg tablet strength was added via amendment dated July 27, 2005.

Watson made paragraph IV certifications to the '341 & '327 patents and was sued on both patents within the 45-day period. Litigfation is ongoing. The 30-month period expires on 2/2/08.

There was a Citizen Petition pending before the agency on this drug product. The petition was answered at the time of approval of Anchen's ANDA.

This ANDa is recommended for Tentative Approval.

9. Gary Buehler Date 1/31/07
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 Date 1/31/07

Review Support Branch Initials TOH

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:

10:30Time notified of approval by phone 10:30Time approval letter faxed

FDA Notification:

1/31/07Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

1/31/07Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

APPEARS THIS WAY
ON ORIGINAL

7/7/15
LOA ESD

Bupropion HCL ER Tablets

128 APP 06

Drug strength: 150 mg
RLD: Wellbutrin XL 21-515
patent certs: PIV ⟶ '341
PIV ⟶ '327
NO unexpired exclusivities

ANDA for filing ☆ PIV 5/20/05 (L.O dated 7/20/05)

7/08/05 stamp

Submission of 300 mg strength
RLD: Wellbutrin XL 21-515
patent certs: PIV ⟶ '341
PIV ⟶ '327

XP 3/28/06

2/24/06 stamp

~~notice sent to Biovail (NY,NY) on 7/21/2005 (150 mg)~~
notice sent to Biovail (Strauchwitz Barbarelo) on 7/21/05 (150 mg)
notice sent to Biovail (Strauchwitz Barbarelo) on 7/28/05 (300 mg)
~~Notice sent to~~
notice sent to SmithKline Beecham (NC) on 7/21/05 (150 mg)
RR from SKB (NC) signed & dated 7/25/2005 (150 mg)
RR from BLRB (NC) signed & dated 8/2/2005 (300 mg)

notice confirmed ☆ MMA

CA# 05 CV 7799 filed in Southern District of NY on 9/6/05 for infringement of both '341 & '327

30 months = 2/2/2008

EER DATA:

EES Data for: 077715

*** Compliance Recommendations ***

App No	Doc Seq No	Date	OC Recommendation
077715	000	8/5/2005	ACCEPTABLE

*** EER Table ***

CFN	Name	Profile Code	Last Milestone Name	Last Milestone Date	Last Status	Last Status Date	OAI Alert
1318933	WATSON LABORATORIES INC	TCM	OC RECOMMENDATION	8/5/2005	AC	8/5/2005	
[redacted]		CSN	OC RECOMMENDATION	7/19/2005	AC	7/19/2005	
		CTL	OC RECOMMENDATION	7/19/2005	AC	7/19/2005	

b(4)

COMIS TABLE:

Comis Application Table Data for Application No: 077715 → *COMIS Application Table Search* → *COMIS Assignment Data*

Drug Name: BUPROPION HYDROCHLORIDE

Potency: 150 MG AND 300 MG NS Dosage Form: EXT **APPL Type:** N

Applicant: WATSON LABS

Status Code: PN **Status Date:** 1/22/2007 **Clock Date:** 5/20/2005 **USP:** Y **Org:** 600

Therapeutic Drug Class: ANTIDEPRESSANTS

Patent Certification: 4 **Patent Expiration Date:** **PEPFAR:**

[illegible]	Seq No	[illegible]	Letter Date	Stamp Date	[illegible]	Decision_Date	[illegible]	Status Date	Priority Flag	Document ID-Click to see Assignment	Priority Date
N → Volume Locator	000		5/19/2005	5/20/2005	NA	11/3/2005	PN	1/22/2007	-1	2707877	12/7/2005
N → Volume Locator	000	MC	7/15/2005	7/18/2005	CL	7/18/2005				2729969	
N → Volume Locator	000	AC	7/27/2005	7/28/2005	OP	7/28/2005				2735213	
N → Volume Locator	000	AF	7/28/2005	7/29/2005	OP	7/29/2005				2735257	
N → Volume Locator	000	MC	9/27/2005	9/28/2005	CL	9/28/2005				2757355	
N → Volume	000	AB	10/12/2005	10/13/2005	OP	10/13/2005				2762523	

Locator											
N ➧ ***Volume Locator***	000	AC	**12/6/2005**	**12/7/2005**	**OP**	**12/7/2005**				2781479	
N ➧ ***Volume Locator***	000	XP	**3/23/2006**	**3/24/2006**	**CL**	**3/24/2006**				2916034	
N ➧ ***Volume Locator***	000	AC	**3/28/2006**	**3/29/2006**	**OP**	**3/29/2006**				2917888	
N ➧ ***Volume Locator***	000	AX	**4/28/2006**	**4/28/2006**	**GR**	**4/28/2006**				2929985	
N ➧ ***Volume Locator***	000	AF	**8/11/2006**	**8/14/2006**	**OP**	**8/14/2006**				2977187	
N ➧ ***Volume Locator***	000	AB	**9/15/2006**	**9/18/2006**	**OP**	**9/18/2006**				2991346	
N ➧ ***Volume Locator***	000	AF	**10/11/2006**	**10/12/2006**	**OP**	**10/12/2006**				3001405	
N ➧ ***Volume Locator***	000	AF	**11/13/2006**	**11/14/2006**	**OP**	**11/14/2006**				3016459	
N ➧ ***Volume Locator***	000	AC	**1/19/2007**	**1/22/2007**	**OP**	**1/22/2007**				3045754	***Comis Document Table Data***

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
021515	001	6096341	OCT 30,2018			
021515	001	6143327	OCT 30,2018			

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 submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
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4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.
5. U.S. Patent Nos. RE 36481 and RE 36520 were relisted for Zocor (NDA 19-766) pursuant to the decision and related order in Ranbaxy Labs. v.Leavitt, No. 05-1838 (D.D.C. April 30, 2006). The '481 and '520 patents remained listed in Approved Drug Products with Therapeutic Equivalence Evaluations until any applicable periods of exclusivity pursuant to section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act were triggered and run. For additional information on this matter, please refer to Docket Nos. 2005P-0008 and 2005P-0046. Patents were subsequently delisted in the December 2006 Orange Book update as the exclusivity periods have triggered and run to expiration.

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FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
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Update Frequency:

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Orange Book Data Updated Through December, 2006
Patent and Generic Drug Product Data Last Updated: January 30, 2007

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/s/

Thomas Hinchliffe
1/31/2007 10:27:05 AM

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

ARCHIVAL COPY

January 26, 2007

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-600)
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

Telephone CMC Amendment

RE: ANDA #77-715
Bupropion Hydrochloride Extended-Release Tablets (XL)
150 mg and 300 mg (Once Daily)

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting this Telephone CMC Amendment to provide a complete response to OGD's faxed comments of January 24, 2007 (see attached) in support of Bupropion HCl Extended-Release Tablets (XL), 150 and 300 mg (Once Daily), ANDA #77-715. FDA's comments appear in bold italic font below, with Watson's response immediately following each comment.

1) ***On January 11 and 17, 2007 in telephone conversations, Watson was asked to provide updated Components and Composition Tables for both the 150 mg and 300 mg strengths. Updates should have included:***

   a) ***'Amount per Coated Tablet (%)' –provided but with errors***

b(4)

b) 'Amount per Tablet (mg)' –not provided

TABLE 1
Calculations for Amount per Tablet (mg)

INGREDIENT	AMOUNT PER 150 MG TABLET (mg)	AMOUNT PER 300 MG TABLET (mg)

b(4)

c) All calculations were asked to be shown –not provided

In the January 26, 2007 teleconference, Watson clarified the necessary calculations as shown in **TABLE 1** above. It was mutually agreed that additional calculations are not required.

According to our calculations, the updated Components and Composition tables provided for both strengths do not fully address this request. Please provide the requested information above. Also, please be sure all Theoretical Core and Coated Tablets weights are updated.

Watson believes the Components and Composition Statements provided herein for both strengths now fully address the Agency's request and that all Theoretical Tablet Core and Coated Tablet Weights are accurate.

Watson has enclosed one (1) Archival and one (1) Review Copy. In accordance with 21 CFR §314.96(b), one (1) Field Copy of the Amendment will be forwarded to the manufacturing facility's District Office, in Jamaica, NY. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the Archival and Review Copies of this Amendment.

Please contact me by telephone at 951-493-5452 or by fax at 951-493-4581 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Christine M. Woods
Associate Director
R&D Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS (HFD-600)
7500 STANDISH PLACE, ROCKVILLE, MD 20855

DATE: January 24, 2007

TO: Chris Woods

PHONE: 951.493.5452

FAX: 951. 493. 4581

FROM Barbara Scott

PHONE: 301-827-5771

FAX: (301) 443-3839

TOTAL NUMBER OF PAGES: 2
(EXCLUDING COVER SHEET)

SPECIAL INSTRUCTIONS:

Please see attached.
re: 77-715 ANDA

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-715 APPLICANT: Watson Laboratories, Inc.

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

Deficiency FAXED to Watson January 24, 2007:

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.

1) On January 11 and 17, 2007 in telephone conversations, Watson was asked to provide updated Components and Composition Tables for both the 150 mg and 300 mg strengths. Updates should have included:

a) 'Amount per Coated Tablet (%)' –provided but with errors
b) 'Amount per Tablet (mg)' –not provided
c) All calculations were asked to be shown – not provided

According to our calculations, the updated Components and Composition tables provided for both strengths do not fully address this request. Please provide the requested information above. Also, please be sure all Theoretical Core and Coated Tablet weights are updated.

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

ARCHIVAL COPY

January 19, 2007

ORIGINAL

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-600)
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N-000-AC

Telephone CMC Amendment

RE: ANDA #77-715
Bupropion Hydrochloride Extended-Release Tablets (XL)
150 mg and 300 mg (Once Daily)

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting this Telephone CMC Amendment to provide a complete response to OGD's telephone comments of January 11 and 17, 2007 in support of Bupropion HCl Extended-Release Tablets (XL), 150 and 300 mg (Once Daily), ANDA #77-715. FDA's comments appear in bold italic font below, with Watson's response immediately following each comment.

1. ***The — coating for the Extended-Release Tablets*** [redacted]

b(4)

RECEIVED
JAN 22 2007
OGD / CDER

311 Bonnie Circle, Corona, CA 92880 • Tel: 800/249-5499 • Website: www.watsonpharm.com

Sincerely,

Christine M. Woods
Associate Director
R&D Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20855

To: ANDA 77284
ANDA 77415
ANDA 77715

From: Barbara M. Davit, Ph.D., J.D., Deputy Director, Division of Bioequivalence, Office of Generic Drugs

Re: Acceptability of in vitro dissolution testing on 300-mg strength of Bupropion Hydrochloride Extended-Release Tablets

Date: December 14, 2006

Upon a final look at the ANDA reviews for bupropion hydrochloride extended-release tablets, we determined that the ANDA applicants' approach to demonstrating bioequivalence for the 300 mg had not been characterized accurately. The reviews indicate that a waiver was granted for the 300 mg strength and 21 CFR 320.22(d) is cited as the regulatory basis for the waiver. The term waiver and 21 CFR 320.22(d) should not have been used to characterize the applicants' approach to demonstrating bioequivalence for the 300 mg strength.

Wellbutrin XL (150 mg) is the reference listed drug. As stated in the response to the Agency's citizen petition, ANDA applicants conducted both fed and fasted in vivo bioequivalence studies (Docket No. 2005P-0498). ANDA applicants used the 150 mg strength in these in vivo studies to demonstrate bioequivalence.

Bioequivalence studies are generally conducted using the highest strength of the drug product. Given the dose-related risk of seizures associated with bupropion, however, we had determined that it was appropriate to conduct the in vivo bioequivalence studies using the 150 mg strength. Bioequivalence studies for the 300 mg dose of the extended-release tablet were conducted in vitro. In other words, we concluded that in vivo bioequivalence studies, which are conducted using healthy volunteers rather than patients, should not be done using the 300 mg strength. Dena Hixon, M.D., OGD's Associate Director for Medical Affairs, previously concurred with this approach for the sustained-release formulation. Based on the labeling for the Wellbutrin products, 300 mg Wellbutrin gives the same daily systemic bupropion exposure regardless of whether the drug product is IR, SR, or XL. One can infer that the 300-mg dose will provide the same toxicity. Therefore, the reasoning regarding bioequivalence studies for the sustained-release product is applicable to the 300 mg dose of the XL tablet.

Therefore, the Agency deemed it appropriate for ANDA applicants to demonstrate bioequivalence for the 300 mg strength by submitting data showing that their 150 and 300 mg strength formulations were proportionally similar in their active and inactive ingredients and establishing acceptable in vitro dissolution profiles. This approach is consistent with 21 CFR 320.24(b)(6).

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/s/

Barbara Davit
12/14/2006 12:02:15 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20855

To: ANDA 77284
ANDA 77415
ANDA 77715

From: Barbara M. Davit, Ph.D., J.D., Deputy Director, Division of Bioequivalence, Office of Generic Drugs

Re: Metabolite measurement in bioequivalence studies of bupropion hydrochloride extended-release tablets submitted to ANDAs

Date: December 14, 2006

Please note that this memo was originally submitted to DFS on December 13, 2006. This memo corrects an error in the title of the December 13th memo, but is otherwise identical.

This memorandum provides clarification on the issue of metabolites discussed in the Agency response to Biovail's December 20, 2005 citizen petition (Docket # 2005P-0498).

Based on its experience and expertise, the Agency developed the guidance titled *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (BA/BE guidance). The BA/BE guidance provides recommendations on bioavailability and bioequivalence (including the Agency's current thinking on when it may be appropriate to measure metabolites).

The sponsor for Wellbutrin XL measured the parent drug bupropion as well as the three metabolites hydroxybupropion, threohydrobupropion, and erythrohydrobupropion. Sponsors submitting new drug applications (NDA) generally conduct studies to demonstrate the safety and effectiveness of the drug and, in the process, often collect as much information as they can to characterize the drug product. This may include information on all detectable metabolites. In this setting, the purpose of an in vivo bioavailability or bioequivalence study is to determine whether certain conditions consistent with a controlled-release dosage form are met. (BA/BE guidance, at p. 15-16; see also 21 CFR 320.25(f)(2)).

Sponsors submitting abbreviated new drug applications (ANDA), on the other hand, generally conduct studies for a different purpose than do NDA applicants. That is, an ANDA applicant is expected to submit information on (among other things) bioequivalence to demonstrate that its product delivers the active ingredient or moiety at the same rate and extent as the NDA sponsor's reference listed drug.

The Agency applied the current recommendations in the BA/BE guidance to ANDA applicants for generic bupropion HCl extended-release tablets in considering which metabolites should be measured for the purposes of generic drug bioequivalence.[1]
Accordingly, we currently expect ANDA applicants for generic bupropion HCl extended-release tablets to measure the parent drug bupropion and the metabolite hydroxybupropion. We do not expect ANDA applicants to measure the other two metabolites (i.e., threohydrobupropion and erythrohydrobupropion). As explained in the Agency's response to the above-referenced citizen petition, our expectation is based, in part, on the relative potencies and exposure of the parent drug and metabolites. In addition, there is currently insufficient scientific evidence upon which we can reasonably determine whether threohydrobupropion and erythrohydrobupropion are formed as a result of gut wall or other presystemic metabolism. We expect that measurement of bupropion, together with the metabolite hydroxybupropion, would be a scientifically reasonable and reliable indicator of the drug's activity for purposes of demonstrating that generic bupropion HCl extended-release tablets are bioequivalent to Wellbutrin XL.

The Office of Generic Drugs consulted with the Division of Neurology Products and the Division of Pharmacology I on the application of the BA/BE guidance with respect to the issue of metabolites. All three components of the Agency concurred that measurement of bupropion, together with the metabolite hydroxybupropion, would be a reliable and reasonable indicator of the drug's activity for the purposes of demonstrating generic drug bioequivalence.

[1] We note that before the Agency developed and posted the BA/BE guidance, the Agency expected ANDA applicants for bupropion HCl tablets to measure the parent drug bupropion as well as the three metabolites hydroxybupropion, threohydrobupropion, and erythrohydrobupropion. After re-evaluating the metabolite issue in light of the current recommendations in the BA/BE guidance, the Agency concluded it was not necessary for ANDA applicants to measure all three metabolites as discussed above.

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/s/

Barbara Davit
12/14/2006 11:57:28 AM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20855

To: ANDA 77284
ANDA 77415
ANDA 77715

From: Barbara M. Davit, Ph.D., J.D., Deputy Director, Division of Bioequivalence, Office of Generic Drugs

Re: Recommendations for in vivo bioequivalence studies of chlorpromazine tablets

Date: December 13, 2006

This memorandum provides clarification on the issue of metabolites discussed in the Agency response to Biovail's December 20, 2005 citizen petition (Docket # 2005P-0498).

Based on its experience and expertise, the Agency developed the guidance titled *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (BA/BE guidance). The BA/BE guidance provides recommendations on bioavailability and bioequivalence (including the Agency's current thinking on when it may be appropriate to measure metabolites).

The sponsor for Wellbutrin XL measured the parent drug bupropion as well as the three metabolites hydroxybupropion, threohydrobupropion, and erythrohydrobupropion. Sponsors submitting new drug applications (NDA) generally conduct studies to demonstrate the safety and effectiveness of the drug and, in the process, often collect as much information as they can to characterize the drug product. This may include information on all detectable metabolites. In this setting, the purpose of an in vivo bioavailability or bioequivalence study is to determine whether certain conditions consistent with a controlled-release dosage form are met. (BA/BE guidance, at p. 15-16; see also 21 CFR 320.25(f)(2)).

Sponsors submitting abbreviated new drug applications (ANDA), on the other hand, generally conduct studies for a different purpose than do NDA applicants. That is, an ANDA applicant is expected to submit information on (among other things) bioequivalence to demonstrate that its product delivers the active ingredient or moiety at the same rate and extent as the NDA sponsor's reference listed drug.

The Agency applied the current recommendations in the BA/BE guidance to ANDA applicants for generic bupropion HCl extended-release tablets in considering which metabolites should be measured for the purposes of generic drug bioequivalence.[1]

---

[1] We note that before the Agency developed and posted the BA/BE guidance, the Agency expected ANDA applicants for bupropion HCl tablets to measure the parent drug bupropion as well as the three metabolites hydroxybupropion, threohydrobupropion, and erythrohydrobupropion. After re-evaluating the metabolite issue in

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The Office of Generic Drugs consulted with the Division of Neurology Products and the Division of Pharmacology I on the application of the BA/BE guidance with respect to the issue of metabolites. All three components of the Agency concurred that measurement of bupropion, together with the metabolite hydroxybupropion, would be a reliable and reasonable indicator of the drug's activity for the purposes of demonstrating generic drug bioequivalence.

light of the current recommendations in the BA/BE guidance, the Agency concluded it was not necessary for ANDA applicants to measure all three metabolites as discussed above.

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/s/

Barbara Davit
12/13/2006 07:48:41 PM
BIOPHARMACEUTICS

To: ANDA 77-715, Watson Laboratories, Inc., Bupropion HCl Extended Release Tablets

From: Barbara M. Davit, Ph.D., J.D., Deputy Director, Division of Bioequivalence, Office of Generic Drugs

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

Re: Results of in vitro alcohol dose-dumping study comparing Watson's Bupropion HCl ER Tablet with Wellbutrin XL

Date: December 4, 2006

ANDA 77-715, Watson, Bupropion HCl Extended-Release Tablets versus Wellbutrin® XL In Vitro Dose-Dumping Study in 0.1 N HCl With Ethanol Added Summary of Study Findings and Discussion of Results

Summary: At the request of the Division of Bioequivalence (DBE), Watson performed an in vitro dose dumping study to determine the effects of increasing amounts of ethanol (EtOH) on the dissolution performance of its Bupropion Hydrochloride (HCl) Extended-Release (ER) Tablet. The DBE concludes that Watson's product shows acceptable in vitro performance under the conditions of this test.

Methods: The in vitro dissolution performance of Watson's Bupropion HCL ER Tablet was compared to that of the corresponding reference listed drug (RLD), Wellbutrin XL, in solutions of 0.1 N hydrochloric acid (HCl) to which was added varying amounts of ethanol. Dissolution was conducted in 900 mL media at 37°C using USP Apparatus II at 75 rpm. Four media were tested: 0.1 N HCl, 0.1 N HCl containing 5% ethanol, 0.1 N HCL containing 20% ethanol, and 0.1 N HCl containing 40% ethanol. During the dissolution test, the media were sampled and analyzed for bupropion concentrations every 15 minutes up to 120 minutes (2 hours). Both the 150- and 300-mg strengths of Watson's product and Wellbutrin XL were tested. The data obtained at each sampling time were from 12 tablets.

Results: Dissolution data tables and profiles are presented in Attachment I. Similar dissolution trends were observed for both the 150- and 300-mg strengths, although Watson's 300-mg strength generally released bupropion at a faster rate than its 150-mg strength. All data are expressed as the % of the labeled amount of bupropion dissolved. Bupropion release from both Watson's product and Wellbutrin XL increased as the % of ethanol increased.

The DBE compared the mean % of the labeled amounts of bupropion dissolved at 2 hours in 0, 5, 20, and 40% alcohol. Bupropion release from Watson's product was greatest in 20% ethanol whereas bupropion release from Wellbutrin XL was greatest in 40% ethanol. For Watson's 150-mg tablet, 23% (range 17-29%) of the bupropion dissolved in 20% ethanol, compared to 2% (range 0 to 5%) in no ethanol. For Wellbutrin XL 150 mg, 11% (range 7 to 18%) dissolved in 20% ethanol, compared to 1% (range 0 to 2%) in no ethanol. For Watson's 300-mg tablet, 30%

(range 26 to 34%) of the bupropion dissolved in 20% ethanol, compared to 12% (range 8 to 16%) in no ethanol. For Wellbutrin XL 300 mg, 13% (range 10 to 17%) dissolved in 20% ethanol, compared to 4% (range 2 to 11%) in no ethanol.

In addition, in 5% ethanol, 20% (range 12 to 28%) of the bupropion in Watson's 300-mg tablet was dissolved, compared to 6% (range 3 to 11%) for Wellbutrin XL 300 mg.[1]

In 40% ethanol, the mean % of the labeled amount of bupropion dissolved from Watson's product versus Wellbutrin XL was comparable for both strengths.

Additional Data: Attachment II shows all dissolution, in vivo, and formulation data submitted to ANDA 77-715. Dissolution of Watson's tablet and Wellbutrin XL was compared in 0.1 N HCl (regulatory method), pH 4.5 buffer, pH 6.8 buffer, and water.

Watson conducted two pivotal bioequivalence studies comparing its Bupropion HCl ER Tablets to Wellbutrin XL, a fasted bioequivalence study and a fed bioequivalence study. The 150-mg strength was studied (rather than the 300-mg strength) for safety reasons. Watson's tablet was bioequivalent to Wellbutrin XL in both studies.

Watson's two strengths, 150-mg and 300-mg, are formulated to be proportionally similar, with the result that the 300-mg strength is twice the size of the 150-mg strength.

Analysis: Watson's 150- and 300-mg tablets released more bupropion in 5, 20, and 40% ethanol than in 0.1 N HCl (no ethanol). In 5 and 20% ethanol, Watson's product released more bupropion than Wellbutrin XL. However, in 40% ethanol, Watson's Bupropion HCL ER Tablets and Wellbutrin XL (both strengths) had comparable dissolution.

Although bupropion dissolution from Watson's product in 5 and 20% ethanol was greater than in 0.1 N HCl with no ethanol, and greater than from Wellbutrin XL, the DBE concludes that the in vitro performance of Watson's product under the conditions of this test is acceptable. The DBE makes this determination by comparing the in vitro performance of Watson's Bupropion HCl ER Tablet in the alcohol dose-dumping test to that of Impax's Bupropion HCl ER Tablet. (For details, see the DBE review of Impax's bioequivalence submission to ANDA 77-415, archived at N 077415 N 000 AB 29-JUN-2005). The DBE previously found Impax's in vitro alcohol dose-dumping study results acceptable. For Impax's tablet, in 20% ethanol after 2 hours, the % bupropion dissolved averaged 34% (range 31 to 37%) for the 150-mg strength, and 30% (range 29-30%) for the 300-mg strength. Under the same conditions, the % bupropion dissolved from Watson's tablet averaged 23% (range 17 to 29%) for the 150-mg strength and 30% (range 26 to 34%) for the 300-mg strength. A similar comparison can be made for the 5% ethanol dissolution test. In 5% ethanol after 2 hours, the % bupropion dissolved from Impax's 300-mg tablet averaged 30% (range 29-30%). Under the same conditions, the % bupropion dissolved from

[1] Bupropion dissolution from Watson's 150-mg tablet was still low in 5% ethanol at 2 hours, however, averaging only 9%.

Watson's 300-mg tablet averaged 20% (range 12-28%).[2] Therefore, (1) since Watson's product dissolved at a rate comparable to Impax's product at 5 and 20% ethanol; and (2) the DBE previously concluded that the rate of bupropion dissolution from Impax's product in 5 and 20% ethanol was acceptable; (3) the DBE concludes that Watson's Bupropion HCl ER Tablet gave acceptable results in the in vitro alcohol dose dumping study.

[2] Impax's product dissolved rapidly in 0.1 N HCl (no ethanol). Because its dissolution rate was only slightly lower as ethanol was added to the medium, the DBE concluded that Impax's Bupropion HCl ER Tablet showed robust performance in the in vitro alcohol dose-dumping study.

Attachment I
Watson's Bupropion HCl Extended-Release Tablets versus Wellbutrin® XL
Results of In Vitro Dose-Dumping Study in 0.1 N HCl With Ethanol (EtOH) Added

Conditions: USP Apparatus I (Basket), 75 rpm, 900 mL, 37°C. Media composition and sampling times are shown in the tables below

Mean % (RSD) of labeled amount of bupropion dissolved at various sampling times, 150-mg Bupropion Extended Release Tablets (n=12)

Product	Medium	0 min	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
Watson	0.1 N HCl	0	0	0	0	0	0	0.2 (105.8)	1 (99.3)	2 (87.4)
	5% EtOH/95% 0.1N HCl	0	0	0	0	0.1 (72.8)	1 (49.7)	2 (53.3)	5 (48.8)	9 (34.5)
	20% EtOH/80% 0.1N HCl	0	0	0.1 (56.8)	2 (27.1)	5 (47.7)	8 (13.4)	13 (18.0)	18 (19.5)	23 (17.2)
	40% EtOH/60% 0.1N HCl	0	1 (39.6)	4 (22.6)	7 (17.6)	9 (14.5)	12 (12.0)	15 (13.0)	18 (10.9)	20 (10.1)
Wellbutrin XL	0.1 N HCl	0	0	0	0	0	0	0.2 (83.2)	0.5 (55.7)	1 (39.8)
	5% EtOH/95% 0.1N HCl	0	0	0	0	0	0	0.4 (83.5)	1 (83.5)	3 (78.6)
	20% EtOH/80% 0.1N HCl	0	0	0	0	0.3 (82.9)	3 (48.6)	5 (48.9)	8 (39.0)	11 (33.3)
	40% EtOH/60% 0.1N HCl	0	0	1 (50.2)	2 (23.9)	4 (23.4)	7 (15.8)	10 (10.2)	13 (9.1)	16 (8.5)

Mean % (RSD) of labeled amount of bupropion dissolved at various sampling times, 300-mg Bupropion Extended Release Tablets (n=12)

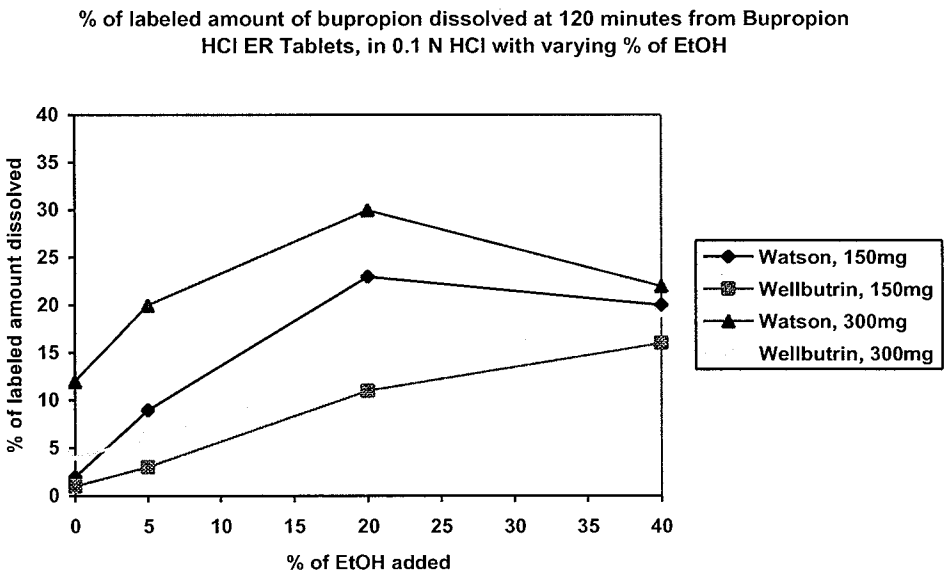
Product	Medium	0 min	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
Watson	0.1 N HCl	0	0	0	0	0.1 (59.9)	1 (65.5)	3 (62.5)	7 (32.5)	12 (20.3)
	5% EtOH/95% 0.1N HCl	0	0	0	0.3 (39.6)	1 (26.3)	5 (52.5)	10 (38.5)	15 (27.1)	20 (22.0)
	20% EtOH/80% 0.1N HCl	0	0	2 (42.1)	5 (24.9)	9 (27.3)	14 (25.1)	20 (17.6)	25 (12.9)	30 (10.1)
	40% EtOH/60% 0.1N HCl	0	2 (21.9)	5 (14.0)	8 (19.8)	11 (22.3)	14 (23.5)	17 (24.0)	19 (23.8)	22 (22.5)
Wellbutrin XL	0.1 N HCl	0	0	0	0	0.1 (95.0)	1 (65.1)	1 (81.5)	2 (77.7)	4 (68.6)
	5% EtOH/95% 0.1N HCl	0	0	0	0	0.4 (56.5)	1 (40.6)	2 (40.9)	4 (42.3)	6 (42.0)
	20% EtOH/80% 0.1N HCl	0	0	0	1 (32.6)	3 (24.2)	5 (19.2)	7 (18.8)	10 (18.7)	13 (17.3)
	40% EtOH/60% 0.1N HCl	0	0	2 (17.4)	4 (11.6)	7 (8.6)	10 (7.3)	13 (6.7)	16 (4.4)	19 (6.2)

TABLE 1: Percent Drug Release of 150 mg Bupropion HCl Extended-Release Tablets, USP in 0.1N HCl with various alcohol levels at 120 minutes (n=12 tablets per product).

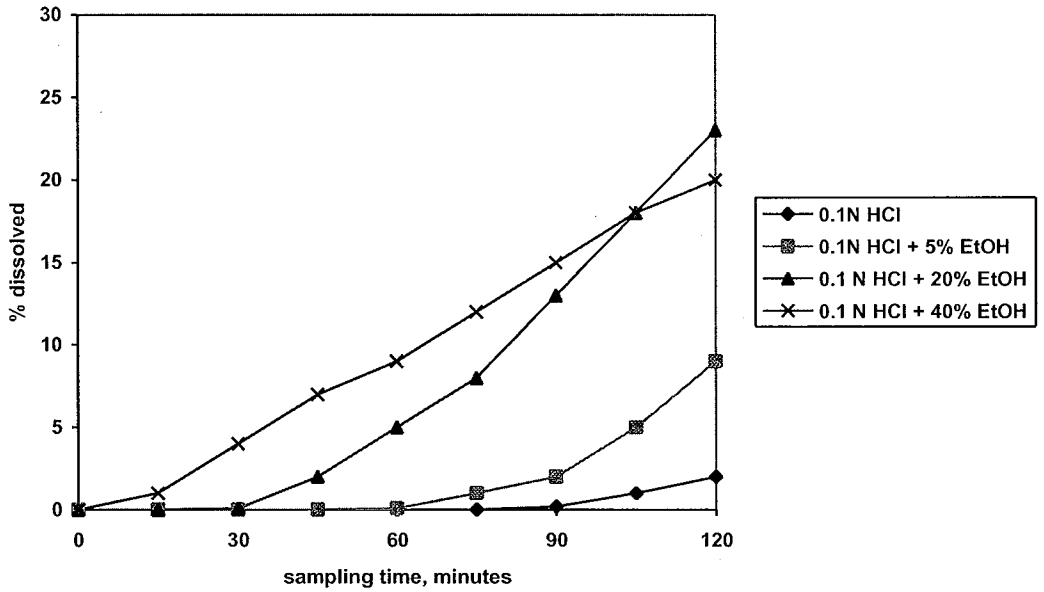
Alcohol Level (% v/v)	Watson Bupropion HCl Extended-Release Tablets, USP, 150 mg (Lot #XT4L029, Mfg. Date: 12/04)			Wellbutrin® XL, 150 mg, (Lot #06E029P, Exp. Date: 08/07)		
	Mean (%)	Range (%)	% CV	Mean (%)	Range (%)	% CV
Test 1: 0%	2	0 to 5	87.4%	1	0 to 2	39.8%
Test 2: 5%	9	4 to 14	34.5%	3	1 to 7	78.6%
Test 3: 20%	23	17 to 29	17.2%	11	7 to 18	33.3%
Test 4: 40%	20	18 to 24	10.1%	16	13 to 18	8.5%

TABLE 2: Percent Drug Release of 300 mg Bupropion HCl Extended-Release Tablets, USP in 0.1N HCl with various alcohol levels at 120 minutes (n=12 tablets per product).

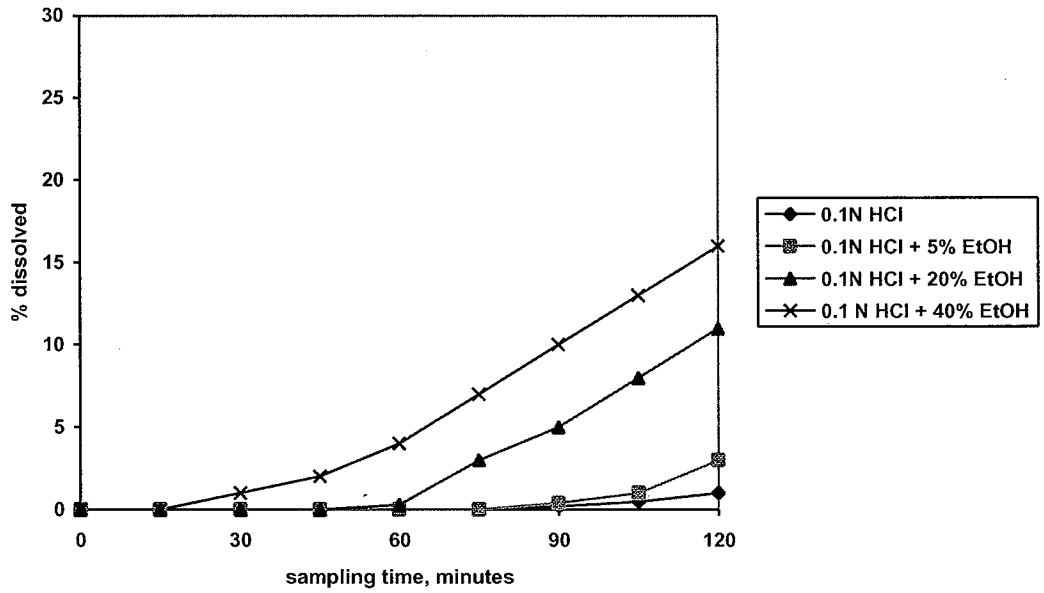
Alcohol Level (% v/v)	Watson Bupropion HCl Extended-Release Tablets, USP, 300 mg (Lot #XC5B013, Mfg. Date: 03/05)			Wellbutrin® XL, 300 mg, (Lot #06E002P, Exp. Date: 08/07)		
	Mean (%)	Range (%)	% CV	Mean (%)	Range (%)	% CV
Test 1: 0%	12	8 to 16	20.3%	4	2 to 11	68.6%
Test 2: 5%	20	12 to 28	22.0%	6	3 to 11	42.0%
Test 3: 20%	30	26 to 34	10.1%	13	10 to 17	17.3%
Test 4: 40%	22	18 to 36	22.5%	19	17 to 20	6.2%



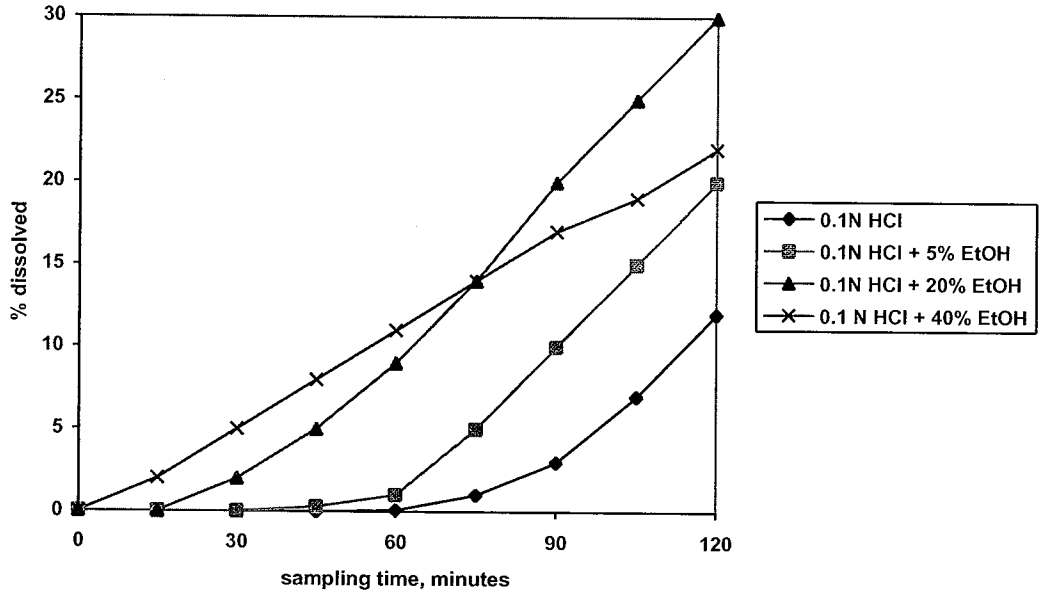
Watson Bupropion HCl ER Tablet, 150mg, In Vitro Dose-Dumping Study



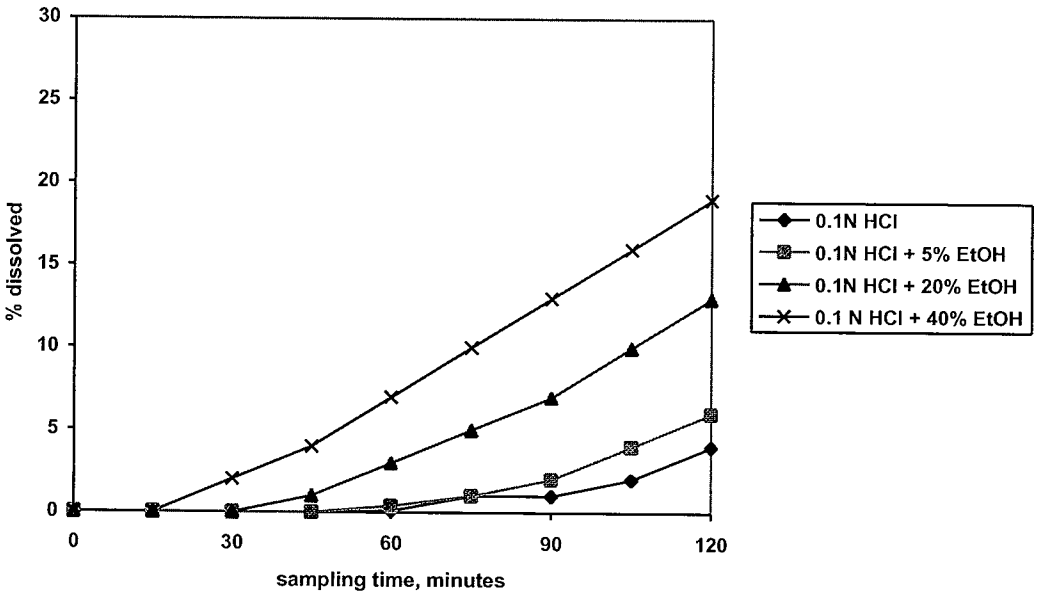
Wellbutrin XL Tablet, 150mg, In Vitro Dose-Dumping Study



Watson Bupropion HCl ER Tablet, 300mg, In Vitro Dose-Dumping Study



Wellbutrin XL, 300mg, In Vitro Dose-Dumping Study



Attachment I

Review of all dissolution data submitted to ANDA 77-715 (data and plots from Dr. Chandra Chaurasia's review)

A. Dissolution Data

Method: USP I (Basket) *(FDA-recommended method)*
Medium: 0.1N HCl, 900 mL
Rotational Speed 75 RPM

Results of In Vitro Dissolution Testing (% dissolved)

Sampling Times (Min)	Test Product: Bupropion Hydrochloride E R Tablets, USP Lot No.: XT4L029 **Strength: 150 mg** No of Dosage Units: 12			Reference Product: Wellbutrin XL® Lot No.: 04D014P **Strength: 150 mg** No of Dosage Units: 12		
	Average	Range	% SD	Average	Range	% SD
120	4	1-14	4.4	1	0-2	0.6
240	34	28-43	4.4	21	11-27	4.9
380	55	50-63	3.8	48	39-55	5.1
480	71	67-77	3.1	72	62-80	5.2
600	82	79-87	2.3	87	83-91	2.7
720	89	87-92	1.7	93	89-95	1.9
840	93	90-95	1.7	95	92-96	1.8
960	94	92-97	1.7	97	93-99	1.7
1080	96	93-98	1.6	98	94-100	1.6
Sampling Times (Min)	Test Product: Bupropion[2] Hydrochloride E R Tablets, USP Lot No.: XC5B013 **Strength: 300 mg** No of Dosage Units: 12			Reference Product: Wellbutrin XL® Lot No.: 4ZP1099 **Strength: 300 mg** No of Dosage Units: 12		
	Average	Range	% RSD	Average	Range	% RSD
120	14	7-24	4.6	4	2-7	1.8
240	40	33-49	4.8	28	23-33	3.3
380	58	51-67	4.6	49	44-55	3.2
480	71	65-80	4.1	67	62-72	2.9
600	81	75-89	3.6	81	76-84	2.3
720	89	85-95	2.8	89	86-91	1.4
840	94	91-97	1.7	93	92-96	1.0
960	96	94-99	1.3	95	93-97	1.1
1080	98	95-100	1.1	96	96-98	1.1

Method: USP I (Basket)
Medium: pH4.5 Acetate Buffer, 900 mL[3]
Rotational Speed 75 RPM

Results of In Vitro Dissolution Testing (% dissolved)

Sampling Times (Min)	Test Product: Bupropion Hydrochloride E R Tablets, USP Lot No.: XT4L029 **Strength: 150 mg** No of Dosage Units: 12			Reference Product: Wellbutrin XL® Lot No.: 04D014P **Strength: 150 mg** No of Dosage Units: 12		
	Average	Range	% SD	Average	Range	% SD
120	0	0-1	0.1	0	0-0	0.1
240	14	9-20	3.1	1	1-4	0.8
380	31	28-35	2.2	6	2-11	3.4
480	43	40-46	2.1	14	7-21	4.3
600	52	49-56	2.3	22	15-30	4.6
720	60	56-63	2.4	31	22.40	5.3
840	67	63-70	2.4	40	30.50	6.4
960	73	69-76	2.2	49	37-60	7.7
1080	78	73-80	2.2	58	44-70	8.5
Sampling Times (Min)	Test Product: Bupropion Hydrochloride E R Tablets, USP Lot No.: XC5B013 **Strength: 300 mg** No of Dosage Units: 12			Reference Product: Wellbutrin XL® Lot No.: 4ZP1099 **Strength: 300 mg** No of Dosage Units: 12		
	Average	Range	% RSD	Average	Range	% RSD
120	1	0-5	1.3	1	0-2	0.6
240	15	8-22	4.2	3	1-9	2.8
380	26	20-33	4.0	6	2-12	3.3
480	36	32-42	3.1	11	2-18	3.9
600	45	40-50	2.9	17	9-23	4.1
720	53	47-57	2.9	23	15-29	4.6
840	60	54-65	3.1	29	22-38	5.2
960	66	60-71	3.3	35	27-46	6.0
1080	72	65-76	3.3	42	32-54	6.8

Method: USP I (Basket)
Medium: pH6.8 Phosphate Buffer, 900 mL[3]
Rotational Speed 75 RPM

Results of In Vitro Dissolution Testing (% dissolved)

Sampling Times (Min)	Test Product: Bupropion Hydrochloride E R Tablets, USP Lot No.: XT4L029 **Strength: 150 mg,** No of Dosage Units: 12			Reference Product: Wellbutrin XL® Lot No.: 04D014P **Strength: 150 mg** No of Dosage Units: 12		
	Average	Range	% SD	Average	Range	% SD
120	37	34-40	2.0	36	35-37	1.1
240	54	50-57	2.1	63	61-65	1.3
380	63	58-66	2.3	79	76-82	1.7
480	68	63-73	3.1	85	83-87	1.3
600	72	66-80	4.4	87	86-89	1.2
720	74	66-80	4.0	88	87-90	1.1
840	74	69-80	3.5	89	87-91	1.1
960	75	70-79	2.9	89	88-91	1.1
1080	74	71-79	2.5	89	88-91	1.1
Sampling Times (Min)	Test Product: Bupropion Hydrochloride E R Tablets, USP Lot No.: XC5B013 **Strength: 300 mg,** No of Dosage Units: 12			Reference Product: Wellbutrin XL® Lot No.: 4ZP1099 **Strength: 300 mg** No of Dosage Units: 12		
	Average	Range	% RSD	Average	Range	% RSD
120	35	32-43	2.7	35	33-38	1.6
240	57	51-70	4.6	59	56-62	1.7
380	70	63-81	4.5	74	71-77	1.9
480	79	70-88	4.5	84	80-87	2.1
600	84	75-87	3.4	90	85-93	2.0
720	85	79-87	2.3	92	87-95	2.1
840	85	81-87	1.7	93	88-96	2.1
960	84	81-86	1.6	93	89-96	2.0
1080	83	80-85	1.5	93	89-96	1.9

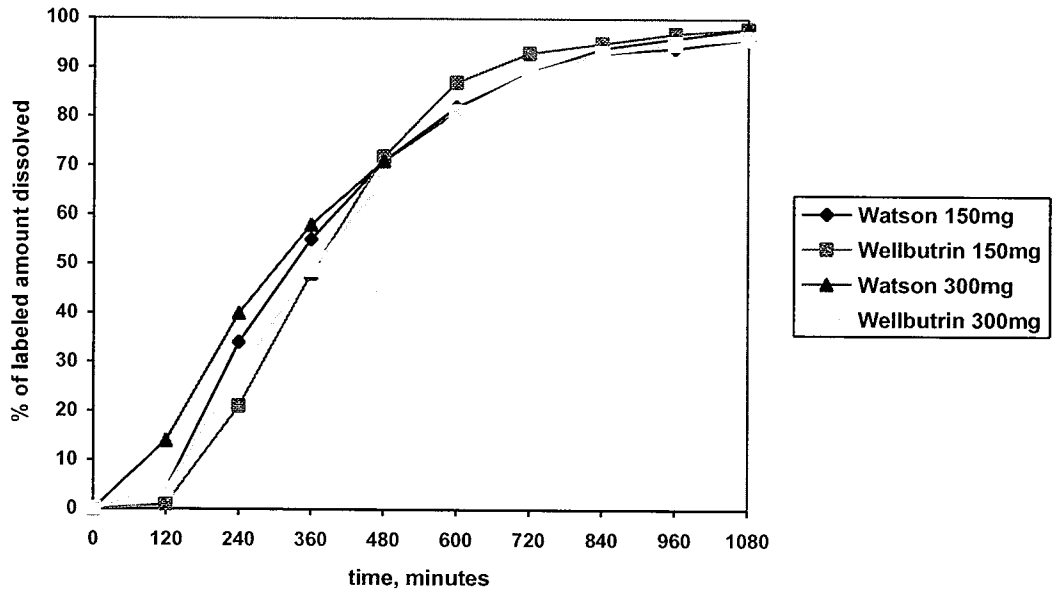
Method: USP I (Basket)
Medium: Water, 900 mL[3]
Rotational Speed 75 RPM

Results of In Vitro Dissolution Testing (% dissolved)

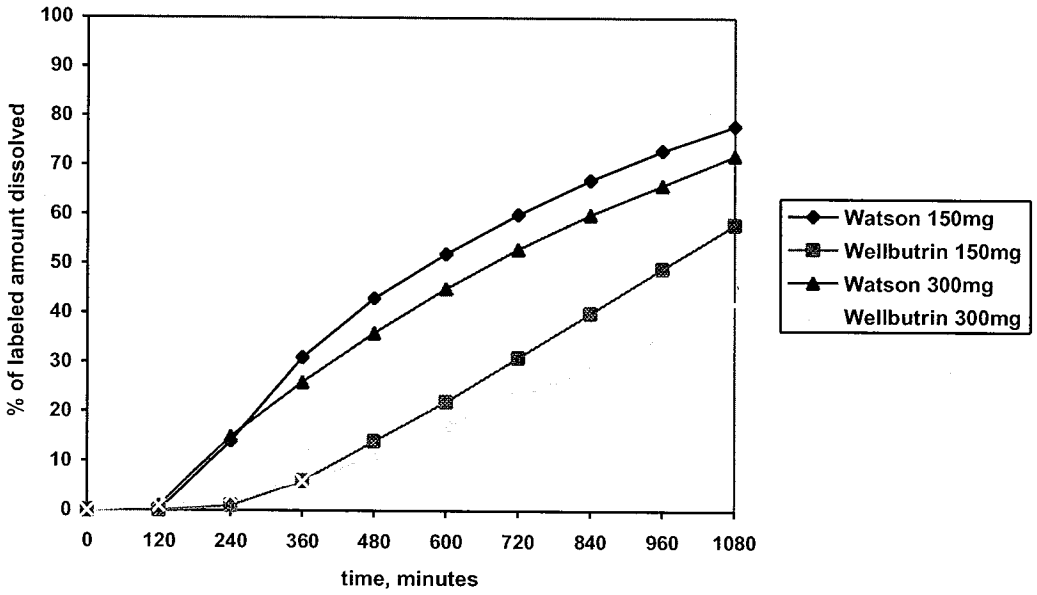
Sampling Times (Min)	Test Product: Bupropion Hydrochloride E R Tablets, USP Lot No.: XT4L029 **Strength: 150 mg** No of Dosage Units: 12			Reference Product: Wellbutrin XL® Lot No.: 04D014P **Strength: 150 mg** No of Dosage Units: 12		
	Average	Range	% SD	Average	Range	% SD
120	1	0-2	0.3	1	0-3	0.6
240	15	2-19	4.1	4	2.10	2.6
380	27	17-32	3.5	13	8-18	2.6
480	38	28-44	3.5	21	18-25	2.1
600	47	37-55	4.0	30	27-34	2.1
720	56	46-66	4.2	38	34-44	2.8
840	62	53-72	4.2	47	42-55	3.9
960	68	60-78	4.1	56	49-57	5.7
1080	72	66-83	4.1	64	55-80	6.8
Sampling Times (Min)	Test Product: Bupropion Hydrochloride E R Tablets, USP Lot No.: XC5B013 **Strength: 300 mg** No of Dosage Units: 12			Reference Product: Wellbutrin XL® Lot No.: 4ZP1099 **Strength: 300 mg** No of Dosage Units: 12		
	Average	Range	% RSD	Average	Range	% RSD
120	4	0-9	3.1	1	1-4	1.0
240	15	4-23	6.3	7	2-12	3.5
380	27	13-34	6.7	15	10-19	2.9
480	37	23-49	7.3	21	16-26	2.9
600	46	33-64	8.0	28	22-33	3.0
720	55	42-75	8.1	34	28-40	3.2
840	62	50-84	8.2	40	34-47	3.5
960	69	58-91	8.0	47	40-54	3.8
1080	74	64-95	7.5	53	47-60	4.1

B. Plots of Dissolution Profiles in Various Media

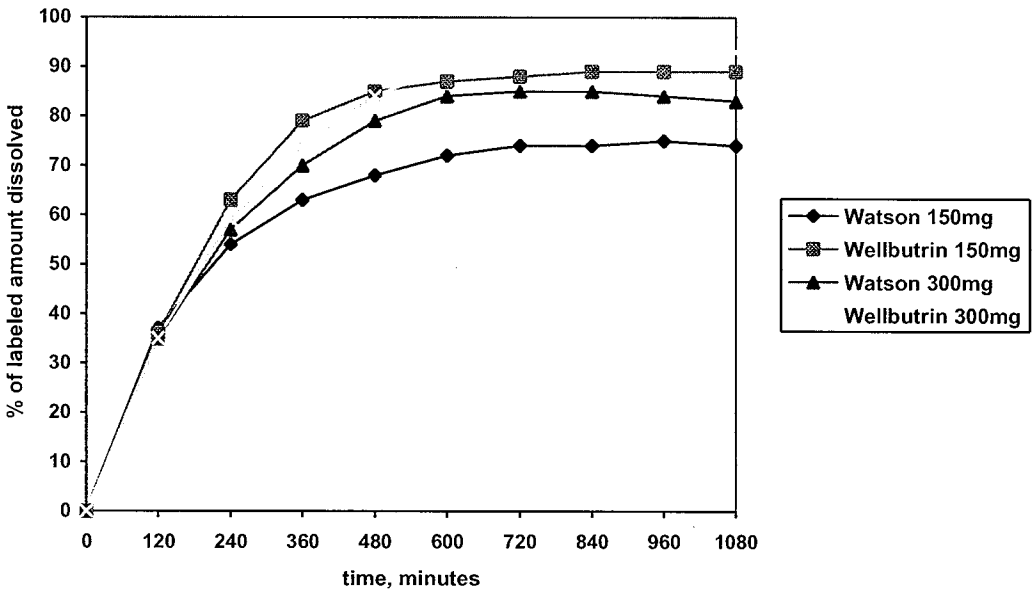
Bupropion HCl ER Tablet dissolution profiles in 0.1 N HCl



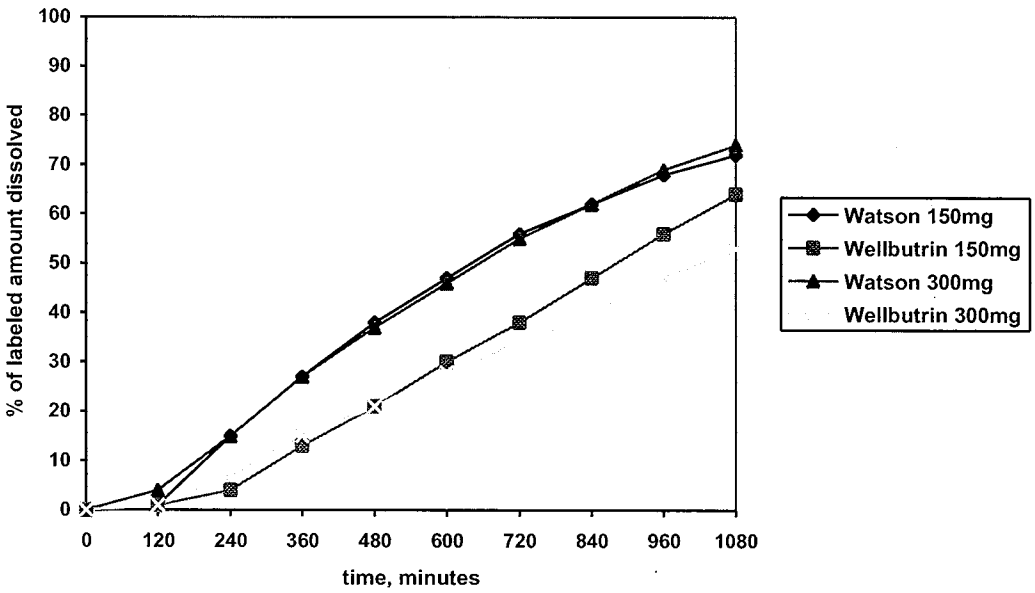
Bupropion HCl ER Tablet dissolution profiles in pH 4.5 buffer



Bupropion HCl ER Tablet dissolution profiles in pH 6.8 buffer



Bupropion HCl ER Tablet dissolution profiles in water



C. In vivo data

Geometric Means and 90% Confidence Intervals for Watson's Bupropion HCl ER Tablet versus Wellbutrin XL in 47 Fasted Subjects

PARAMETER	Test	Reference	T/R	90% CI	
				Lower	Upper
LAUCT	693.34	764.90	0.91	86.73	94.73
LAUCI	730.74	805.99	0.91	86.85	94.64
LCMAX	65.38	69.18	0.95	87.28	102.34

Arithmetic Mean Pharmacokinetic Parameters from Fasting BE Study (Test = Watson, Reference = Wellbutrin XL)

PARAMETER		Test		Reference		T/R
		Mean	%CV	Mean	%CV	
AUCT	ng•hr/mL	730.08	33.40	798.64	29.76	0.91
AUCI	ng•hr/mL	767.52	32.68	840.10	29.14	0.91
CMAX	ng/mL	68.93	33.94	73.48	35.75	0.94
TMAX	hr	4.79	16.83	4.69	13.44	1.02
KE	hr-1	0.04	36.34	0.04	40.48	1.07
THALF	hr	18.22	35.11	19.94	36.91	0.91

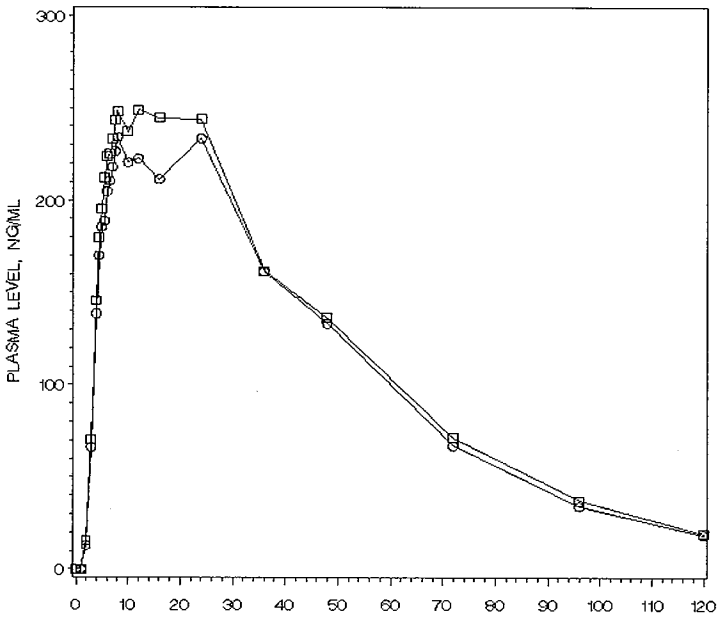
Geometric Means and 90% Confidence Intervals for Watson's Bupropion HCl ER Tablet versus Wellbutrin XL in 47 Fed Subjects

PARAMETER	Test	Reference	T/R	90% CI	
				Lower	Upper
LAUCT	890.66	955.65	0.93	89.25	97.32
LAUCI	933.79	997.05	0.94	89.84	97.63
LCMAX	73.49	80.69	0.91	85.34	97.18

Arithmetic Mean Bupropion Pharmacokinetic Parameters in Fed BE Study (Test = Watson, Reference = Wellbutrin XL)

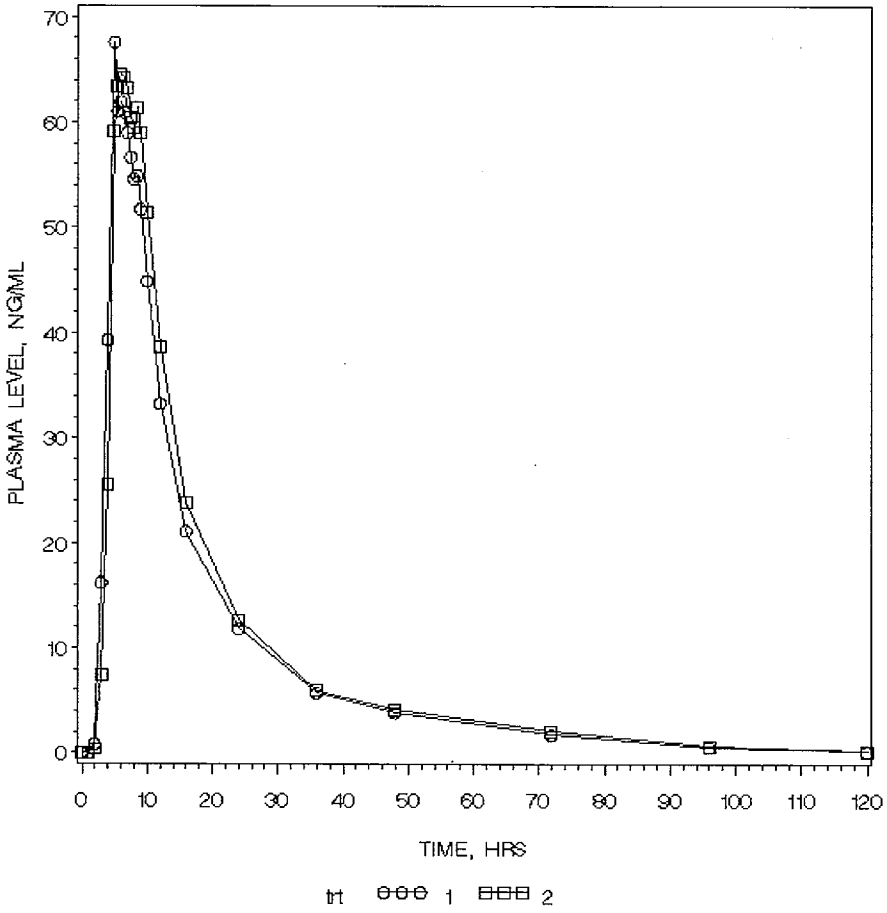
PARAMETER		Test		Reference		
		Mean	%CV	Mean	%CV	T/R
AUCT	ng•hr/mL	938.72	32.27	1003.36	31.57	0.94
AUCI	ng•hr/mL	980.77	31.26	1045.28	31.05	0.94
CMAX	ng/mL	77.81	36.12	83.94	29.61	0.93
TMAX	hr	6.47	21.47	7.01	25.56	0.92
KE	hr-1	0.04	36.27	0.04	43.56	1.00
THALF	hr	19.73	30.87	20.14	30.99	0.98

PLASMA HYDROXYBUPROPION LEVELS
Bupropion XL TABLET , 150 MG ANDA # 77-715
UNDER FAST CONDITIONS
DOSE= 1 X 150 MG



1= TEST 2= REF

PLASMA Bupropion XL LEVELS
Bupropion XL TABLET , 150 MG ANDA # 77-715
UNDER FED CONDITIONS
DOSE= 1 X 150 MG



1= TEST 2= REF

D. Formulation Data

Composition of Watson's Bupropion HCl ER Tablet

Ingredients	Amount per Tablet	
	150 mg	300 mg

b(4)

Composition of Wellbutrin XL

Component	150 mg Quantity (mg)	300 mg Quantity (mg)	Function	Reference to Standard

b(4)

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

/s/

Barbara Davit
12/4/2006 05:21:49 PM
BIOPHARMACEUTICS

Dale Conner
12/4/2006 05:31:27 PM
BIOPHARMACEUTICS

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

November 13, 2006

ORIGINAL

Gary Buehler, R.Ph.
Director
OGD/CDER/FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
N/A

Labeling Amendment

RE: Abbreviated New Drug Application #77-715
Bupropion Hydrochloride Extended-Release Tablets (XL), USP
150 mg & 300 mg (Once Daily)

**** ELECTRONIC FINAL PRINTED LABELING INCLUDED****

Dear Mr. Buehler:

Watson Laboratories, Inc. (Watson) is submitting this Labeling Amendment to provide a complete response to telephone comments by Ann Vu, OGD Labeling Reviewer, dated November 07, 2006 to Christine Woods of Watson, regarding Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg (Once Daily), ANDA #77-715.

FDA's comment appears in bold and italic font below with Watson's response immediately following the comment.

Labeling Request:

1. MEDICATION GUIDE

Please provide 12 hard copies of the Medication Guide for Bupropion Hydrochloride Extended-Release Tablets (XL) as Final Printed Labeling from the tear-off pad, which is to accompany the 1000-count bottles.

As requested, Watson has provided the 12 Final Printed Labeling hard copy Medication Guides in **EXHIBIT 1**.

In accordance with 21 CFR §314.94(d)(ii) as effected June 08, 2004, which required the submission of electronic labeling, Watson's Labeling Amendment dated October 11, 2006, provided Watson's Final Printed Labeling in MS Word, Adobe PDF and XML formats. Please note that the content of Watson's labeling has not been revised since Watson's Labeling Amendment dated October 11, 2006 and, therefore, no side-by-side labeling comparison is provided. However, the Medication

Guide has been reformatted to fit onto one (1) double-sided page, rather than seven (7) separate pages as in Watson's Labeling Amendment dated October 11, 2006.

Watson encloses one volume each of one (1) Archival, one (1) Review and one (1) Desk Copy for Ann Vu, OGD Labeling Reviewer.

It is Watson's view that this Labeling Amendment adequately addresses the cited request. Please contact me by telephone at 951-493-5446 or via facsimile at 951-493-4581, if you have any questions or if I can assist you with the review of this application.

Sincerely,

Ernest Lengle, Ph.D.

Ernest Lengle, Ph.D.
Executive Director, R&D Regulatory Affairs

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

October 11, 2006

ARCHIVAL COPY

Gary Buehler, R.Ph.
Director
OGD/CDER/FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
W1/AF

RECEIVED
OCT 12 2006
OGD / CDER

Labeling Amendment

RE: Abbreviated New Drug Application #77-715
Bupropion Hydrochloride Extended-Release Tablets (XL), USP
150 mg & 300 mg (Once Daily)

**** ELECTRONIC FINAL PRINTED LABELING INCLUDED ****

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting this Labeling Amendment to provide a complete response to OGD's faxed comments dated September 15, 2006 (see attached) regarding Bupropion Hydrochloride Extended-Release Tablets (XL), 150 mg and 300 mg (Once Daily), ANDA #77-715.

FDA comments appear in bold and italic font below. Watson's response immediately follows each comment.

Labeling Deficiencies:

1. ***CONTAINER (bottles of 30s, for the 150 mg strength, bottles of 30s and 1000s for the 300 mg strength)***

   Principal display panel- revise the established name to read: "BuPROPion Hydrochloride Extended-Release Tablets (XL)" [delete USP].

   As requested, USP has been deleted from the established name on the principal display panel, which now reads "BuPROPion Hydrochloride Extended-Release Tablets (XL)."

2. ***INSERT***

   a. ***GENERAL COMMENT***

      Add "(XL)" to the established name wherever WELLBUTRIN XL is used, including the black box warning and medication guide.

"USP" has been deleted, and "(XL)" has been added to the established name throughout the Package Insert, as requested.

b. Add "Rx Only" directly below the title of the insert.

"Rx only" has been added directly below the title of the insert as requested. ✓

c. Revise the established name in the title to Bupropion Hydrochloride Extended-Release Tablets (XL)". ✓

"USP" has been deleted, and "(XL)" has been added to the established name in the title, as requested.

d. DESCRIPTION

i. First paragraph, revise to read: Bupropion hydrochloride extended-release tablets (XL)..." ✓

"USP" has been deleted, and "(XL)" has been added to the established name throughout the Package Insert, as requested.

ii. Second paragraph, first sentence delete "USP". ✓

"USP" has been deleted, and "(XL)" has been added to the established name throughout the Package Insert, as requested.

iii. Add "USP drug release test is pending" at the end of the second paragraph. ✓

The statement, "USP drug release test is pending" has been added to the end of the second paragraph, as requested.

e. CONTRAINDICATIONS

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

The second paragraph under "CONTRAINDICATIONS" has been revised to the above statement, as requested.

ii. Start a new paragraph for "The concurrent administration of bupropion hydrochloride extended-release tablets (XL) and a monoamine oxidase...." ✓

A new paragraph was started as indicated above.

f. WARNINGS

Screening Patients for Bipolar Disorder, second paragraph, revise to "Patients should be made aware that bupropion hydrochloride extended release tablets (XL) contain the same active ingredient found in ZYBAN®, used as an aid to smoking cessation treatment, and that bupropion hydrochloride extended release tablets (XL) should not be used in combination with ZYBAN®, or any other medications that contain bupropion, such as WELLBUTRIN SR® (bupropion hydrochloride extended release tablets (SR), the sustained-release formulation or WELLBUTRIN® (bupropion hydrochloride tablets), the immediate-release formulation." ✓

The corresponding paragraph under "WARNINGS – Screening Patients for Bipolar Disorder" has been revised to the above statement, as requested.

g. PRECAUTIONS

Clinical Worsening and Suicide Risk, second paragraph, revise to "Patients should be made aware that bupropion hydrochloride extended release tablets (XL) contain the same active ingredient found in ZYBAN®, used as an aid to smoking cessation treatment, and that bupropion hydrochloride extended release tablets (XL) should not be used in combination with ZYBAN®, or any other medications that contain bupropion, such as WELLBUTRIN SR® (bupropion hydrochloride extended-release tablets (SR), the sustained-release formulation, or WELLBUTRIN® (bupropion hydrochloride tablets), the immediate-release formulation." ✓

The corresponding paragraph under "PRECAUTIONS – Clinical Worsening and Suicide Risk" has been revised to the above statement, as requested.

h. ADVERSE EVENTS

i. Table 4, footnote *, add "bronchitis, dysmenorrhea, and dyspepsia". ✓

The three adverse events ("bronchitis, dysmenorrhea, dyspepsia") were added to the Table 4 footnote as requested.

ii. Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials, revise "Table 6" to "Table 4".

✓

"Table 6" was revised to "Table 4" under "ADVERSE EVENTS - Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials," as requested

i. DOSAGE AND ADMINISTRATION

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

✓

The corresponding paragraph under "DOSAGE AND ADMINISTRATION" has been revised to the above statement, as requested.

j. HOW SUPPLIED

Please add below the storage temperature statement "The following are registered trademarks of their respective manufacturers: Zyban®/GlaxoSmithKline, Wellbutrin®/GlaxoSmithKline, Wellbutrin SR®/GlaxoSmithKline."

The above trademark statement was added below the storage temperature statement, as requested.

3. ***MEDICATION GUIDE***

a. ***Who should not take bupropion hydrochloride extended-release tablets (XL)? Do not take bupropion hydrochloride extended-release tablets if you:***

Second bullet, revise to "...• are taking ZYBAN® (used to help people stop smoking) or any other medicines that contain bupropion hydrochloride, such as WELLBUTRIN® (bupropion hydrochloride tablets) or WELLBUTRIN SR® (bupropion hydrochloride extended-release tablets (SR). Bupropion is the same active ingredient that is in bupropion hydrochloride extended-release tablets (XL)."

The second bullet under "Who should not take bupropion hydrochloride extended-release tablets (XL)?" has been revised to the above statement, as requested.

b. ***What should I tell my doctor before using bupropion hydrochloride extended-release tablets (XL)? Second and third bullet, revise "bupropion hydrochloride extended-release tablets" to "bupropion".***

"Bupropion hydrochloride extended-release tablets" has been revised to "bupropion" in the second and third bullets under "What should I tell my doctor before using bupropion hydrochloride extended-release tablets (XL)?" as requested.

c. ***Place "How should I store bupropion hydrochloride extended-release tablets (XL)?" on a separate paragraph.***

A new paragraph was started as indicated above.

d. ***Please add Zyban®, Wellbutrin® and Wellbutrin SR® in your list of registered trademarks and their manufacturers.***

"Zyban®," "Wellbutrin®" and "Wellbutrin SR®" were added to the list of registered trademarks with their manufacturer, GlaxoSmithKline, as requested.

Please revise your label and labeling as described above and submit electronically. The immediate container labels and carton labeling may be submitted either electronically or in hard copy.

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/SPL2alG_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.
To assist in our review, we request that labeling also be submitted in MS Word format.

Watson has revised its labeling as requested. In accordance with 21 CFR §314.94(d)(ii) as effected June 8, 2004, which required the submission of electronic labeling, Watson provides one (1) computer CD ROM containing Watson's proposed labeling in MS Word, Adobe PDF and XML formats. The CD ROM is located at the front of the blue Archival Copy of this submission. Please refer to the Table of Contents contained on the enclosed CD ROM for access to the files and directory pathways.

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

Watson acknowledges that it may be necessary to revise its labeling subsequent to approved changes for the reference listed drug.

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.

As required by 21 CFR §314.94(a)(8)(iv), Watson has included the side-by-side comparison of its proposed final printed Container labels, Package Insert, and Medication Guide/Patient Information Leaflet with the previously submitted versions of Watson's labeling (Container labels, Package Insert, and Medication Guide/Patient Information Leaflet, all dated August 2006), with all differences annotated and explained.

Watson encloses one volume each of one (1) Archival and one (1) Review Copy.

Finally, it is Watson's view that this response adequately addresses each of the cited comments. Please contact me by telephone at 951-493-5452 or by fax at 951-493-4581 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Christine M. Woods
Associate Director, R&D Regulatory Affairs

U.S. Department of Health and Human Services
Food and Drug Administration

Fax Cover Sheet

Public Health Service
Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling & Program Support
Labeling Review Branch
Rockville, Maryland 20855

To: Janie Gwin **DATE:** 9/15/06

Firm: Watson Laboratories, Inc.

Phone: **Fax:** 951-493-4581

SUBJECT: Labeling comments for 77-715 (Bupropion Hydrochloride Extended-Release Tablets (XL)150 mg and 300 mg (Once Daily))

From: Ann Vu

Phone: (301) 827-7342 **Fax:**

Number of Pages: four
(Including Cover Sheet)

Comments:

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

ANDA Number:	77-715
Date of Submissions:	August 11, 2005
Applicant's Name:	Watson Laboratories, Inc.
Established Name:	Bupropion Hydrochloride Extended-release Tablets (XL) 150 mg and 300 mg (Once Daily)

Labeling Deficiencies

1. CONTAINER (bottles of 30s, for the 150 mg strength, bottles of 30s and 1000s for the 300 mg strength)

   Principal display panel- revise the established name to read: "BuPROPion Hydrochloride Extended-Release Tablets (XL)" [delete USP].

2. INSERT

   a. GENERAL COMMENT

      Add "(XL)" to the established name wherever WELLBUTRIN XL is used, including the black box warning and medication guide.

   b. Add "Rx Only" directly below the title of the insert.

   c. Revise the established name in the title to "Bupropion Hydrochloride Extended-Release Tablets (XL)".

   d. DESCRIPTION

      i. First paragraph, revise to read; "Bupropion hydrochloride extended-release tablets (XL)..."

      ii. Second paragraph, first sentence, delete "USP".

      iii. Add "USP drug release test is pending" at the end of the second paragraph.

   e. CONTRAINDICATIONS

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

      ii. Start a new paragraph for "The concurrent administration of bupropion hydrochloride extended-release tablets (XL) and a monoamine oxidase...."

   f. WARNINGS

      Screening Patients for Bipolar Disorder, second paragraph, revise to " **Patients should be made aware that bupropion hydrochloride extended release tablets (XL) contain the same active ingredient found in ZYBAN®, used as an aid to smoking cessation treatment, and that bupropion hydrochloride extended release tablets (XL) should not be used in combination with ZYBAN®, or any other medications that contain bupropion, such as WELLBUTRIN SR® (bupropion hydrochloride extended release tablets (SR), the sustained-release formulation or WELLBUTRIN® (bupropion hydrochloride tablets), the immediate-release formulation.**"

g. PRECAUTIONS

Clinical Worsening and Suicide Risk, second paragraph, revise to "Patients should be made aware that bupropion hydrochloride extended release tablets (XL) contain the same active ingredient found in ZYBAN®, used as an aid to smoking cessation treatment, and that bupropion hydrochloride extended release tablets (XL) should not be used in combination with ZYBAN®, or any other medications that contain bupropion, such as WELLBUTRIN SR® (bupropion hydrochloride extended-release tablets (SR), the sustained-release formulation, or WELLBUTRIN® (bupropion hydrochloride tablets), the immediate-release formulation."

h. ADVERSE EVENTS

i. Table 4, footnote *, add "bronchitis, dysmenorrhea, and dyspepsia".

ii. Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials, revise "Table 6" to "Table 4".

i. DOSAGE AND ADMINISTRATION

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

j. HOW SUPPLIED

Please add below the storage temperature statement "The following are registered trademarks of their respective manufacturers: Zyban®/GlaxoSmithKline, Wellbutrin®/GlaxoSmithKline, Wellbutrin SR®/GlaxoSmithKline."

3. MEDICATION GUIDE

a. Who should not take bupropion hydrochloride extended-release tablets (XL)? Do not take bupropion hydrochloride extended-release tablets if you:

Second bullet, revise to "...**are taking ZYBAN® (used to help people stop smoking) or any other medicines that contain bupropion hydrochloride, such as WELLBUTRIN® (bupropion hydrochloride tablets) or WELLBUTRIN SR® (bupropion hydrochloride extended-release tablets (SR).** Bupropion is the same active ingredient that is in bupropion hydrochloride extended-release tablets (XL)."

b. What should I tell my doctor before using bupropion hydrochloride extended-release tablets (XL)? Second and third bullet, revise "bupropion hydrochloride extended-release tablets" to "bupropion".

c. Place "How should I store bupropion hydrochloride extended-release tablets (XL)?" on a separate paragraph.

d. Please add Zyban®, Wellbutrin® and Wellbutrin SR® in your list of registered trademarks and their manufacturers.

Please revise your label and labeling as described above and submit electronically. The immediate container labels and carton labeling may be submitted either electronically or in hard copy.

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

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

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

ARCHIVAL COPY

September 15, 2006

N/AB

Gary Buehler, R.Ph.
Director, Office of Generic Drugs
Center for Drug Evaluation and Research (HFD-600)
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Bioequivalency Amendment

RE: Abbreviated New Drug Application #77-715
Bupropion Hydrochloride Extended-Release Tablets, USP
150 mg and 300 mg

Dear Mr. Buehler:

Watson Laboratories, Inc. (Watson) is submitting this Bioequivalency Amendment to provide a complete response to the OGD's fax comments dated July 12, 2006 (see attached) regarding Bupropion Hydrochloride Extended-Release Tablets, USP, ANDA #77-715. FDA comments appear in bold and italic font below. Watson's response immediately follows each comment.

Bioequivalence Deficiencies:

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

1. ***Based on the submitted dissolution results, your proposed dissolution specifications are not acceptable. Please acknowledge the acceptance of the following dissolution method and specifications for your test product:***

   The dissolution testing should be conducted in 900 mL of 0.1 N HCl at 37 °C using USP Apparatus 1 (basket) at 75 rpm. The test products should meet the following specifications:

   2 hours:
   4 hours: [redacted] b(4)
   8 hours: [redacted]
   12 hours:

   Watson confirms that future dissolution testing of Bupropion Hydrochloride Extended-Release Tablets, USP shall be conducted per the FDA-recommended dissolution method and specifications given above. The blank drug product Specification and Quality Assurance Reports (SQAR) have been revised to

311 Bonnie Circle, Corona, CA 92880 • Tel: 800/249-5499 • Website: www.watsonpharm.com

OGD's recommended specifications. Please refer to **EXHIBIT 1** for copies of the revised drug product SQARs, #RCBS-00002-04 (150 mg) and #RCBS-00010-02 (300 mg).

2. ***Due to concern of dose dumping for the drug product, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:***

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

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

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

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

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

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

   Per OGD's request, Watson conducted additional dissolution testing using both test and RLD products in various concentrations of ethanol in 0.1 N HCl.

   The summary of the data at 120 minutes is presented in **TABLE 1** (150 mg) and **TABLE 2** (300 mg) below:

TABLE 1: Percent Drug Release of 150 mg Bupropion HCl Extended-Release Tablets, USP in 0.1N HCl with various alcohol levels at 120 minutes (n=12 tablets per product).

Alcohol Level (% v/v)	Watson Bupropion HCl Extended-Release Tablets, USP, 150 mg (Lot #XT4L029, Mfg. Date: 12/04)			Wellbutrin® XL, 150 mg, (Lot #06E029P, Exp. Date: 08/07)		
	Mean (%)	Range (%)	% CV	Mean (%)	Range (%)	% CV
Test 1: 0%	2	0 to 5	87.4%	1	0 to 2	39.8%
Test 2: 5%	9	4 to 14	34.5%	3	1 to 7	78.6%
Test 3: 20%	23	17 to 29	17.2%	11	7 to 18	33.3%
Test 4: 40%	20	18 to 24	10.1%	16	13 to 18	8.5%

TABLE 2: Percent Drug Release of 300 mg Bupropion HCl Extended-Release Tablets, USP in 0.1N HCl with various alcohol levels at 120 minutes (n=12 tablets per product).

Alcohol Level (% v/v)	Watson Bupropion HCl Extended-Release Tablets, USP, 300 mg (Lot #XC5B013, Mfg. Date: 03/05)			Wellbutrin® XL, 300 mg, (Lot #06E002P, Exp. Date: 08/07)		
	Mean (%)	Range (%)	% CV	Mean (%)	Range (%)	% CV
Test 1: 0%	12	8 to 16	20.3%	4	2 to 11	68.6%
Test 2: 5%	20	12 to 28	22.0%	6	3 to 11	42.0%
Test 3: 20%	30	26 to 34	10.1%	13	10 to 17	17.3%
Test 4: 40%	22	18 to 36	22.5%	19	17 to 20	6.2%

The data summarized above demonstrate that the percent release rate for both 150 mg and 300 mg strengths of Watson's Bupropion Hydrochloride Extended-Release Tablets, USP in dissolution medium with various concentrations of alcohol increases marginally when compared to that in 0.1 N HCl dissolution medium without alcohol. In addition, the observed increase in the percent release rates for both Watson's Bupropion Hydrochloride Extended-Release Tablets, USP and Wellbutrin® XL Tablets are very similar.

The individual, mean, range and %CV data for the requested four dissolution tests with 0%, 5%, 20%, and 40% (v/v) alcohol for Watson's Bupropion Hydrochloride Extended-Release Tablets, USP 150 mg (Lot #XT4L029) and 300 mg (Lot #XC5B013) and Wellbutrin® XL Tablets, 150 mg (Lot #06E029P) and 300 mg (Lot #06E002P) are presented in **EXHIBIT 2**.

Watson believes that the information provided in this amendment is sufficient to address the Agency's concern on dose dumping for Watson's Bupropion Hydrochloride Extended-Release Tablets, USP in 0.1 N HCl dissolution medium with varying concentrations of alcohol.

Watson encloses one volume each of one (1) Archival and one (1) Review Copy.

Finally, it is Watson's view that this response adequately addresses each of the cited comments. Please contact me by telephone at 951-493-5452 or by fax at 951-493-4581 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Christine M. Woods
Associate Director, Regulatory Affairs

ARCHIVAL COPY

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

August 11, 2006

Gary Buehler, R.Ph.
Director
OGD/CDER/FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
N-AF

Labeling Amendment

RE: Abbreviated New Drug Application #77-715
Bupropion Hydrochloride Extended-Release Tablets, USP
150 mg and 300 mg

ELECTRONIC DRAFT LABELING INCLUDED

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting this Labeling Amendment to provide a complete response to the OGD's fax comments dated May 1, 2006 (see attached) regarding Bupropion Hydrochloride Extended-Release Tablets, USP, ANDA #77-715.

Please note that the innovator has received approval for a new indication and new labeling for the reference product, Wellbutrin XL®, since the time Watson received OGD's fax comments dated May 1, 2006. Based on a phone conversation between Anh Vu, OGD, Labeling Review Branch, and Janie Gwinn of Watson Laboratories, held on July 27, 2006, the labeling submitted in this Labeling Amendment addresses not only the FDA comments dated May 1, 2006, but also updates Watson's labeling to match the innovator labeling, except (as described below) that information relating to the new indication exclusivity (I-497) will not be included in Watson's labeling until such exclusivity has expired. In addition, Watson's labeling is updated to address all comments from the letters and labels posted on the FDA website on June 12, 2006 and July 3, 2006 for Wellbutrin XL®.

A new Exclusivity Statement indicating that Watson's labeling will not include the new indication (I-497, Seasonal Major Depressive Episodes in Patients with Seasonal Affective Disorder) until the Exclusivity expires, is provided as **EXHIBIT 1.**

FDA comments appear in bold and italic font below. Watson's response immediately follows each comment.

RECEIVED
AUG 14 2006
OGD / CDER

Labeling Deficiencies:

1. ***CONTAINER (bottles of 30s, for 150 mg strength, bottles of 30s and 1000s for the 300 mg strength)***

   a. ***In order to ensure that safety information is provided with all antidepressant products, we encourage you to distribute the products only 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; however, if you choose to market your product in bulk packages, please describe how many medication guides and patient information leaflets will be provided and how you plan to ensure that the medication guides and patient information leaflets arrive at the pharmacy with your product.***

   Please note that, per the latest approved Wellbutrin XL® labeling, patient information is not provided as a separate Patient Information Leaflet, but is contained instead in the text of the Medication Guide.

   Watson's unit-of-use (*e.g.* 30-count) containers have one Medication Guide/Patient Information Leaflet affixed to the container, which has a child-resistant closure.

   Additionally, Watson does choose to market in bulk packages (*e.g.,* 1,000-count bottles) and has a standard procedure in place for ensuring that sufficient Medication Guides/Patient Information Leaflets are provided for unit-of-use containers. Specifically, for each 1,000-count bottle that is ordered, Watson will ship a tear-off pad of 50 Medication Guides/Patient Information Leaflets per tear-off pad.

   b. ***Principal display panel- revise the established name to read: "BuPROPion Hydrochloride Extended-Release Tablets USP (XL)" [add "(XL)"].***

   The established name on the principal display panel has been revised to read "BuPROPion Hydrochloride Extended-Release Tablets USP (XL)" as requested.

c. Add the following statement to the container label, preferably on the principal display panel if space permits: "ATTENTION: Dispense with Medication Guide".

The statement "ATTENTION: Dispense with Medication Guide" has been added to the principal display panel as requested.

d. Dosage: add "Take one tablet daily or as directed by physician."

The statement "Take one tablet daily or as directed by physician." has been added to the Dosage section on the side panel.

e. Revise "Each Tablet contains:" to "Each Extended-Release Tablet contains:".

The phrase "Each tablet contains" has been revised to "Each Extended-Release Tablet contains" as requested.

f. Add "Zyban® is a registered trademark of GlaxoSmithKline." to the side panel of the container label.

The statement "Zyban® is a registered trademark of GlaxoSmithKline" has been added to the side panel of the container label as requested.

g. Please ensure your labels comply with the bar code requirements prior to full approval.

Watson Laboratories is submitting draft labeling for this amendment; its final printed labels will comply with the bar code requirements prior to full approval.

h. Please ensure that your container labels will print in color in both PDF and Word files. Currently, only the Word files print in color. You are reminded that your labels submitted in electronic format must be actual size, color and clarity.

The previously submitted PDF files printed in color with Watson's color printers. For this submission, Watson checked this functionality for its container labels on multiple computers and color printers at Watson and they printed successfully in color; Watson hopes that they will print in color for you.

Although Watson is submitting draft container labels in this amendment, the container labels have been resized to address the final height and width proportionality of the container labels. Watson's final printed labeling amendment will provide container labels in actual size, color and clarity.

2. ***INSERT***

a. ***Update your labeling based on the attached approved labeling for the reference listed drug, Wellbutrin XL, approved February 28, 2006. Your package insert should be submitted in portable document formal (PDF).***

Watson has updated its labeling based on the reference listed drug (RLD) Wellbutrin XL® labeling approved February 28, 2006, as supplied by the agency. Watson's labeling was further updated based on the Wellbutrin XL® labeling approved June 12, 2006, noting that information relating to the Exclusivity for Prevention of Seasonal Major Depressive Episodes in Patients with Seasonal Affective Disorder (I-497) will not be included in Watson's labeling until such exclusivity has expired. The side-by-side comparisons of Watson's proposed draft Package Insert and Medication Guide/Patient Information Leaflet with the previously submitted versions of Watson's labeling (dated July 2005), are provided; all changes resulting from the updated RLD labeling are annotated and explained in the side-by-side comparisons. For reviewer convenience, Watson has provided an electronic copy of the RLD labeling approved on February 28, 2006, as well as that approved on June 12, 2006.

b. ***PRECAUTIONS:***
PREGNANCY: TERATOGENIC EFFECTS, delete all references to [redacted] b(4)

All references to [redacted] have been deleted from Watson's labeling.

3. ***MEDICATION GUIDE***

c. ***HOW TO TRY TO PREVENT SUICIDAL THOUGHTS AND ACTIONS:***

i. ***Third paragraph, fifth bullet, change (see other side) to (see Section 3).***

"(see other side)" has been changed to "(see Section 3)" as requested.

ii. Fourth paragraph, delete the extra space between the "s" and "i" in "visits".

This extra space was generated when converting the Word format document to the PDF format document, Watson has checked to ensure this did not occur again.

d. THERE ARE BENEFITS AND RISKS WHEN USING ANTIDEPRESSANTS: Replace the symbol ™ with ® for Prozac®, Zoloft® and Anafranil®.

In the "THERE ARE BENEFITS AND RISKS WHEN USING ANTIDEPRESSANTS:" section the symbol ™ has been replaced with ® for Prozac®, Zoloft® and Anafranil® as requested.

e. IS THIS ALL I NEED TO KNOW IF MY CHILD IS BEING PRESCRIBED AN ANTIDEPRESSANT?:
Add a new paragraph to this section to acknowledge the registered trademarks as follows: Prozac® is a registered trademark of Eli Lilly and Company, Zoloft® is a registered trademark of Pfizer Pharmaceuticals, and Anafranil® is a registered trademark of Mallinckrodt Inc.

The registered trademarks were acknowledged by adding the following statement in the Medication Guide:

Prozac® is a registered trademark of Eli Lilly and Company, Zoloft® is a registered trademark of Pfizer Pharmaceuticals, Luvox® is a registered trademark of Solvay Pharmaceuticals, and Anafranil® is a registered trademark of Mallinckrodt Inc.

Please note, in the letter posted on the FDA website on July 3, 2006 regarding labeling for Wellbutrin XL® (bupropion hydrochloride) Extended-Release Tablets, Watson interprets the following to be relevant to the bottle labels.

NDA 21-515/S-014 dated October 18, 2005

- These supplements to the IR, SR, and XL formulations provide for a larger and more prominent font to state the number of times a day the bupropion formulation should be taken. This was changed to address the potential for confusion among different modified-release bupropion products.

Thus, the font size for "Once Daily" on the principal display panel has been increased, and the font size on the side panel for the "Dosage" section has been increased and formatted to bold for all bottle labels submitted in this Labeling Amendment.

Please revise your label and labeling as described above and submit electronically. The immediate container labels and carton labeling may be submitted either electronically or in hard copy.

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/SPL2alG_20051006_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.

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

Watson has revised its labeling as requested. In accordance with 21 C.F.R. § 314.94(d)(ii) as effected June 8, 2004, which required the submission of electronic labeling, Watson provides one (1) computer CD ROM containing Watson's proposed labeling in MS Word and Adobe PDF format. The CD ROM is located at the front of the blue Archival Copy of this submission. Please refer to the Table of Contents contained on the enclosed CD ROM for access to the files and directory pathways.

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

Watson acknowledges that it may be necessary to revise its labeling subsequent to

approved changes for the reference listed drug.

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.

As required by 21 C.F.R. § 314.94(a)(8)(iv), Watson has included the side-by-side comparison of its proposed draft Container labels, Package Insert, and Medication Guide/Patient Information Leaflet with the previously submitted versions of Watson's labeling (container labels dated April 2005, Package Insert/Patient Information Leaflet dated July 2005, and Medication Guide dated April 2005), with all differences annotated and explained.

Watson encloses one volume each of one (1) Archival and one (1) Review Copy.

Finally, it is Watson's view that this response adequately addresses each of the cited comments. Please contact me by telephone at 951-493-5443 or by fax at 951-493-4581 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Janie M. Gwinn, B.Sc.
Director, Regulatory Affairs

BIOEQUIVALENCY AMENDMENT

ANDA 77-715

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: Watson Laboratories, Inc. TEL: 951-493-5452

ATTN: Christina M. Woods FAX: 951-493-4581

JUL 12 2006

FROM: Aaron Sigler PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on May 19, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Extended-release Tablets, USP, 150 mg.

Reference is also made to your amendment dated March 28, 2006.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 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

ANDA: 77-715 APPLICANT: Watson Laboratories, Inc.

DRUG PRODUCT: Bupropion Hydrochloride Extended Release Tablets, USP 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:

1. Based on the submitted dissolution results, your proposed dissolution specifications are not acceptable. Please acknowledge the acceptance of the following dissolution method and specifications for your test product:

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

   2 hours:
   4 hours:
   8 hours:
   12 hours:

   b(4)

2. Due to concern of dose dumping for the drug product, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

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

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

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

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

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

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

Sincerely yours,

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

ANDA 77-715 Bupropion HCl ER TABLETS

U.S. Department of Health and Human Services
FDA Food and Drug Administration

Fax Cover Sheet

Public Health Service
Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling & Program Support
Labeling Review Branch
Rockville, Maryland 20855

To: Christine M. Woods DATE: 5/1/06

Phone: 951-493-5452 Fax: 951-493-4581

SUBJECT: Labeling comments for 77-715 (Bupropion Hydrochloride Extended-Release Tablets USP, 150 mg and 300 mg)

From: Ann Vu

Phone: (301) 827-7642 Fax:
Number of Pages: three
(Including Cover Sheet)

Comments: Please email me at thuyanh.vu@fda.hhs.gov for the most recent RLD labeling.

---

*This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, this communication is not authorized. If you have received this document in error, immediately notify us by telephone and return it to us at the above address by mail. Thank you.

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

ANDA Number:	77-715
Date of Submissions:	5/19/05 (original submission); 7/28/05 (addition of 300 mg strength)
Applicant's Name:	Watson Laboratories, Inc.
Established Name:	Bupropion Hydrochloride Extended-release Tablets USP, (XL) 150 mg and 300 mg (Once Daily)

Labeling Deficiencies

1. CONTAINER (bottles of 30s, for the 150 mg strength, bottles of 30s and 1000s for the 300 mg strength)

   a. In order to ensure that safety information is provided with all antidepressant products, we encourage you to distribute the products only 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. However, if you choose to market your product in bulk packages, please describe how many medication guides and patient information leaflets will be provided and how you plan to ensure that the medication guides and patient information leaflets arrive at the pharmacy with your product.

   b. Principal display panel- revise the established name to read: "BuPROPion Hydrochloride Extended-Release Tablets USP (XL)" [add "(XL)"].

   c. Add the following statement to the container label, preferably on the principal display panel if space permits: "ATTENTION: Dispense with Medication Guide".

   d. Dosage: add "Take one tablet daily or as directed by physician."

   e. Revise "Each Tablet contains:" to "Each Extended-Release Tablet contains:".

   f. Add "Zyban® is a registered trademark of Glaxo SmithKline." to the side panel of the container label.

   g. Please ensure your labels comply with the bar code requirements prior to full approval.

   h. Please ensure that your container labels will print in color in both PDF and Word files. Currently, only the Word files print in color. You are reminded that your labels submitted in electronic format must be actual size, color and clarity.

2. INSERT

   a. Update your labeling based on the attached approved labeling for the reference listed drug, Wellbutrin XL, approved February 28, 2006. Your package insert should be submitted in portable document format (PDF).

   b. PRECAUTIONS:
   PREGNANCY: TERATOGENIC EFFECTS, delete all references to [redacted] b(4)

3. MEDICATION GUIDE

   a. HOW TO TRY TO PREVENT SUICIDAL THOUGHTS AND ACTIONS:
      i. Third paragraph, fifth bullet, change (see other side) to (see Section 3).
      ii. Fourth paragraph, delete the extra space between the "s" and "I" in "visits".

b. THERE ARE BENEFITS AND RISKS WHEN USING ANTIDEPRESSANTS: Replace the symbol ™ with ® for Prozac®, Zoloft® and Anafranil®.

c. IS THIS ALL I NEED TO KNOW IF MY CHILD IS BEING PRESCRIBED AN ANTIDEPRESSANT?: Add a new paragraph to this section to acknowledge the registered trademarks as follows: Prozac® is a registered trademark of Eli Lilly and Company, Zoloft® is a registered trademark of Pfizer Pharmaceuticals,and Anafranil® is a registered trademark of Mallinckrodt Inc.

Please revise your label and labeling as described above and submit electronically. The immediate container labels and carton labeling may be submitted either electronically or in hard copy.

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_20051006_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.
To assist in our review, we request that labeling also be submitted in MS Word format.

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

Attachment: RLD insert labeling

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

ARCHIVAL COPY

ORIG AMENDMENT
N-000 AC

March 28, 2006

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-600)
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Telephone CMC Amendment

RE: ANDA #77-715
Bupropion HCl Extended-Release Tablets, USP

RECEIVED
MAR 29 2006
OGD / CDER

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting this Telephone CMC Amendment to provide a complete response to the OGD's faxed comments of March 20, 2006 (see attached) in support of Bupropion HCl Extended-Release Tablets, ANDA #77-715. The FDA comment appears in bold italic font below, with our response immediately following the comment.

A. Deficiencies

1. ***Please commit to updating the drug product specifications to incorporate the drug release testing requirements as specified by the Division of Bioequivalence when requested by DBE.***

   Watson commits to updating the drug product specifications to incorporate the drug release testing requirements as specified by the Division of Bioequivalence when it is requested by DBE.

2. ***Please clarify what role the [redacted] bags will play in the container/closure system for the 150 and 300 mg strengths. Will the bags be in contact with the drug product?***

   b(4)

   The [redacted] bags are identified as In-Process Containers in the Major Amendment, Addition of 300 mg Product Strength, submitted July 27, 2005. As such they are used between steps in the manufacturing process, such as after

final packaging configuration(s). Quality and safety information regarding these [redacted] bags was provided on pages 710-715 and 730-743, respectively, of the Major Amendment, dated July 27, 2005. The [redacted] bags play no role in the final container/closure system. Because the drug product is tested and released after packaging in the final container/closure system, any effect these [redacted] bags may have on the drug product is evaluated. b(4)

3. ***There appears to be a discrepancy in the limit for RSD in the in-process controls on pp.661 and 655 of vol.3.1. Please explain.***

   The Blend Uniformity RSD limit of [redacted]% in the in-process controls (Data Sheet for Blend Uniformity Testing) on page 661 is the protocol specification for the Exhibit Batch only. The Blend Uniformity RSD of NMT [redacted]% on page 655 is the regulatory specification for process validation of post approval production batches.

4. ***Please verify that the reference standards used in the testing of the 300 mg strength of the drug product are the same as those used for the 150 mg strength in the original ANDA. If they are not the same please provide details with regard to source, lot number and expiration date.***

   The USP reference standard used for the testing (In-Process and Release) of the 300 mg strength product is the same used for the 150 mg strength in the original ANDA. This information is provided on page 86 of the original ANDA submitted May 19, 2005. The reference standard used was the USP reference standard for Bupropion Hydrochloride, Lot F0C123. This lot expired February 2006. The current USP reference standard, Lot G0E048, is being used for stability testing.

5. ***Please provide sample information (lot number) used in the analytical methods for the 300 mg strength.***

   For the typical chromatograms provided in the analytical methods in the Major Amendment, Addition of 300 mg Product Strength, dated July 27, 2005, the "Sample Name" contains the lot number. For example for the typical chromatograms for: assay (Figure 4) the lot number was Lot #F-0003-098; for Chromatographic Purity (Figure 6) the lot number was Lot #F0003080B; and for [redacted] content (Figure 8) the lot number was Lot #F-0003-098-1. b(4)

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

1. Please submit all available room temperature stability data.

Please see **EXHIBIT #1** for Controlled Room Temperature Stability Data through 12 months for the 150 mg strength (ANDA Exhibit Batch #XT4L029) and through 9 months for the 300 mg strength (ANDA Exhibit Batch #XC5B013).

We have enclosed one (1) Archival and one (1) Review copy. In accordance with 21 CFR §314.96(b), one (1) field copy of the application will be forwarded to the manufacturing facility's district office, in Buffalo, NY. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copy of this amendment.

Please contact me by telephone at (951) 493-5446 or by fax at (951) 493-4581 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Ernest Lengle, Ph.D.
Executive Director, Regulatory Affairs
Enclosure

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

March 23, 2006

XP

Gary Buehler, R.Ph.
Director, Office of Generic Drugs
Center for Drug Evaluation and Research (HFD-600)
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Patent Amendment

RE: ANDA #77-715
Bupropion HCl Extended-Release Tablets, USP (150 mg and 300 mg)
PATENT NOTIFICATION

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application, ANDA #77-715 for Bupropion Hydrochloride Extended-Release Tablets, USP.

Watson Laboratories, Inc. ("Watson") is amending the subject application as follows:

- in accordance with 21 C.F.R. §314.95(b) and §314.95(e), to provide documentation that notice of Watson's Paragraph IV Certification against U.S. Patent #6,096,341 ("the '341 patent") and Patent #6,143,327 ("the '327 patent") were provided and received

Watson certifies that on July 21, 2005 and July 28, 2005 it sent notice of its Paragraph IV Certification against the '341 and '327 patents to Biovail Laboratories, Inc. and SmithKline Beecham Corp, dba GlaxoSmithKline (hereafter referred to as GlaxoSmithKline) in accordance with 21 C.F.R. §314.95(a). GlaxoSmithKline is the licensee of the '341 and '327 patents from Biovail and is the holder of the approved application under §505(b) of the Federal Food, Drug and Cosmetic Act for the listed drug, Wellbutrin XL®. Watson is seeking approval of a generic version of Wellbutrin XL®. The content of Watson's notice letter complied with the requirements set forth in 21 C.F.R. §314.95(c). The notice to Biovail Laboratories, Inc. was sent via Registered Mail, return receipt requested and the notice to GlaxoSmithKline was sent via Registered mail, return receipt requested.

As proof of receipt of notification pursuant to 21 C.F.R. §314.95(e), Watson encloses the following documentation:

As proof of receipt of notice of the '341 and '327 patents by Biovail Laboratories, Inc. (Notices for each strength [150 and 300 mg] were sent separately.) (Please see **EXHIBIT 1**):

- Copy of the International Registered Mail label to Biovail Laboratories, Inc., St. Michael, Barbados (July 21, 2005 post for 150 mg strength)
- Copy of International Return Receipt indicating delivery on August 19, 2005 (For 150 mg strength)
- Copy of the International Registered Mail label to Biovail Laboratories, Inc., St. Michael, Barbados (July 28, 2005 post for 300 mg strength)
- Please note: the Return Receipt for the International Registered Mail originally sent to Biovail Laboratories, receipt was not returned, provided is a copy of the Return Receipt sent to Biovail Laboratories, Inc.

As proof of receipt of notice of the '341 and '327 patents by GlaxoSmithKline. (Notices for each strength [150 and 300 mg] were sent separately.) (Please see **EXHIBIT 2**):

- Copy of the Domestic Registered Mail label to GlaxoSmithKline, Research Triangle Park, NC (July 21, 2005 post for 150 mg strength)
- Copy of the Domestic Return Receipt indicating delivery on July 25, 2005 (For 150 mg strength)
- Copy of the Domestic Registered Mail label to GlaxoSmithKline, Research Triangle Park, NC (July 28, 2005 post for 300 mg strength)
- Copy of the Domestic Return Receipt indicating delivery on August 2, 2005 (For 300 mg strength)

Additionally, we have received notification from Biovail Laboratories International SRL (Biovail), of the filing of a lawsuit for infringement of the United States Patents #6,096,341 and #6,143,327. The complaint was filed in the Southern District of New York on September 6, 2005 and assigned Civil Action No. 05-CV-7799. A copy of this complaint is included for your reference (**EXHIBIT 3**).

We have enclosed one volume each of (1) Archival and one (1) Review copy. Should you have any questions concerning this amendment, please contact me by telephone at (951) 493-5446 or by fax at (951) 493-4581.

Sincerely,

Ernest Lengle, Ph.D.
Director, Regulatory Affairs
Enclosure

FDA FAX

ANDA 77-715

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: Watson Laboratories, Inc. TEL: 951-493-5452

ATTN: Christina M. Woods FAX: 951-493-4581

FROM: Thomas Hinchliffe PROJECT MANAGER: (301) 827-5771

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated May 19, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Extended-release Tablets, USP, 150 mg.

Pages (including cover): 2

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: 77-715 APPLICANT: Watson Laboratories Inc.
DRUG PRODUCT: Bupropion Hydrochloride Extended Release Tablets USP, 150 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 commit to updating the drug product specifications to incorporate the drug release testing requirements as specified by the Division of Bioequivalence when requested by DBE.

2. Please clarify what role [redacted] will play in the container/closure system for the 150 and 300 mg strengths. Will the [redacted]gs be in contact with the drug product? b(4)

3. There appears to be a discrepancy in the limit for RSD in the in-process controls on pp. 661 and 655 of vol. 3.1. Please explain.

4. Please verify that the reference standards used in the testing of the 300 mg strength of the drug product are the same as those used for the 150 mg strength in the original ANDA. If they are not the same, please provide details with regard to source, lot number and expiration date.

5. Please provide sample information (lot number) used in the analytical methods for the 300 mg strength.

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

1. Please submit all available room temperature stability data.

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

ARCHIVAL COPY

December 06, 2005

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-600)
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
W/A C

Major CMC Amendment

RE: ANDA #77-715
Bupropion HCL Extended-Release Tablet, USP
150 mg and 300 mg

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting this Major CMC Amendment to provide a complete response to OGD's faxed comments of November 03, 2005 (see attached) in support of Bupropion HCL Extended-Release Tablets, USP, ANDA #77-715. OGD's comments appear in bold italic font below, with our response immediately following each comment.

A. Deficiencies:

1. ***Please provide cGMP certification for the Watson Laboratories site located in Corona, CA.***

   Watson's cGMP Certification is not site specific; it certifies all sites including both the Carmel, New York facility and the Corona, California facility. I spoke with our Project Manager, Thomas Hinchliffe, on November 14, 2005 and he said this was an acceptable practice. The cGMP certification for the 150 mg product was submitted on Page 358 of the original ANDA and that for the 300 mg product was submitted on Page 221 of the Major Amendment dated July 27, 2005. Both cGMP Certifications are presented in **EXHIBIT #1** for the reviewer's reference.

2. ***Please provide chemical structures for all impurities contained in both the drug substance and the drug product.***

   The three Related Substances listed below are common to both the API and Finished Product and all have acceptance limits specified in the Drug Substance Specification as well as in the Drug Product Specification.

RECEIVED
DEC 0 7 2005
OGD / CDER

CHEMICAL NAME
[redacted]

b(4)

Please see **EXHIBIT #2** for the chemical structures of each of these three Related Substances.

3. ***Please provide more information with regard to the two sites of manufacture of the drug substance by [redacted] The addresses and cGMP certificates for both sites should be provided.***

Bupropion HCl API is produced by [redacted] at either of two manufacturing sites in [redacted] The addresses for both sites are provided on [redacted] DMF Letter of Authorization presented on Page 63 of the original application and below.

b(4)

API Manufacturing Sites:

- [redacted]
- [redacted]

[redacted] Bupropion HCl Lot # [redacted] (Watson's Lot #E1263AE) was used to manufacture both the 150 mg and 300 mg ANDA Exhibit Batches, although we filed both [redacted] manufacturing sites in the ANDA and provided a non-site specific cGMP Statement of Commitment (Page 67 of original ANDA) for "all ([redacted]) facilities" as well as the most recent Establishment Inspection Report for each of the two manufacturing sites (Page 69 and 70 of original ANDA). Please see **EXHIBIT #3** for [redacted] DMF Letter of Authorization, cGMP Statement of Commitment and Establishment Inspection Reports for their two API manufacturing sites.

b(4)

4. ***Please indicate on the COA for the drug substance which [redacted] site was used in the synthesis.***

The API manufacturer's Certificate of Analysis lists the address of the manufacturing site of the respective API lot. Please see **EXHIBIT #4** for [redacted] API Certificate of Analysis for Bupropion HCl Lot [redacted] (Watson's Lot #E1263AE), which was previously presented on Page 73 of the original ANDA and specifies the [redacted] manufacturing facility.

b(4)

5. ***Please provide comparison testing data for the in-house and USP methods for Assay and Related substances in the drug substance and drug product.***

   Please see **EXHIBIT #5** for comparison testing data for the in-house and USP methods for Assay and Related Substances in the Drug Substance and Drug Product.

6. ***Please update the drug product specifications to incorporate the drug release testing requirements as specified by the Division of Bioequivalence.***

   I spoke with our Bioequivalence Reviewer, Christina Thompson, on November 14, 2005 regarding this comment and she noted that DBE did not specify a Drug Release Specification and cannot until the Comparative Dissolution Testing that was requested by DBE on October 05, 2005 is received and evaluated. I later spoke with our Project Manager, Thomas Hinchliffe, on November 14, 2005 and he agreed that Watson's Drug Product Specifications need not be updated until requested and specified by DBE.

   Watson provided Single Media Dissolution Profiles for each of the two strengths of the Test and Reference Products (water, acetate buffer at pH 4.5 and phosphate buffer at pH 6.8) on Pages 47-54 of an amendment submitted on July 27, 2005 and again as Exhibit #1 of our October 12, 2005 response to OGD's faxed Bioequivalency Comments of October 05, 2005. For the convenience of the reviewer, these profiles are presented again as **EXHIBIT #6** along with a memo correcting a typographical error describing the media used for pH 6.8 phosphate buffer dissolution profiles of 300 mg Test and Reference Batches.

7. ***The COA for the finished product provided on p. 877 of the ANDA has RCBT-00006-00 listed as the method for all Tests. Please explain why the Test Method is the same when all of the Tests are different.***

   The comprehensive Finished Product Test Method RCBT-00006-02 (for 150 mg) is presented in **EXHIBIT #7** and contains all methods necessary to analyze all required test attributes as listed on the Finished Product Specification and Certificate of Analysis. Because Test Method RCBT-00006-02 contains all Finished Product methods necessary, it is listed on the Certificate of Analysis as the Test Method utilized after each Test Attribute. The same situation holds true for the 300 mg Finished Product Test Method RCBT-00013-01, which is also is presented in **EXHIBIT #7.**

8. ***Please change the protocol to provide controlled room temperature data for the exhibit batch out to the proposed expiration date.***

   We have revised the Controlled Room Temperature Research and Development Stability Evaluation Report for the 150 mg ANDA Exhibit Batch #XT4L029 (Protocol #RDSPCOR0160403) to show columns for 12, 18, 24 and 36 months stability data. Although the proposed expiration period for this product is —months, this stability study continues through 36 months for information only. Please see **EXHIBIT #8** for the revised 150 mg Research and Development Stability Evaluation Report. b(4)

9. ***Please revise the expiration date to include the statement that calculation of the expiration date begins when the API is added to the blend.***

   Please see **EXHIBIT #9** for the Proposed Expiration Period Statement, which has been revised to note that calculation of the expiration date begins when the API is first added or mixed with another ingredient.

10. ***Please remove "300 mg" from the entire text of the ANDA with regard to the drug product, analytical methods and validation.***

    On July 27, 2005, we amended the 300 mg strength to ANDA #77-715. In anticipation of this addition, our Drug Product Test Methods were developed and validated to include both the 150 and 300 mg strengths. Because our application includes the 300 mg strength, we believe it is appropriate for the Test Methods and Validation Reports to also include this strength and we therefore respectfully decline to remove "300 mg" from the entire text of the ANDA with regard to the Drug Product Analytical Methods and Validations.

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

1. ***Please submit all available room temperature stability data.***

   Please see **EXHIBIT #8** for Controlled Room Temperature Stability Data through 9 months for the 150 mg strength (ANDA Exhibit Batch #XT4L029) and through 6 months for the 300 mg strength (ANDA Exhibit Batch #XC5B013). Although the proposed expiration period for this product is — months, these stability studies continue through 36 months for information only. b(4)

2. ***We acknowledge your amendment dated July 27, 2005 for the addition of a new strength. This amendment will be considered a major amendment and will be reviewed in the second cycle, after you have responded to the above deficiencies.***

   We acknowledge that you have received our July 27, 2005 Amendment to add the 300 mg strength and that it will be reviewed in the second cycle, after you receive this amendment responding to the comments dated November 03, 2005.

Additionally, we have taken this opportunity to provide, in **EXHIBIT #10**, a corrected footnote for [redacted] in our 150 and 300 mg Components and Composition Statements and Proportionality Data Tables. b(4)

We have enclosed one (1) Archival and one (1) Review Copy. In accordance with 21 CFR §314.96(b), one (1) Field Copy of this CMC Amendment will be forwarded to the manufacturing facility's district office, in Buffalo, NY. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the Archival and Review Copies of this Amendment.

We trust the information submitted in this CMC Amendment is sufficient for this application to be evaluated. Please contact me by telephone at 951-493-5452 or by facsimile at 951-493-4581 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Christine M. Woods
Associate Director, Regulatory Affairs

2.1

MAJOR AMENDMENT

ANDA 77-715

NOV 0 3 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: Watson Laboratories, Inc.

TEL: 951-493-5452

ATTN: Christina M. Woods

FAX: 951-493-4581

FROM: Thomas Hinchliffe

PROJECT MANAGER: (301) 827-5771

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated May 19, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Extended-release Tablets, USP, 150 mg.

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 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 will be 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:
FDA's Office of Generic Drugs is now accepting and encouraging electronic ANDA submissions.

NOV 0 3 2005

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-715 APPLICANT: Watson Laboratories Inc.

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

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1) Please provide cGMP certification for the Watson Laboratories site located in Corona, CA.

2) Please provide chemical structures for all impurities contained in both the drug substance and the drug product.

3) Please provide more information with regard to the two sites of manufacture of the drug substance by [redacted] The addresses and cGMP certificates for both sites should be provided. b(4)

4) Please indicate on the COA for the drug substance which [redacted] site was used in the synthesis.

5) Please provide comparison testing data for the in-house and USP methods for Assay and Related substances in the drug substance and drug product.

6) Please update the drug product specifications to incorporate the drug release testing requirements as specified by the Division of Bioequivalence.

7) The COA for the finished product provided on p. 877 of the ANDA has RCBT-00006-00 listed as the method for all Tests. Please explain why the Test Method is the same when all of the Tests are different.

8) Please change the protocol to provide controlled room temperature data for the exhibit batch out to the proposed expiration date.

9) Please revise the expiration date to include the statement that calculation of the expiration date begins when the API is added to the blend.

10) Please remove "300 mg" from the entire text of the ANDA with regard to the drug product, analytical methods and validation.

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

1) Please submit all available room temperature stability data.

2) We acknowledge your amendment dated July 27, 2005 for the addition of a new strength. This amendment will be considered a major amendment and will be reviewed in the second cycle, after you have responded to the above deficiencies.

Sincerely yours,

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

Memo

To: File

From: R&D Operations 10/12/05

CC:

Date: October 12, 2005

Re: Biowavier Dissolution Profile Results of Bupropion Hydrochloride ER Tablets, 300mg

---

There was a typographical error in the attached dissolution profile results for the above-mentioned sample. The dissolution media that were used for the Watson lot # XC5B013 and GlaxoSmithKline lot # 4ZP1099 should read as "pH 6.8 phosphate Buffer", instead of "pH 6.8 Acetate Buffer".

APPEARS THIS WAY
ON ORIGINAL

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

ARCHIVAL COPY

ORIG AMENDMENT
N/AB

October 12, 2005

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-600)
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED
OCT 13 2005
OGD/CDER

Bioequivalency Amendment

RE: ANDA #77-715
Bupropion HCL Extended-Release Tablet, USP
150 mg and 300 mg

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting this Bioequivalency Amendment to provide a complete response to the OGD's faxed comments of October 5, 2005 (see attached) in support of Bupropion HCL Extended-Release Tablets, USP, ANDA #77-715. The comments appear in bold italic font below, with our response immediately following each comment.

Comments:

1. ***Please conduct comparative dissolution testing using 12 units of each test and reference product in three other dissolution media (water, USP buffer media at pH 4.5, and 6.8) using USP Apparatus 1 (Basket) at 75 rpm. Sufficient sampling times are recommended to provide assurance against premature release of the drug (dose dumping) from the formulation.***

   Watson Laboratories filed a Major Amendment to ANDA #77-715 for the addition of the 300 mg product strength of Bupropion HCl Extended-Release Tablets, USP on July 27, 2005. On pages 47-54 of that amendment, Single Media Dissolution profiles were presented for each of the two strengths of the test and reference products (water, acetate buffer at pH 4.5 and phosphate buffer at pH 6.8). For the convenience of the reviewer these profiles are presented again as **Exhibit 1.**

   This study includes data from the 150 mg test and reference batches (Lots #XT4L029 and #04D014P, respectively) used in the Bioequivalence Studies

(Protocol #40431 for the fed study and Protocol #40432 for the fasted study) provided in the original ANDA, as well as from the 300 mg test and reference batches (Lots # XC5B013 and #4ZP1099, respectively) from the Biowaiver provided in the Amendment dated July 27, 2005.

Exhibit 2 includes a memo correcting a typographical error describing the media used for pH 6.8 phosphate buffer dissolution profiles of 300 mg test and reference batches, which are included here in **Exhibit 1** as well as the Major Amendment dated July 27, 2005.

We have enclosed one volume each of one (1) Archival and one (1) Review Copy.

We trust the information submitted in this Bioequivalency Amendment is sufficient for this application to be evaluated. Please contact me by telephone at (951) 493-5452 or by fax at (951) 493-4581 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Christine M. Woods
Associate Director, Regulatory Affairs

Enclosures

BIOEQUIVALENCY AMENDMENT

ANDA 77-715

OCT 05 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: Watson Laboratories, Inc. TEL: 951-493-5452

ATTN: Christine M. Woods FAX: 951-493-4581

FROM: Christina Thompson CT PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on May 19, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Extended-release Tablets, USP, 150 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached one 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:

OCT 05 2005

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-715 APPLICANT: Watson Laboratories, Inc.

DRUG PRODUCT: Bupropion HCl Extended Release Tablet, USP 150 mg

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 deficiency has been identified:

Please conduct comparative dissolution testing using 12 units of each test and reference product in three other dissolution media (water, USP buffer media at pH 4.5, and 6.8) using USP Apparatus 1 (Basket) at 75 rpm. Sufficient sampling times are recommended to provide assurance against premature release of the drug (dose dumping) from the formulation.

We acknowledge that you have provided in-vivo study data, dissolution data, and formulation data in the electronic format recommended by the Division of Bioequivalence.

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

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

REGULATORY AFFAIRS

FACSIMILE TRANSMITTAL SHEET

TO:
Iain Margand, Pharm. D.
Project Manager, OGD

FROM:
Christine M. Woods
Associate Director, Regulatory Affairs

COMPANY:
Office of Generic Drugs, CDER

DATE:
09/27/05

FAX NUMBER:
(301) 443-3847

TOTAL NO. OF PAGES INCLUDING COVER:
9

PHONE NUMBER:
(301) 827-5835

SENDER'S REFERENCE NUMBER:
ANDA #77-715

RE:
ANDA #77-715: Telephone Amendment
Bupropion HCl ER Tablets, USP
150 mg & 300 mg

YOUR REFERENCE NUMBER:

☐ URGENT ☑ FOR REVIEW ☐ PLEASE COMMENT ☐ PLEASE REPLY ☐ PLEASE RECYCLE

Dear Dr. Margand:

Please find attached our Telephone Amendment to OGD in response to the request for documentation we received on September 26, 2005 regarding ANDA #77-715, Bupropion HCl ER Tablets, USP.

If you require additional information, please contact me by telephone at (951) 493-5452, or by fax at (951) 493-4581.

Sincerely,

Christine M. Woods
Associate Director, Regulatory Affairs

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc

September 27, 2005

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-600)
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Telephone Amendment

RE: ANDA #77-715
Bupropion HCl Extended-Release Tablets, USP

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting this Telephone Amendment to provide a complete response to the telephone request of September 26, 2005 by Mr. Iain Margand, OGD Regulatory Project Manager, in support of Bupropion HCl Extended-Release Tablets, ANDA #77-715. The FDA comment appears in bold italic font below, with our response immediately following the comment.

Please provide original signed copies of the following documents listing both strengths of Bupropion HCl Extended-Release Tablets, USP, 150 mg & 300 mg:

- ***Generic Drug Enforcement Act Statement***
- ***Environmental Impact Statement***
- ***Outside Firms***
- ***Reprocessing Statement***

Please find enclosed original signed copies of the Generic Drug Enforcement Act Statement and Environmental Impact Statement for Bupropion HCl Extended-Release Tablets, USP, 150 mg & 300 mg, as requested. Please also find enclosed the Outside Firms Table (Section X.1) and the Reprocessing Statement (Section XI.4).

We have enclosed one (1) Archival and one (1) Review copy. In accordance with 21 CFR §314.96(b), one (1) field copy of the application will be forwarded to the manufacturing facility's district office, in Buffalo, NY. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copy of this amendment.

Please contact me by telephone at (951) 493-5452 or by fax at (951) 493-4581 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Christine M. Woods
Associate Director, Regulatory Affairs
Enclosure

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

ARCHIVAL COPY

July 28, 2005

ORIG AMENDMENT
N/HF

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

Labeling Amendment

RE: Abbreviated New Drug Application #77-715
Bupropion Hydrochloride Extended-Release, Film-Coated Tablets, USP
150 mg and 300 mg

ELECTRONIC DRAFT LABELING INCLUDED

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting this Amendment to our original Abbreviated New Drug Application #77-715 for Bupropion Hydrochloride Extended-Release, Film-Coated Tablets, USP, 150 mg. We inadvertently did not include the labeling CD for the Major Amendment dated July 27, 2005, so it is being provided in this Amendment.

In accordance with 21 CFR §314.94(d)(ii) as effected June 8, 2004 which required the submission of electronic labeling, Watson provides one (1) computer CD ROM containing Watson proposed labeling in Adobe PDF format. Side-by-side comparisons of Watson's proposed draft labeling and Wellbutrin XL® with all differences annotated and explained are also provided. The CD ROM is located at the front of the blue Archival Copy of this submission. Please refer to the Table of Contents contained on the enclosed CD ROM for file names and directory pathways.

We trust the information submitted is sufficient for this Amendment to be evaluated. Please contact me by telephone at 951-493-5452 or by fax at 951-493-4581 if you have any questions or if I can assist you with the review of this Amendment.

Sincerely,

Christine M. Woods
Associate Director, Regulatory Affairs

RECEIVED
JUL 29 2005
OGD/CDER

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

ARCHIVAL COPY

July 27, 2005

ORIG AMENDMENT

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

Major Amendment
Addition of 300 mg Product Strength

RE: Abbreviated New Drug Application #77-715
Bupropion Hydrochloride Extended-Release, Film-Coated Tablets, USP
150 mg and 300 mg

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting this Amendment to our original Abbreviated New Drug Application #77-715 for Bupropion Hydrochloride Extended-Release, Film-Coated Tablets, USP, 150 mg. We seek to add the 300 mg strength product to our application and have provided the relevant information in this Amendment. We have also taken this opportunity to provide updated or additional information on the 150 mg strength product.

We have included revisions to the following sections in this submission:

- Executive Summary
- Introduction to the ANDA
- Basis for ANDA Submission
- Patent Certification – Paragraph IV
- Exclusivity Statement
- Comparison Between ANDA Drug and Reference Listed Drug
- Labeling
- Certificate of Analysis for Wellbutrin XL® 300 mg
- Request for Waiver of *In-Vivo* Bioequivalence Studies for 300 mg
- Components and Composition Statement
- Proportionality Data Table
- Inactive Ingredients for Approved Drug Products Table
- cGMP Information
- Active Ingredient Information
- Inactive Ingredient Certificates of Analysis, Specifications and Methods

RECEIVED
JUL 28 2005
OGD/CDER

- Description of Manufacturing Facilities
- Description of Manufacturing Process
- Comparison of Manufacturing Process between ANDA Exhibit Batch and Proposed Production Batches
- Batch Manufacturing Records
- Batch Packing Records
- Comparison of Equipment for ANDA Exhibit Batch and Production Runs
- Packaging Materials Controls
- Controls for Finished Dosage Form
- Analytical Methods
- Stability of Finished Dosage Form
- Samples

These documents will serve as either replacements or additions to the original ANDA. We have provided herein only documents and data that are new, revised or have not previously been provided. Information and data that were previously provided and remain unchanged are not provided in this submission and in some cases are cross referenced from this Amendment back to the original ANDA. The attached table (**Table 1**) is a comprehensive list of all affected sections of the original ANDA included in this submission.

We have enclosed two volumes each of one (1) Archival and one (1) Review Copy and a single-volume (1) Bioequivalence Copy. In accordance with 21 CFR § 314.96(b), one (1) Field Copy of this Amendment will be forwarded to the manufacturing facility's district office in Buffalo, NY. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the Archival and Review Copies of this submission.

We trust the information submitted is sufficient for this Amendment to be evaluated. Please contact me by telephone at 951-493-5452 or by fax at 951-493-4581 if you have any questions or if I can assist you with the review of this Amendment.

Sincerely,

Christine M. Woods
Associate Director, Regulatory Affairs

ANDA 77-715

Watson Laboratories, Inc.
Attention: Christine M. Woods
311 Bonnie Circle
Corona, CA 92880

JUL 20 2005

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 also made to the telephone conversation dated July 14, 2005 and your correspondence dated July 18, 2005.

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

DATE OF APPLICATION: May 19, 2005

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 20, 2005

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 judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Thomas Hinchliffe
Project Manager
301-827-5849

Sincerely yours,

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

cc: ANDA 77-715
DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610
HFD-143/OIM/DRM

Endorsement:
HFD-615/M.Shimer, Chief, RSB _____ date 20 July 05
HFD-615/L.Zadecky, CSO _____ date 5-17-05

Word File \\CDSNAS\OGDS11\FIRMSNZ\LTRS&REV\77715.ack

F/T

ANDA Acknowledgment Letter!

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 77-715 **FIRM NAME:** WATSON LABORATORIES INC.

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: BUPROPION HYDROCHLORIDE
DOSAGE FORM: EXTENDED- RELEASE TABLETS
USP, 150 MG

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

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

Letter Date: MAY 19, 2005	**Received Date:** MAY 20, 2005
Comments: EC- 1 YES **On Cards:** YES **Therapeutic Code:** 2020100 ANTIDEPRESSANTS	
Archival Format: PAPER **Sections** I **(356H Sections per EDR Email)** **Review copy:** YES E-Media Disposition: YES SENT TO EDR Not applicable to electronic sections Field Copy Certification (Original Signature) YES	
Methods Validation Package (3 copies PAPER archive) **YES USP** (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 Zadecky, Leo** **Date 07/13/2005**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date:	**Date:** 19 July 05
ADDITIONAL COMMENTS REGARDING THE ANDA: **AGENT: Christine Woods 951 493 5452** Need: Environmental impact statement and GDEA with Original Signatures. See T-con dated 7-14-05	
Top 200 Drug Product:	

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES (Statement regarding Rx/OTC Status) RX YES	☒
Sec. II	**Basis for Submission** **NDA# : 21-515** Ref Listed Drug: WELLBUTRIN XL Firm: SMITHKLINE BEECHAM (GLAXOSMITHKLINE) 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: n/a	☒
Sec. III	**Patent Certification** 1. Paragraph: IV to the 341 and 327 patents 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** Complete Electronic 1. 4 copies of draft (each strength and container) or 12 copies of FPL *1 draft in edr* ***No Bulk labels*** 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 (	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) YES , 3454 **2. Request for Waiver of In-Vivo Study(ies): NA** **3. Formulation data same?**n/a **4. Lot Numbers of Products used in BE Study(ies):** *rld 04014p vs Batch xt4L029* 5. Study Type: **IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
Study Type	IN-VIVO PK STUDY(IES) (i.e., fasting/fed/sprinkle) FASTING AND FED ON 150 MG a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) yes, meets criteria on fast and fed studies b. EDR Email: Data Files Submitted: YES SENT TO EDR c. In-Vitro Dissolution: YES , 12 tab data provided on page 41	☒

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO a. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. Adhesion Study c. Skin Irritation/Sensitization Study	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. Solutions (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. Suspensions (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation yes pg 57 2. Inactive ingredients as appropriate yes see inactive ingredient justification	☒

ANDA 77-215 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.

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 XC 150 21515

15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.

18) Pull USP information. (USP ✓ yes ____ no)

19) Final Grammar review on letter.

20) Verify information in OGD Patent Tracking System.

21) EES slip.

22) Document in record book.

Signature [signature] date 19 July 05

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

ARCHIVAL COPY

July 15, 2005

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-600)
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MC

Telephone Amendment

RE: ANDA #77-715
Bupropion HCl Extended-Release Tablets, USP

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting this Telephone Amendment to provide a complete response to the telephone request of July 14, 2005 by Mr. Leo Zadecky, OGD Regulatory Project Manager, DLPS in support of Bupropion HCl Extended-Release Tablets, ANDA #77-715. The FDA comment appears in bold italic font below, with our response immediately following the comment.

Please provide the original signed Generic Drug Enforcement Act Statement.

Please find enclosed the signed original Generic Drug Enforcement Act Statement for Bupropion HCl Extended-Release Tablets, USP as requested. Please also find enclosed the signed original Certificate of cGMP and signed original Environmental Impact Statement. The corresponding pagination is as follows, and is identical to the original ANDA submitted on May 19, 2005: page 358 (Section IX), page 1125 (Section XIX) and page 1127 (Section XX).

We have enclosed one volume of one (1) Archival Copy.

Please contact me by telephone at (951) 493-5452 or by fax at (951) 493-4581 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Christine M. Woods
Associate Director, Regulatory Affairs
Enclosure

RECEIVED
JUL 18 2005
OGD/CDER

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 77-715 **FIRM NAME:** WATSON LABORAATORIES INC.

RELATED APPLICATION(S): NA

First Generic Product Received? NO

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

DRUG NAME: BUPROPION HYDROCHLORIDE
DOSAGE FORM: EXTENDED- RELEASE TABLETS, 150 MD AND 300 MG (NEW STRENGTH 300 MG ADDED)

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

Letter Date: JULY 27, 2005	**Received Date:** JULY 28, 2005
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 Not applicable to electronic sections	E-Media Disposition: YES SENT TO EDR
Field Copy Certification (Original Signature) YES	
Methods Validation Package (3 copies PAPER archive) **NO** (Required for Non-USP drugs)	
Cover Letter YES	**Table of Contents** YES
PART 3 Combination Product Category (Must be completed for ALL Original Applications)	N Not a Part3 Combo Product Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST **Iain Margand** **Date 9/29/05**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: Sandra J. Middleton for MS **Date:** 9/29/05	

ADDITIONAL COMMENTS REGARDING THE ANDA:
9/26/05: Requested a statement or listing for outside firms used in this application.
Requested a Reprocessing Statement
Requested an Environmental Impact statement.
Requested a Debarment Certification and List of Convictions statement.

Contact: Christine Woods 951-493-5452

Top 200 Drug Product:

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES (Statement regarding Rx/OTC Status) RX YES	☒
Sec. II	**Basis for Submission** **NDA# : 21-515** Ref Listed Drug: WELLBUTRIN XL Firm: SMITHKLINE BEECHAM ANDA suitability petition required? NA 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 patents '341 and '327 2. Expiration of Patent: 10-30-2018 A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement:** YES No Exclusivities	☒
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use OK 2. Active ingredients OK 3. Route of administration OK 4. Dosage Form OK 5. Strength OK	☒
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) Electronic submission 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 **2. Request for Waiver of In-Vivo Study(ies): YES ON 300 MG** pg. 39 **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) **4. Lot Numbers of Products used in BE Study(ies):** Strengths are proportional **5. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below) 150mg – XT4L029 300mg – XC5B013	☒
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING AND FED WAS DONE ON 150 MG a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted: NO c. In-Vitro Dissolution: Yes pg. 43	☒

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 pg. 56-57 2. Inactive ingredients as appropriate Excipients are acceptable per IIG (refer to 150mg strength application)	☒

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients (Refer to 150mg application, no changes)** 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 (Information supplied for lots used in 300mg application only)** a. Source of inactive ingredients identified pg. 72 b. Testing specifications (including identification and characterization) Y c. Suppliers' COA (specifications and test results) Y d. Applicant certificate of analysis Y	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. CFN numbers	☒
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address Y 2. Functions Y 3. CGMP Certification/GLP See original application 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 300mg - [redacted] 3.If sterile product: Aseptic fill / Terminal sterilization N/A 4.Filter validation (if aseptic fill) N/A 5. Reprocessing Statement Y	☒ b(4)
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 Ty: [redacted] 2. In-process Controls - Specifications and data Y Ay: [redacted] packaged: 30 - [redacted] 1000 - [redacted]	☒ b(4)
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) pg. 670 2. Components Specification and Test Data (Type III DMF References) Y 3. Packaging Configuration and Sizes [redacted] and [redacted] bottles (refer to 150mg application for [redacted] bottle information) 4. Container/Closure Testing Y 5. Source of supply and suppliers address pg. 671	☒ b(4)

Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data same as 150mg strength with noted revisions 2. Certificate of Analysis for Finished Dosage Form Y	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted same as 150mg strength 2. Post Approval Commitments same as 150mg strength 3. Expiration Dating Period same as 150mg strength 4. Stability Data Submitted a. 3 month accelerated stability data Y b. Batch numbers on stability records the same as the test batch XC5B013	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance 2. Finished Dosage Form 3. Same lot numbers	☒
Sec. XVII	**Environmental Impact Analysis Statement**	☒
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other**: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A 2. Debarment Certification (original signature): YES 3. List of Convictions statement (original signature) YES 4. Field Copy Certification (original signature) YES	☒

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

BIOEQUIVALENCY AMENDMENT

ANDA 77-715

)FFICE 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: Watson Laboratories, Inc. TEL: 951-493-5452

JUL 12 2006

ATTN: Christina M. Woods FAX: 951-493-4581

FROM: Aaron Sigler PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on May 19, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Bupropion Hydrochloride Extended-release Tablets, USP, 150 mg.

Reference is also made to your amendment dated March 28, 2006.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 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

ANDA: 77-715 APPLICANT: Watson Laboratories, Inc.

DRUG PRODUCT: Bupropion Hydrochloride Extended Release Tablets, USP 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:

1. Based on the submitted dissolution results, your proposed dissolution specifications are not acceptable. Please acknowledge the acceptance of the following dissolution method and specifications for your test product:

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

   2 hours:
   4 hours:
   8 hours:
   12 hours:

   b(4)

2. Due to concern of dose dumping for the drug product, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

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

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

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

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

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

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

Sincerely yours,

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

ANDA 77-715 Bupropion HCl ER TABLETS

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

May 19, 2005

77-715

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

RE: **Abbreviated New Drug Application**
Bupropion Hydrochloride Extended-Release Tablets, USP, 150 mg

Dear Mr. Buehler:

Watson Laboratories, Inc. submits herein an original Abbreviated New Drug Application for Bupropion Hydrochloride Extended-Release Tablets, USP, 150 mg.

The drug product described above is the same as Wellbutrin XL® (bupropion hydrochloride ER tablets) 150 mg distributed by GlaxoSmithKline. We have submitted comparative information to indicate that our product is the same as the reference listed drug product Wellbutrin XL®. This information is presented in tabular form in Section IV, comparing: active ingredient; conditions of use; route of administration; dosage form; strength; bioequivalence; and labeling for the products as supplied by Watson Laboratories, Inc. and by GlaxoSmithKline.

Watson Laboratories, Inc. commits to resolve any issues identified in the method validation process after approval.

In accordance with 21 CFR 314.94(d)(ii) as effected June 8, 2004 which required the submission of electronic labeling, Watson provides one (1) CD ROM containing Watson proposed labeling in Adobe PDF and Microsoft Word format. The CD ROM is located at the front of Volume 1 of the Archival Copy of this submission.

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

311 Bonnie Circle, Corona, CA 92880 • Tel: 800/249-5499 • Website: www.watsonpharm.com

We have enclosed one (1) archival and one (1) review copy. As required, two (2) additional separately bound copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient and finished dosage form) are included.

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

Blue Archival Copy	- 19 volumes
Orange Review Copy	- 17 volumes
Red Review Copy	- 3 volumes
Burgundy Field Copy	- 3 volumes

In accordance with 21 CFR §314.94(d)(5), one (1) field copy of the application will be forwarded to the manufacturing facility's district office, in Buffalo, NY. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copy of this application.

We trust the information submitted is sufficient for this Abbreviated New Drug Application to be evaluated. Please contact me by phone at (951) 493-5452 or by fax at (951) 493-4581 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Christine M. Woods
Associate Director, Regulatory Affairs

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA# _____ **FIRM NAME** Watson Laboratories, Inc.

RELATED APPLICATION(S) _____ **FIRST GENERIC?** _____

DRUG NAME: Bupropion Hydrochloride, USP
DOSAGE FORM: Extended-Release Tablets

Electronic Submission: E-mail notification sent: Comments: _____

Random Assignment Queue: Chem Team Leader: PM:

Labeling Reviewer: ___ Micro Review: _____ PD study (Med Ofcr): _____

Letter Date May 19, 2005	**Received Date**
Comments	**On Cards** **Therapeutic Code**
Methods Validation Package (3 copies) (Required for Non-USP drugs) Present	
Archival, and Review copies Field Copy Certification (Original Signature) Present	
Cover Letter Present	
Table of Contents Present	

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** (Statement regarding Rx/OTC Status) Present	☒
Sec. II	**Basis for Submission** **NDA: 21-515** RLD: Wellbutrin XL® Firm: GlaxoSmithKline (SmithKline Beecham) ANDA suitability petition required? no If yes, consult needed for pediatric study requirement.	☒
Sec. III	**Patent Certification** 1. Paragraph: IV 2. Expiration of Patent: October 30, 2018 A. Pediatric Exclusivity Submitted? No B. Pediatric Exclusivity Tracking System checked?N/A **Exclusivity Statement Present**	☒

Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Indicated for the treatment of major depressive disorder. 2. Active ingredients bupropion hydrochloride 3. Route of administration oral 4. Dosage Form extended-release tablets 5. Strength 150 mg	☒
Sec. V	**Labeling** 1. 4 copies of draft (each strength and container) or 12 copies of FPL Present (electronic copies) 2. 1 RLD label and 1 RLD container label Present 3. 1 side by side labeling comparison with all differences annotated and explained Present	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) Present **2. Request for Waiver of In-Vivo Study(ies):** N/A **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) N/A **4. Lot Numbers of Products used in BE Study(ies):** XT4L029 and 04D014P **5. Study Type:** In Vivo PK Studies (Continue with the appropriate study type box below)	☒
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) Fasting and Fed a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) yes b. Data Files (Computer Media) Submitted Present c. In-Vitro Dissolution Present	☒
Study Type	**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. Data Files (Computer Media) Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 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. Data Files (Computer Media) Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** a. Solutions (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. Suspensions (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. Data Files (Computer Media) 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. Data Files (Computer Media) 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)** 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 Present 2. Inactive ingredients as appropriate Present	☒
Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers Present b. Type II DMF authorization letters or synthesis Present c. COA(s) specifications and test results from drug substance mfgr(s) Present d. Applicant certificate of analysis Present e. Testing specifications and data from drug product manufacturer(s) Present f. Spectra and chromatograms for reference standards and test samples Present g. CFN numbers N/A 2. **Inactive Ingredients** a. Source of inactive ingredients identified Present b. Testing specifications (including identification and characterization) Present c. Suppliers' COA (specifications and test results) Present d. Applicant certificate of analysis Present	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) Present 2. CGMP Certification Present 3. CFN numbers Present	☒

Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address Present 2. Functions Present 3. CGMP Certification/GLP Present 4. CFN numbers Present	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including MicrobiologicalValidation, if Appropriate) Present 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified Present 3.If sterile product: Aseptic fill / Terminal sterilization N/A 4.Filter validation (if aseptic fill) N/A 5. Reprocessing Statement Present	☒
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record (Antibiotics/3 Batches if bulk product produced by fermentation) with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation Present 2. In-process Controls - Specifications and data Present	☒
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) Present 2. Components Specification and Test Data (Type III DMF References) Present 3. Packaging Configuration and Sizes Present 4. Container/Closure Testing Present 5. Source of supply and suppliers address Present	☒
Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data Present 2. Certificate of Analysis for Finished Dosage Form Present	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted Present 2. Post Approval Commitments Present 3. Expiration Dating Period Present 4. Stability Data Submitted Present a. 3 month accelerated stability data Present b. Batch numbers on stability records the same as the test batch yes	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance Present 2. Finished Dosage Form Present 3. Same lot numbers yes	☒
Sec. XVII	**Environmental Impact Analysis Statement** Present	☒

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) Present 3. List of Convictions statement (original signature) N/A	☒

Reviewing CSO/CST **Date**	**Recommendation:** ☐ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: _____	**Date:** _____
Duplicate copy sent to bio: (Hold if RF and send when acceptable) Duplicate copy to **HFD-** for consult: Type:	

ADDITIONAL COMMENTS REGARDING THE ANDA:

OGD Form Revised 11/30/2001
MSWord Template revised: 8/7/2002