CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-108

MEDICAL REVIEW(S)

7/19/7

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 19, 2007

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for not approvable action for Bupropion HBr ER tablets for MDD

TO: File NDA 22-108
[Note: This overview should be filed with the sponsor's 9-27-06 application.]

Background

This is a 505(b)(2) application for an extended release (once daily) formulation of bupropion hydrobromide. The sponsor has produced two tablet strengths (174 mg and 348 mg) to match the two available strengths of Wellbutrin XL (150 mg and 300 mg). [Note: Data in support of a 522 mg strength were submitted 4-26-07, but could not be reviewed in this initial cycle.] The basis for this application is the CMC information to support this new formulation and bioequivalence data that the sponsor feels is an adequate demonstration of bioequivalence for these two formulations. The work in support of this application was done under IND 73,781. Unfortunately, the sponsor never sought advice from us on this program. Thus, their biopharm program is limited to a MD steady state BE study, a food effect study, and a SD dose proportionality study. Importantly, they did not conduct a SD bioequivalence study, and this is considered a critical deficiency by OCP, necessitating a not approvable action.

Summary of Conclusions and Recommendations from Review Teams

CMC

The CMC reviewer was Lyudmila Soldatova, Ph.D. She identified a number of drug substance and drug product deficiencies, however, she felt that these are sufficiently resolvable that they could be noted in an approvable letter. The site inspections were acceptable, and a categorical exclusion was granted. They also have some comments for labeling. We will convey all of these comments in the not approvable letter. As noted, it was not possible to review the information for a higher strength (522 mg—submitted 4-26-07) in this cycle.

Pharm/Tox

The sponsor conducted several additional studies (convulsant potential in mice, 28-day tox study in rats, and an Ames test). These contributed no important new information. However, there remain some impurity issues that need to be resolved, either by lowering the limits or additional testing, and these are fully addressed in the CMC comments that we will be conveying to the sponsor.

OCP

As noted, the OCP reviewer, Andre Jackson, Ph.D., has identified the failure to conduct a SD bioequivalence study as a critical deficiency that should preclude even an approvable action for this application. They feel that a steady state study, as conducted by the sponsor, is not sufficiently sensitive to detect differences. Indeed, they estimate based on simulation that a SD study will likely fail, both for the parent and the major metabolite. This position is supported by Ray Baweja, Ph.D. and Mehul Mehta, Ph.D., also from OCP. [Note: Although the sponsor never sought any meetings with the agency regarding this program, I would note that their proposed development plan was submitted on 10-24-05, and was reviewed by OCP. I would further note that OCP did not object in principle to the sponsor's plan to conduct a steady state bioequivalence study at that time.]

I have mixed feelings about this requirement for a SD bioequivalence study. Although it is true that a SD study is more sensitive, and perhaps likely that a SD study will fail, it is also true that, for this condition, a MD study may be more relevant. MDD is a chronic illness in which patients need chronic treatment, and furthermore, it would not be expected that patients would immediately worsen upon switching to a formulation that might deliver, on the first dose, an exposure to parent and major metabolite that may be as much as 50% less than the exposures seen with the reference formulation. During steady state, however, the new formulation delivers an acceptable exposure, and this is probably more relevant from a clinical perspective. Indeed, even if the sponsor conducted a SD study that failed, we might well overlook this outcome and approve this formulation in any case, given the MD results. On the other hand, current guidance requires a SD study in this setting, and it would not be helpful to create this precedent. In addition, clinicians should know about the inadequate exposures that would likely result in the setting of single doses. Thus, I will accept this advice from OCP and ask for a SD study.

As a separate matter, OCP has proposed dissolution specifications that we will convey in the NA letter as well.

Clinical

Robert Levein, M.D., from the clinical group, reviewed the safety data for this application. He concluded that the profile of adverse events observed for this new formulation is similar to that seen for the other bupropion formulations, and he found it to be a reasonably safe formulation.

DMETS

Although we do not have a final consult from DMETS at this time, they have conveyed preliminary concerns about the originally proposed name, i.e., [redacted]. They are concerned that prescribers will confuse this with other bupropion formulations, and they note that the name does not convey the important information that this is a controlled release formulation. However, the sponsor has now withdrawn the name [redacted] and we will consult the new proposed names to DMETS. b(4)

DSI

The site at which the MD bioequivalence study was conducted was inspected, and the data from this site were deemed to be acceptable.

Labeling

The sponsor proposed labeling in PLR format, and the review team has evaluated this document. Since we will be issuing a NA letter, we will not include draft labeling at this time. However, the letter will include some suggested changes to labeling, should the sponsor wish to resubmit this application at some future time.

CONCLUSIONS AND RECOMMENDATIONS

I will issue a not approvable letter, noting that the critical OCP deficiency, and separately the other deficiencies that would need to be addressed before an approval action.

cc:
Orig NDA 22-108
HFD-130/TLaughren/MMathis/RLevin/RGrewal

DOC: Bupropion HBr ER_Laughren_NA Memo.doc

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/s/

Thomas Laughren
7/19/2007 03:12:21 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: 12 July 2007

FROM: Mitchell V. Mathis, M.D.
Deputy Director
Division of Psychiatry Products, HFD-130

TO: File NDA 22-108

SUBJECT: Recommendation of Not Approvable Action for Biovail Laboratories' Bupropion Hydrobromide Extended-Release Tablets (BuHBr ER) for the Treatment of Major Depressive Disorder

1 BACKGROUND AND REGULATORY HISTORY

The sponsor has submitted this 505(b)(2) application for a once-daily (extended-release) formulation of bupropion hydrobromide (174 mg and 348 mg tablets) for the treatment of Major Depressive Disorder. This application is based on demonstrating bioequivalence to GlaxoSmithKline's Wellbutrin XL® 150 mg and 300 mg tablets (the hydrochloride salt compound which is the reference listed drug (RLD) for this development program). There are no new clinical efficacy data to review, but the program does include safety data from the pharmacokinetic studies done to support bioequivalence.

BuHBr ER was developed under IND 73,781. The Division issued a May Proceed letter on 7 February 2006 and the sponsor conducted three studies under the IND to establish bioequivalence to the RLD.

- Steady state (multiple dose) fasting study
- Food effect study
- Single dose dosage proportionality study (to determine proportionality between 2 tablets of BuHBr ER 174 mg with one tablet of BuHBr ER 348 mg).

No EOP2 or pre-NDA meetings were requested, and the sponsor did not request guidance from the review team prior to submitting their NDA. The NDA was filed on 12 November 2006.

This application was reviewed by Dr. Levin from the Clinical Team, Dr. Soldatova from the Chemistry Team, and Dr. Jackson from the Clinical Pharmacology/Biopharmaceutics Review Team.

2 CHEMISTRY

The chemists recommend an APPROVABLE action contingent upon satisfactory resolution of the drug substance and drug product deficiencies identified, and upon the determination of an adequate status of the DMF. No Phase 4 commitments were identified. A list of deficiencies to be communicated to the sponsor are included in Dr. Soldatova's review (see pages 55-56). The chemists also have comments for labeling in their review.

3 PHARMACOLOGY/TOXICOLOGY

This 505(b)(2) application has no new pharmacology/toxicology information for review.

4 CLINICAL PHARMACOLOGY

The Clinical Pharmacologists have recommended an NOT APPROVABLE action. Their reasoning is that the multiple-dose study used to compare bupropion hydrobromide and bupropion hydrochloride modified release formulations minimizes the differences in the formulations and is therefore not an appropriate way to evaluate bioequivalence. OCP will require a single-dose fasting bioequivalence study comparing these two formulations before they can determine bioequivalence. OCP has provided comments to the sponsor requesting a single-dose fasting bioequivalence study on page 3 of Dr. Jackson's review.

5 CLINICAL DATA

5.1 Pharmacology Studies

The sponsor is seeking approval for BuHBr ER based on a demonstration of bioequivalence of their 174 mg and 348 mg tablets with the RLD (Wellbutrin XL® 150 mg and 300 mg tablets [hydrochloride salt of bupropion]). The two different salts contain the same amount of the active ingredient bupropion.

Three open-label PK studies were conducted to support this application. The primary objective was to demonstrate bioequivalence to the RLD. Secondary objectives were to evaluate food effects and dosage proportionality between two BuHBr ER 174 mg tablets and one BuHBr ER 348 mg tablets.

A total of 144 healthy adults were enrolled after meeting appropriate medical inclusion criteria. The studies are summarized below.

Study 3230: Multiple-Dose Fasting Comparison

Forty healthy adults participated in this multiple-dose, fasted-state study evaluating the relative bioavailability between BuHBr ER 348 mg tablets and Wellbutrin XL® 300 mg tablets. The design was a randomized two-way crossover which included a dose escalation phase wherein each subject received the RLD at 150 mg per day after an overnight fast for 3 consecutive days. After dose escalation, all subjects received either (randomly assigned) the RLD at 300 mg per day or BuHBr ER 348 mg per day (each under fasting conditions and for Days 4-13), and PK data were collected.

This study demonstrated that BuHBr ER 348 mg tablets were equivalent *in vivo* to 300 mg of the RLD with respect to Cmax, AUC, and Cmin at steady state.

Study 3229: Single-Dose Food Effect Study

Forty-eight healthy adults participated in this single-dose study to evaluate the effect of food on the pharmacokinetics of BuHBr ER. The design was a randomized two-way crossover which BuHBr 348 mg was administered either with a high-fat breakfast or under fasting conditions with the collection of PK data for comparison.

The results indicated that food resulted in a marginal increase in AUC of bupropion (19%) and no real change in Cmax or Tmax. Dr. Levin did not find this food effect to be clinically meaningful and I agree with him.

Study 3228: Dosage Form Proportionality Study
Forty-six health adult subjects participated in this open-label, randomized, single-dose, two-way crossover study to evaluate dosage-form proportionality between BuHBr ER tablets (two 174 mg vs. one 348 mg).

The dosage forms were found to be proportional in this study with regard to Cmax and AUC for bupropion and its metabolites.

5.2 Safety Data
One hundred and forty-two healthy adult subjects received at least one dose of BuHBr ER 348 mg during the development program. Of these, 56 subjects received between 7 and 10 daily doses in the multiple-dose study. The total exposure to BuHBr ER was 3.04 patient-years.

5.3 Adverse Events
No deaths or serious adverse events were reported during the clinical pharmacology studies. There were two discontinuations due to adverse events (both with rash). There was a single case of syncope in a subject enrolled in the single-dose study 3228. This episode resolved without complication and the subject had normal vital signs and ECG.

The most commonly reported adverse events not leading to discontinuation were headache (6.3%), dizziness (5.6%), rash (2.1%), and pruritus (2.1%). These adverse events are consistent with adverse events seen with the RLD and no new or unexpected adverse events were identified with BuHBr ER.

There were no clinical laboratory abnormalities which could reasonably be attributed to BuHBr ER.

6.0 Conclusion Regarding Safety
Short-term treatment of healthy adults with BuHBr ER appears to have been reasonably safe and there were no unexpected adverse events.

7.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING
This NDA was not presented to the PDAC.

8.0 DSI INSPECTIONS
DSI audited the clinical and analytical portions of study 3230 conducted in Canada. They identified discrepancies in two subjects who were excluded from the analysis despite DSI having found no evidence of analytical problems or non-compliance; the DSI Final Classification was Voluntary Action Indicated (VAI).

9.0 LABELING AND ACTION LETTER
The sponsor has included a PLR-formatted label based upon the RLD and modified with language to reflect the different chemical name and structure as well as changes to the Pharmacokinetics section that describe the trials used to establish bioequivalence. Dr. Levin has reviewed this labeling and incorporated changes from the Chemistry and OCPB teams, but this will require further modification (incorporation of the single-dose study data requested by OCPB) before a positive action can be taken on this application.

The Action Letter should state the primary reason for the NOT APPROVABLE action is the lack of a single-dose bioequivalence study comparing BuHBr ER to the RLD. We should also include the multiple deficiencies identified by the Chemistry Team in the letter.

9.2 DMETS

The proposed trade name has been evaluated by DMETS, but their official consult has yet to be finalized. They have forwarded the minutes of their meeting with the Division to Dr. Grewal. These minutes identify the following problems with the selected trade name: b(4)

- Potential confusion exists with the other forms of bupropion.
- HBR does not indicate the extended release profile of the drug.

Therefore, it is unlikely that DMETS will agree with the proposed trade name when their consult to the Division is finalized. This issue will have to be resolved prior to taking a positive action on this application.

b(4)

10.0 PHASE 4 COMMITMENTS

No Phase 4 requirements have been identified.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted insufficient data to support that BuHBr ER is bioequivalent to the RLD and so this application should not be approved. We should send a letter to the sponsor describing the need for a single-dose bioequivalence study and communicating the deficiencies noted by the Chemistry Team. We will communicate the findings from DMETS when they are finalized.

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/s/

Mitchell Mathis
7/18/2007 02:34:15 PM
MEDICAL OFFICER
NA Rec

6/28/07

Review of Clinical Data for NDA 22-108

NDA number	22-108
Related IND	73-781
Sponsor	Biovail Laboratories International SLR
Drug name:	Bupropion hydrobromide extended release
Proposed trade name	[redacted] b(4)
Drug class	Antidepressant
Indication	Major Depressive Disorder
Formulations	348 mg and 174 mg tablets
Submission date	September 27, 2006
Action date	July 28, 2007
Clinical reviewer	Robert Levin, M.D., Division of Psychiatry Products

I. Introduction and Background

The sponsor has submitted a 505(b)(2) application for once-daily formulations of bupropion hydrobromide (174 mg and 348 mg) for the treatment of Major Depressive Disorder. The product consists of a change in the inactive salt ingredient compared to the listed drug, bupropion hydrochloride, which contains the same active moiety. The extended-release formulation of bupropion hydrochloride (Wellbutrin XL®), manufactured for GlaxoSmithKline by Biovail, was approved in the U.S. on August 28, 2003 (NDA 21-515) for the treatment of Major Depressive Disorder. On June 12, 2006, Wellbutrin XL® was approved for the prevention of seasonal major depressive episodes in patients with Seasonal Affective Disorder.

The NDA submission is based on data from three (3) clinical pharmacology studies in healthy volunteers. Standard safety data were gathered in these studies. Efficacy data were not required for this application. This review will focus on the clinical safety data. For detailed results of the biopharmaceutic analysis, please refer to the FDA Biopharmaceutics review performed by Andre Jackson, Ph.D. (Clinical Pharmacology/Biopharmaceutics Review, June 15, 2007).

The sponsor seeks approval for bupropion HBr based on a demonstration of bioequivalence between Bupropion HBr extended-release (174 mg and 348 mg) and Bupropion HCl extended-release (150 mg and 300 mg). The two salts contain the same amount of the active ingredient, bupropion. The table below illustrates the molecular weight and base equivalence relationships between Bupropion HBr and Bupropion HCl.

Formulation	Bupropion HBr	Bupropion HCL	Base equivalents mg HBr	Base equivalents mg HCL
MW base	[redacted]			
MW salt				
Total MW	320.65	276.20		

b(4)

(Source: FDA biopharmaceutics review by Andre Jackson, Ph.D.)

II. Description of the Clinical Pharmacology Studies

Three open-label pivotal pharmacokinetic studies were conducted to support this NDA. The primary objective was to demonstrate that bupropion HBr extended-release 348 mg tablets provide equivalent peak (C_{max}) and systemic (AUC) exposure to Wellbutrin XL® 300 mg Tablets. Secondary objectives included the assessment of a potential food effect and an evaluation of dosage strength proportionality. Subjects were healthy male and female adults. The medical inclusion and exclusion criteria were appropriate. A total of 144 healthy adult, male (72) and female (72) subjects participated. The average age was 35.5 years. The average BMI was 25.1. The ethnicity of subjects was as follows: Caucasian (41%), African American (25.7 %), Latino (21.5 %), Asian American (10.4 %), and Other (1.4%). A total of 10 subjects (7%) discontinued from the studies. Two (2) subjects from Study 3228 discontinued due to adverse events (subjects 002 and 025 discontinued due to rash). The other eight early discontinuations were reportedly due to personal reasons.

A. Study 3230: Multiple-Dose Fasting Study B06-756PK-10121

This was a multiple-dose, fasted-state study evaluating the relative bioavailability between bupropion HBr extended-release 348 mg tablets and Wellbutrin XL® 300 mg tablets in 40 healthy adult, male and female subjects. The study used a randomized, two-way crossover, open-label design. Subjects included 20 males and 20 females. For Days 1-3 (dose escalation phase), all subjects were administered one Wellbutrin XL 150 mg tablet with water after a 10-hour overnight fast once in the morning for 3 consecutive days. In the crossover phase, all subjects were administered Treatment A and Treatment B, in randomized order, separated by a washout period of at least two weeks between treatment periods.

Treatment A:
On Days 4-13, subjects were administered one bupropion HBr 348 tablet with water after a 10-hour overnight fast each morning for 10 consecutive days; or

Treatment B:
On Days 4-13, subjects were administered one Wellbutrin XL 300 mg tablet with water after a 10-hour overnight fast each morning for 10 consecutive days.

B. Study 3229: Single-Dose Food Effect Study B06-754PK-10121 (3229)

This was a single-dose, food effect study evaluating the effect of food administration on the pharmacokinetics of bupropion HBr extended-release 348 mg tablets in 48 healthy adult, male and female subjects. The study used a randomized, two-way crossover, open-label design. Subjects included 24 males and 24 females.

All subjects participated in both Treatment A and Treatment B, in randomized order. There was a washout period of at least two weeks between treatment periods A and B or B and A. In Treatment A, subjects were administered one bupropion HBr XL 348 mg tablet with water after a high-fat breakfast. In Treatment B, subjects were administered one bupropion HBr XL tablet with water after a 10-hour overnight fast.

C. Study 3228: Dosage Form Proportionality Study B06-755PK-10121 (3228)

This was a dosage-form proportionality study of two strengths of bupropion HBr extended-release tablets (2 x 174 mg vs. 1 x 348 mg) in 46 healthy adult, male and female subjects. The study used a randomized, two-way crossover, open-label, single-dose design. There were 23 male subjects and 23 female subjects who completed the study. In Treatment A, subjects were administered two bupropion HBr XL 174 mg tablets with water after a 10-hour overnight fast. In Treatment B, subjects were administered one bupropion HBr XL 348 mg tablet with water after a 10-hour overnight fast. All subjects participated in both Treatment A and Treatment B. There was a washout period of at least two weeks between treatment periods.

III. Overview of Biopharmaceutics Findings

Following a single oral administration of bupropion HBr XL 348 tablets to healthy volunteers, the median T_{max} was 5 hours. The mean C_{max} and AUC_{0-8} were 125.9 ± 34.5 ng/mL and 1572 ± 421 ng*hr/mL, respectively. The apparent half-life for bupropion was 21.3 ± 6.7 hours.

In a multiple-dose, fasting study, bupropion 348 mg tablets were demonstrated to be equivalent in-vivo to Wellbutrin XL® 300 mg Tablets with respect to C_{max} and AUC_{0-t} and C_{min} at steady state for bupropion, hydroxybupropion, bupropion threoamino alcohol, and bupropion erythroamino alcohol. Steady-state for bupropion was reached within 7 days after repeated dosing. At steady state, the mean Cmax and AUC_{0-t} values for bupropion were 134.3 ± 38.2 ng/mL and 1409 ± 346 ng*hr/mL, respectively. The AUC_{0-t} ratios of metabolite relative to bupropion were 15.6, 6.8, and 1.5 for hydroxybupropion, bupropion threoamino alcohol, and bupropion erythroamino alcohol, respectively.

In a single-dose, food effect study, administration of bupropion HBr 348 mg tablets with food resulted in a marginal increase in AUC of bupropion 19 %. The presence of food did not affect Cmax and Tmax. The sponsor concludes that the food effect is not clinically significant.

Bupropion HBr 174 mg and 348 mg tablets were found to be dosage strength proportional in a dosage form proportionality study. A single dose of 2 x 174 mg tablets had Cmax and AUC equivalent to those for 1 x 348 mg tablets for bupropion and metabolites.

Subgroup Analysis (Age, Gender, Ethnicity, and BMI)
There was no noticeable effect of age on AUC, Cmax, or $T_{1/2}$. There was no significant difference in pharmacokinetics between male and female subjects for Cmax. The mean AUC from female subjects was 13 % higher than for male subjects. It does not appear that there were significant differences in pharmacokinetics among different ethnic groups. Furthermore, there were no significant trends in AUC, Cmax and $t_{1/2}$ with changing BMI.

Biopharmaceutics Conclusions and Recommendations

The FDA Biopharmaceutics reviewer, Andre Jackson, Ph.D has concluded the following:

1. The relative bioavailability for the extent of absorption for bupropion hydrobromide was 90% of that observed for bupropion hydrochloride.
2. The 2 x 174 mg vs. 1 x 348 mg study demonstrated dosage strength equivalence
3. There was no significant effect of food on the absorption of bupropion with the bupropion HBr tablet
4. Data about the single-dose PK profile of bupropion is not available, since the sponsor did not conduct a single-dose bioequivalence study.

OCP requests that the sponsor conduct a fasting, single-dose bioequivalence study, since a multiple dose comparison minimizes differences in formulations. Dr. Jackson notes that when both the test and reference product are modified release formulations, a single dose bioequivalence study provides the most sensitive conditions for testing the similarity of test and reference formulations.

IV. Safety Review

A. Exposure to Bupropion HBr and Bupropion HCl

A total of 142 subjects were administered at least one dose of 348 mg of bupropion HBr XL. There were 96 healthy volunteers who were administered between 1 to 2 doses of 348 mg bupropion HBr the single-dose studies. There were 56 subjects who were administered between 7 and 10 doses of 348 mg bupropion HBr XL in the multiple-dose study. In the multiple-dose study, 48 subjects were also administered Wellbutrin XL (150- 300 mg). The total exposure for bupropion HBr was 3.04 person-years.

B. Adverse Events

There were no deaths or serious adverse events reported in the clinical pharmacology studies. Two subjects discontinued due to adverse events. Both of these subjects discontinued due to the development of rash. There was one case of syncope in single-dose study 3228. Subject 3228-042 was an African American woman who had a syncopal episode that resolved without complication. The screening ECG, EEG, and vital signs

were normal (heart rate was 56, and blood pressure was 120/80). The Division has requested additional safety information about this subject.

The most commonly reported adverse events were: headache (6.3%), dizziness (5.6%), rash (2.1%), and pruritus (2.1%). Based on previous findings with bupropion, all of the adverse events listed above could be related to treatment with bupropion HBr. There were no new or unexpected adverse events that were likely to be related to treatment with bupropion hydrobromide. All adverse events reported in the three pharmacology are listed in the below.

Table. (Source: Table 3 from Sponsor's Clinical Summary Module 2.7)

Adverse Events (MedDRA Preferred Term)	Wellbutrin XL® 150 mg Tablets n=48	Bupropion HBr XL 348 mg Tablets n = 142	Wellbutrin XL® 300 mg Tablets n =43
Percentage of Subjects with at least 1 AE and Percentage Relative to Population	*8 (16.7 %)*	*35 (26.4 %)*	*15 (34.9 %)*
Abdominal pain	0	1	1
Anorexia	0	2	0
Arthralgia	0	1	0
Asthenia	0	1	0
Back pain	0	1	0
Catheter site oedema	0	1	0
Catheter site pain	0	1	0
Chest pain	0	1	0
Constipation	0	0	1
Cough	2	1	1
Diarrhoea	0	0	1
Dizziness	0	6	2
Dry skin	0	1	0
Dysmenorrhoea	0	1	1
Dysphonia	0	1	1
Dysuria	0	0	1
Epistaxis	0	1	0
Erythema	0	1	0
Eye discharge	1	0	0
Eye irritation	2	0	0
Eye pruritus	0	0	1
Furuncle	0	1	0
Headache	0	8	1
Heart rate increased	1	0	0
Herpes simplex	1	0	0
Hyperhidrosis	0	1	0
Hypotension	0	1	0
Influenza like illness	0	1	0
Menstrual disorder	0	1	0
Musculoskeletal pain	1	0	0
Musculoskeletal stiffness	0	1	1
Nasal congestion	0	1	1
Nausea	0	2	0
Neck pain	0	1	1

Adverse Events (MedDRA Preferred Term)	Wellbutrin XL® 150 mg Tablets n=48	Bupropion HBr XL 348 mg Tablets n = 142	Wellbutrin XL® 300 mg Tablets n =43
Ocular hyperaemia	1	1	0
Pain	0	1	0
Pallor	0	1	0
Peripheral oedema	0	1	0
Pruritus	0	2	1
Pyrexia	0	2	0
Rash	0	1	1
Rash pruritic	0	0	1
Somnolence	0	0	1
Stomach discomfort	0	0	0
Syncope	0	1	0
Throat irritation	2	1	0
Upper respiratory tract infection	0	1	0
Venipuncture site pain	0	1	0

C. Clinical Laboratory Findings

There were few abnormalities of clinical laboratory tests. These are listed in the table below. It is unlikely that any of the laboratory abnormalities were related to treatment with bupropion hydrobromide.

Abnormal Laboratory Results at Study Completion (MedDRA Preferred Term)	Multiple-Dose Fasting Study B06-756PK-10121 (3230) n=48	Single-Dose Food Effect Study B06-754PK-10121 (3229) n=48	Dosage Form Proportionality Study B06-755PK-10121 (3228) n=48
Alanine aminotransferase increased	0	0	1
Aspartate aminotransferase increased	0	0	1
Blood creatinine increased	0	0	1
Blood urine present	0	0	2
Nitrite urine present	2	0	1
Platelet count increased	2	0	0
Protein urine present	1	0	1
Urine ketone body present	0	0	1
White blood cells urine positive	0	0	1

1 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical-_____

There is no safety or other clinical concern with the studies. I recommend that the Division take an approvable or approval action, if the Biopharmaceutics and Chemistry teams conclude that the application is acceptable.

Robert Levin, M.D., June 26, 2007
Medical Reviewer
FDA CDER ODE1 DNDP HFD 130

cc: NDA
HFD 130
T Laughren
M Mathis
N Khin
R Grewal

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Robert Levin
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Mitchell Mathis
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