CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-108

CROSS DISCIPLINE TEAM LEADER REVIEW

4/18

Team Leader Memo

Date	April 10, 2008
From	Robert Levin, M.D.
Subject	Team Leader Review
NDA #	22-108
Sponsor	Biovail Laboratories International SLR
Proprietary/ Established name	Aplenzin™ Bupropion Hydrobromide Extended Release
Dosage forms / strength	348 mg and 174 mg tablets for oral administration
Indication	Major Depressive Disorder
Recommended:	Approvable action

1. Introduction and Summary

On September 27, 2006, the sponsor submitted a 505(b)(2) application for once-daily formulations of bupropion hydrobromide (174 mg, 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 identical 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 initial NDA 22-108 submission was based on data from three (3) clinical pharmacology studies in healthy subjects. Standard safety data were gathered in these studies. Efficacy data were not required for this application. Thus, 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 Division took a Not Approvable action on the initial NDA submission. The multiple-dose studies demonstrated the steady-state bioequivalence between bupropion hydrobromide and the reference drug product; however, the sponsor had not conducted a single-dose bioequivalence study. The Office of Clinical Pharmacology requested that the sponsor conduct a fasting, single-dose bioequivalence study as the most sensitive test, since, since a multiple-dose comparison between drug products has the potential to minimize differences between formulations. Dr. Jackson and other reviewers in OCP note that in cases in which both the test and reference product are modified-release formulations, a single-dose bioequivalence study will provide the most sensitive conditions for testing the similarity between test and reference drug products.

The sponsor requested that the Division consider accepting simulation results that could provide extrapolation from actual steady-state data to predicted single-dose pharmacokinetic data. The Division agreed to review the simulation data. Thus, the current submission consists primarily of simulated single-dose data. In addition, the sponsor has responded to requests for CMC data.

In summary, the sponsor has responded fully. The Office of Clinical Pharmacology finds the simulation data adequate for demonstrating the single-dose bioequivalence between Bupropion hydrobromide and the reference-listed product (Wellbutrin XL). The CMC reviewers have concluded that the sponsor has responded fully to all requests. However, only a ——— expiration date can be granted for the 522 mg strength. The Pharmacology/Toxicology reviewers have concluded that the earlier issues regarding impurities have been resolved. The Division of Medication Errors and Technical Support finds the proposed tradename, Aplenzin acceptable. Finally, there are no clinical concerns regarding the approvability of the application; there are no new clinical data, and the safety data from the previously reviewed clinical pharmacology studies did not reveal any new or unexpected findings with bupropion hydrobromide treatment. We will recommend several minor changes in proposed labeling. b(4)

2. Chemistry, Manufacturing, and Controls

The CMC reviewer, Lyudmila N. Soldatova, Ph.D. has concluded that the application is approvable. The drug substance and drug product deficiencies were resolved, and the status of the DMF ——— is adequate (per Review #3 dated April 4, 2008). The 24-month expiration period for Bupropion HBr XL Tablets, 174 mg and 348 mg can be granted, given the proposed dissolution specifications. The ——— expiration date can be granted currently for Bupropion HBr XL 522 mg tablets, based on the stability data evaluated using the final dissolution specifications proposed by OCPB. Biovail will need to revise the dissolution specification in the drug product specifications according to that proposed by the Agency. b(4)

On April 07, 2008, the Division (Renmeet Grewal) sent an email communication to the sponsor (Lidia Mostovy and Robert Ashworth) regarding the expiry for the 522 mg dose strength:

"Based on the 12-month stability data submitted for the 522 mg strength Bupropion HBr XL Tablets, only a ___ expiration date can be granted at this time for the 522 mg strength. One of the three 522 mg batches in 90 counts bottles did not meet the specification of NLT -> (at 8 hours) when measured at the 12-month time point. In addition, the dissolution results at the 8 hour time point exhibit a downward trend [over] time, and this trend is more pronounced with the higher count packaging." b(4)

3. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer, Linda Fossom has concluded that the sponsor has addressed both impurity issues. The sponsor has lowered the specification for the potentially genotoxic impurity ____ from the previous specification ____ in the drug substance (see Dr. Soldatova's 2nd review, dated 2/29/08). Per Dr. Fossom's review: "This will result in ____ of the impurity administered clinically at the highest recommended human daily dose of 522 mg (which is equivalent to 450 mg of bupropion HCl); this is considered near enough (within rounding error) to the limit of ____ per day currently accepted for a genotoxic impurity. Secondly, the Sponsor (in a submission to this NDA, letter-dated March 17, 2008; also see Dr. Soldatova's 3rd review dated 4/4/08) has agreed to lower the specification for ____ which is the specification for this impurity listed in the USP for the reference listed drug." b(4)

4. Clinical Pharmacology/Biopharmaceutics

The sponsor completed a simulation of single-dose pharmacokinetics of bupropion hydrobromide based on actual data from the multiple-dose clinical pharmacology studies from the initial NDA submission. Andre Jackson, Ph.D. analyzed the simulation data, and he concluded that the steady-state study data yielded the same 90% confidence interval data as the more sensitive single-dose study simulation. "The simulations clearly showed that the single dose studies 3228 and 3229 predicted the observed multiple dose data from study 3230." As a result, a single-dose bioequivalence study will not be requested for the approval of the NDA.

5. Clinical

(This is the identical clinical review contained in the initial NDA review)

5.1 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.

Overview of Biopharmaceutics Findings

Following a single oral administration of bupropion HBr XL 348 tablets to healthy volunteers, the median Tmax was 5 hours. The mean Cmax 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 Cmax and AUC_{0-t} and Cmin 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 notable 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.

Molecular Weights of the Test and Reference Bupropion Products

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

b(4)

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

5.2. 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.

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.

6 Labeling

Individual sections of labeling that require changes are listed below. The full text of our revised labeling is included as an appendix.

6.1 Pharmacology/Toxicology

The pharm/tox team has recommended one change in labeling regarding mutagenesis:

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Bupropion produced a positive response (2 to 3 times control mutation rate) in 2 of 5 strains in one Ames bacterial mutagenicity assay, but was negative in another. Bupropion produced an increase in chromosomal aberrations in 1 of 3 in vivo rat bone marrow cytogenetic studies.

b(4)

In the adverse events sections, we have changed 'adverse event' to 'adverse reaction.' Currently, there are no other substantive changes.

The full-text label is presented below. The edits have been made in track changes. The base document is the sponsor's proposed clean label.

Appears This Way
On Original

45 Page(s) Withheld

_____ Trade Secret / Confidential

6 Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Medical-*_____

Robert L. Levin, M.D., April 10, 2008
Medical Officer,
FDA CDER ODE1 DPP HFD 130

cc: IND 22-108
HFD 130
T Laughren
M Mathis
R Grewal

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