

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-108

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Bupropion Hydrobromide
PRODUCT (Brand Name):	Tradename
DOSAGE FORM:	Extended Release Tablets
DOSAGE STRENGTHS:	522 mg Tablets
NDA:	22-108
NDA TYPE:	New Strength
SUBMISSION DATE:	October 24, 2007
SPONSOR:	BioVail
REVIEWER	Andre Jackson

**REVIEW OF AN AMENDMENT INTRODUCING A NEW STRENGTH, 522 MG,
FOR A NEW BUPROPION HYDROBROMIDE SALT ER FORMULATION FOR
BUPROPION****Executive Summary**

A new strength of 522 mg for Bupropion HBr was submitted by the firm. A steady-state study was submitted to describe the bioavailability/BE of the new strength. Subsequent to this submission the firm completed a simulation (Report for simulation study appended to this review) study in which they showed that for Bupropion HBr a steady-state study gave the same 90% confidence interval information as the more sensitive single dose study. Based upon this outcome, a single dose study will not be requested for the approval of this new 522 mg strength.

The following dissolution conditions and specifications should be adopted by the firm and applied to the 174mg, 348 mg and 522 mg strengths of Bupropion HBr extended release tablets:

Dissolution Conditions

MEDIUM: 900 ml 0.1N HCl
APPARATUS 1: BASKET
SPEED: 75 rpm
Sampling Times: 2, 4, and 8 hrs

FDA PROPOSED DISSOLUTION SPECIFICATIONS		
2 HOURS		DISSOLVED
4 HOURS		DISSOLVED
8 HOURS	NLT 	DISSOLVED

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A 2-way Crossover Fasting Steady State Dosage Strength Proportionality Study of Bupropion Hydrobromide XL Tablets (522 mg vs. 3x174 mg) in Healthy Non-Smoking Adult Volunteers

Biovail Protocol No. B06-802PK-10121

STUDY OBJECTIVES

The objective of this study was to assess the dosage strength proportionality of one 522 mg tablet and three 174 mg tablets of Biovail bupropion HBr under multiple dose fasting conditions. The relative bioavailability of both dosage strengths of these formulations was assessed for bupropion, hydroxybupropion, bupropion threoamino alcohol, and bupropion erythroamino alcohol.

Overall Study Design and Plan

This was an open-label, randomized, 2-way crossover, 2-sequence, multiple-dose, dosage strength proportionality study designed to assess the relative bioavailability of a new dosage strength of one 522 mg tablet and three 174 mg tablets for bupropion HBr under fasting conditions. This relative bioavailability study was performed on 40 healthy, non-smoking, adult volunteers. There was no washout period between treatments.

A group of 40 healthy non-smoking subjects (29 males and 11 females) who had satisfied the screening evaluation were admitted to the study center in the evening prior to dosing (Day -1).

On Days 1 to 36, subjects fasted overnight for at least 10 hours before dosing. On Days 22 and 36, subjects fasted overnight until at least 4 hours post-dose.

On Days 1 to 36, standard meals were served approximately 4 and 9 hours after dosing, and an evening snack was served at appropriate times.

On Days 1 to 15 and Days 23 to 29, subjects fasted for at least 1 hour post-dose, when a standard breakfast was served.

On Days 16 to 21 and Days 30 to 35, subjects fasted for at least 2 hours post-dose, when a standard breakfast was served.

On Day 37, subjects fasted overnight for at least 10 hours before the blood draw for the end of study repeat laboratory tests. On Day 37, a morning snack was served.

In the morning of Days 1 to 3, all subjects received a dose titration consisting of a single oral dose of Bupropion HBr XL 174 mg tablet with 240 mL of water at room temperature, under fasting conditions. In the morning of Days 4 to 8, all subjects were administered a 2 tablet dose of Bupropion HBr XL 174 mg (total dose of

348 mg) with 240 mL of water at room temperature, under fasting conditions. In the morning of Days 9 to 22, subjects either received one tablet of the test product 522 mg bupropion hydrobromide or three tablets of the reference product (3 x 174 mg) bupropion hydrobromide (for a total dose of 522 mg), administered with 240 mL of water at room temperature. Subjects received each dose under fasting conditions. In the mornings of Days 23 to 36, subjects received the alternate treatment. There was no washout between treatments. Blood samples for PK (1 x 6 mL) were obtained from subjects immediately prior to dosing (Hour 0), on Days 1, 19, 20, 21, 22, 33, 34, 35 and 36 and at Hour 0 up to 24 hours post-dose on days 22 and 36.

Test and Reference Products, Dose, Mode of Administration, and Batch Number:

Bupropion HBr XL 522 mg tablets (test product), Manufactured by Biovail Corporation; Lot No.: 06M119P; Bulk Lot No.: 06M303.

Bupropion HBr XL 174 mg tablets (product for titration and reference product), Manufactured by Biovail Corporation; Lot No.: 06M062P; Bulk Lot No.: 06D117.

Demographics

Table 14.1.2. Demographic Information for All Subjects

Subject Number	Sequence		Gender	Age (Years)	Height (cm)	Weight (kg)	S.M.I. (kg/m ²)	Smoking Habits	Race	Completed Study According to Protocol?	Included in Safety Analysis?
	Initials	Randomized									
1	AB	AB	MALE	40	163	67.0	25.18	TOBACCO NON-USER	CAUCASIAN	YES	YES
2	BA	BA	MALE	37	162	81.8	24.70	TOBACCO NON-USER	BLACK	NO	YES
3	AB	AB	MALE	27	191	101.2	27.72	TOBACCO NON-USER	BLACK	NO	YES
4	BA	BA	MALE	31	183	100.0	26.63	TOBACCO NON-USER	BLACK	YES	YES
5	AB	AB	MALE	23	187	79.5	23.60	TOBACCO NON-USER	CAUCASIAN	YES	YES
6	BA	BA	MALE	36	188	77.4	21.99	TOBACCO NON-USER	BLACK	YES	YES
7	BA	BA	MALE	30	184	72.7	21.43	TOBACCO NON-USER	HISPANIC	YES	YES
8	BA	BA	MALE	26	180	78.7	24.42	TOBACCO NON-USER	BLACK	YES	YES
9	AB	AB	MALE	54	183	99.7	29.81	TOBACCO NON-USER	BLACK	YES	YES
10	BA	BA	MALE	44	165	71.3	26.16	TOBACCO NON-USER	BLACK	YES	YES
11	AB	AB	MALE	19	174	62.1	20.53	TOBACCO NON-USER	HISPANIC	YES	YES
12	BA	BA	MALE	27	179	85.9	26.65	TOBACCO NON-USER	BLACK	YES	YES
13	AB	AB	MALE	42	169	67.0	23.33	TOBACCO NON-USER	HISPANIC	YES	YES
14	AB	AB	MALE	22	169	66.3	23.24	TOBACCO NON-USER/SUBJECT SMOKED 3 CIGARETTES PER DAY	BLACK	YES	YES
15	BA	B	MALE	39	174	89.8	29.67	TOBACCO NON-USER	CAUCASIAN	NO	YES
16	AB	AB	MALE	41	182	88.1	26.56	TOBACCO NON-USER	CAUCASIAN	YES	YES
17	BA	BA	MALE	24	174	62.7	20.59	TOBACCO NON-USER	BLACK	YES	YES
18	AB	A	MALE	23	173	81.1	27.19	TOBACCO NON-USER	BLACK	NO	YES
19	BA	BA	MALE	26	174	70.0	23.00	TOBACCO NON-USER	BLACK	YES	YES
20	BA	BA	MALE	27	164	76.0	28.32	TOBACCO NON-USER/SUBJECT SMOKED 10 CIGARETTES PER DAY	BLACK	YES	YES
21	AB	AB	MALE	20	174	72.7	24.00	TOBACCO NON-USER	CAUCASIAN	YES	YES
22	AB	A	MALE	30	184	89.5	26.40	TOBACCO NON-USER	BLACK	NO	YES
23	AB	AB	MALE	39	185	88.7	25.61	TOBACCO NON-USER	BLACK	YES	YES

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Notes:

PHARMACOKINETIC METHODS

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The pharmacokinetic parameters for plasma bupropion, hydroxybupropion, bupropion threoamino alcohol and bupropion erythroamino alcohol were calculated on Days 22 and 36, as follows:

$AUC_{0-\tau}$	The area under the plasma concentration versus time curve over the final dosing interval (0-24 hours) on Days 22 and 36, as calculated by the linear trapezoidal method.
C_{pd}	Pre-dose concentration determined immediately before a dose on Days 19, 20, 21, 22 and on Days 33, 34, 35, 36, used to assess steady state.
$C_{max,n}$	Maximum measured plasma concentration over the dosing interval on Days 22 and 36.
$C_{min,n}$	Concentration at the end of the dosing interval ($t = 24$ hours) on Days 22 and 36.
$T_{max,n}$	Time of the maximum measured plasma concentration over the dosing interval on Days 22 and 36. If the maximum value occurred at more than one point, $T_{max,n}$ was defined as the first time point with this value.
C_{ss}	$\frac{AUC_{0-\tau}}{\tau}$, where $\tau = 24$ hours
% Fluctuation:	Degree of concentration fluctuation at steady state = $\frac{(C_{max,n} - C_{min,n})}{C_{ss}} * 100$
% Swing:	Degree of concentration swing at steady state = $\frac{(C_{max,n} - C_{min,n})}{C_{min,n}} * 100$
M/P Ratio:	Metabolite/Parent ratio based on $AUC_{0-\tau}$ corrected for molecular weight. The following M/P ratios were computed: (1) Bupropion Erythroamino Alcohol/Bupropion (2) Bupropion Threoamino Alcohol/Bupropion (3) Hydroxybupropion/Bupropion

Steady State Analysis

Two steady state analyses were performed on the ln-transformed pre-dose concentrations of bupropion, hydroxybupropion, bupropion threoamino alcohol, bupropion erythroamino alcohol and PAWC. The first analysis was executed using the pre-dose concentrations on Days 19, 20, 21 and 22, whereas the second analysis was performed using the pre-dose concentrations on Days 33, 34, 35 and 36. The comparison between timepoints was based on Helmert's contrasts 5. The ANOVA model included treatment, time and the interaction treatment*time as fixed effects. In order to model the correlation within every subject, an appropriate variance-covariance matrix structure was chosen among the following: unstructured (UN), compound symmetry (CS), compound symmetry heterogeneous (CSH), variance component (VC), autoregressive (AR(1)), autoregressive heterogeneous (ARH(1)) and autoregressive moving average (ARMA(1,1)), using the Akaike's Burnham and Anderson criterion (AICC, smaller is better). If the treatment*time interaction was not statistically significant, at a 5% level, the interaction term was dropped from the model. If a statistically significant interaction was found, results were presented by treatment, separately. Helmert's contrasts were constructed such that each time point was compared to the mean of the subsequent time points. The contrasts were:

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Contrast	Steady State Assessments Days 19 to 22
Compar.1	Pre-dose Day 19 vs. mean of (Pre-dose Days 20, 21 and 22)
Compar.2	Pre-dose Day 20 vs. mean of (Pre-dose Days 21 and 22)
Compar.3	Pre-dose Day 21 vs. Pre-dose Day 22

Contrast	Steady State Assessments Days 33 to 36
Compar.1	Pre-dose Day 33 vs. mean of (Pre-dose Days 34, 35 and 36)
Compar.2	Pre-dose Day 34 vs. mean of (Pre-dose Days 35 and 36)
Compar.3	Pre-dose Day 35 vs. Pre-dose Day 36

For each analysis on Days 19-22 and Days 23-36, steady state was concluded only if Helmert's contrasts were not statistically significant on at least three pre-dose concentration values at a level of 5%.

Additionally, geometric means were calculated for each treatment at each time point.

Analyses of Variance

Analyses of variance were performed on the ln-transformed pharmacokinetic parameters AUC_{0-T}, C_{max,ss} and C_{min,ss}. The ANOVA model included sequence, treatment, and period (Days 9 to 22 and Days 23 to 36) as fixed effects, and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term, at a 10% level of significance. Each ANOVA included calculation of LSM, the difference between treatment LSM, and the standard error associated with this difference. The above statistical analyses were performed using the appropriate SAS® procedure.

ANALYTICAL

ASSAY VALIDATION

Parameter	Bupropion	Bupropion Erythroamino Alcohol	Bupropion Threoamino Alcohol	Hydroxybupropion
Method	LC\ Mass Spectrometric \ Mass Spectrometric Detection			
Freeze-thaw	3 cycles	3 cycles	3 cycles	3 cycles
Benchtop Stability at RT	24 hrs	24 hrs	24 hrs	24 hrs
Long term at -70° C	178 days(3 and 772 ng/ml)	178 days(2 and 752 ng/ml)	178 days(2.9 and 750 ng/ml)	178 days(11 and 2942 ng/ml)

Recovery Average of Low QC, High QC	93%	94%	94%	94%
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First Subject Dosed Jan 16, 2007
 Last Sample Analyzed Feb 27, 2007
 Total Storage Time 40 days

Parameter	Bupropion	Bupropion Erythroamino Alcohol	Bupropion Threoamino Alcohol	Hydroxybupropion
Method	HPLC with Mass Spectrometric Detection			
Sensitivity/ LOQ	1 ng/ml	1 ng/ml	1 ng/ml	3.9 ng/ml
Linearity (Standard curve samples)	1-1023 ng/ml	1-1024 ng/ml	1-1024 ng/ml	3.9-3999 ng/ml
Quality Control (QC) Samples	3, 191, 767 ng/ml	3,192,768 ng/ml	3, 192, 768 ng/ml	11.7, 749, 2999 ng/ml
Precision of Standards (%CV)	5.8% @ 1 ng/ml 5.8%@ 1023 ng/ml	6.1% @ 1 ng/ml 6.3%@ 1024ng/ml	7.1% @ 1 ng/ml 5.8%@ 1024 ng/ml	4.9% @ 3.9 ng/ml 6.2%@3998.99 ng/ml
Precision of QC Samples (%CV)	5 %@ 3 ng/ml 5.7 %@ 767 ng/ml	8.6 %@ 3 ng/ml 5.2 %@ 768 ng/ml	7.2 %@ 3 ng/ml 5.7%@ 768 ng/ml	4.8 %@ 11.7 ng/ml 5.3 %@ 2999 ng/ml
Accuracy of Standards (%)	105%@ 1 ng/ml 99%@ 1023 ng/ml	100%@ 1 ng/ml 98%@ 1023 ng/ml	101%@ 1 ng/ml 98%@ 1024 ng/ml	100%@ 3.9 ng/ml 98%@ 3998ng/ml

Accuracy of QC Samples (%)	97 %@ 3 ng/ml 104 %@ 767 ng/ml	99 %@ 3 ng/ml 104 %@ 768 ng/ml	99 %@ 3 ng/ml 99 %@ 768 ng/ml	99 %@ 11.7ng/ml 100 %@ 2999 ng/ml
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RESULTS

Table 1 Least-Squares Mean Concentrations and Helmert Contrast p-values for Bupropion in Periods 1 and 2

Analyte	Day	Least-Squares Mean (ng/mL)	Contrast	p-value
Bupropion Period 1	19	35.389	Compar. 1	0.0546
	20	34.294	Compar. 2	0.0761
	21	31.703	Compar. 3	0.7855
	22	32.108	-	-
Bupropion Period 2	33	29.763	Compar. 1	0.9850
	34	28.295	Compar. 2	0.0896
	35	30.697	Compar. 3	0.7879
	36	30.294	-	-

Period 1: Compar. 1 Pre-dose Day 19 vs. mean of (Pre-dose Days 20, 21 and 22)
 Compar. 2 Pre-dose Day 20 vs. mean of (Pre-dose Days 21 and 22)
 Compar. 3 Pre-dose Day 21 vs. Pre-dose Day 22
 Period 2: Compar. 1 Pre-dose Day 33 vs. mean of (Pre-dose Days 34, 35 and 36)
 Compar. 2 Pre-dose Day 34 vs. mean of (Pre-dose Days 35 and 36)
 Compar. 3 Pre-dose Day 35 vs. Pre-dose Day 36

In Period 1, pre-dose plasma concentrations of bupropion had reached steady state levels by Day 19, as all contrasts were not statistically different (> 0.05). With the change in treatment administration in Period 2, steady state was maintained for bupropion pre-dose concentrations. These results demonstrate that the relative bioavailability of bupropion for both dosage strength tablets was assessed under steady state conditions on Days 22 and 36.

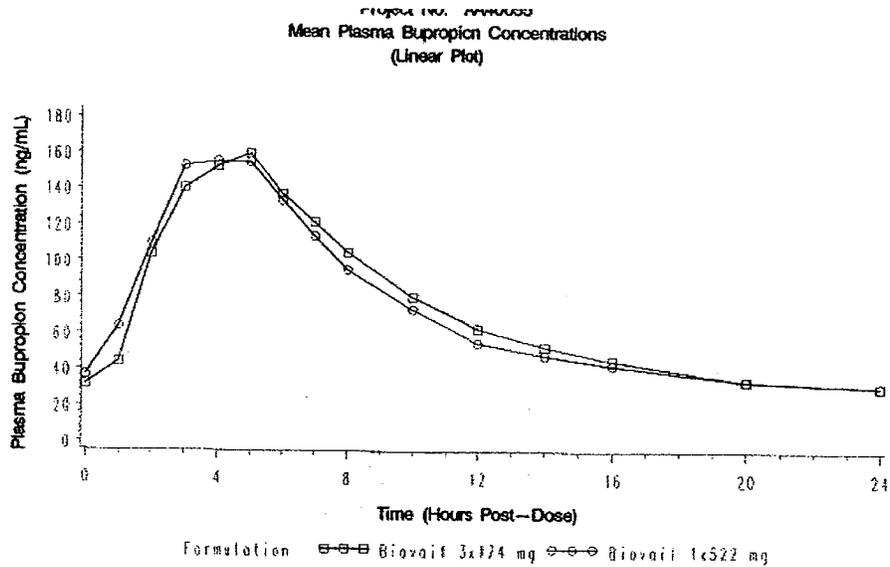


Table 2. Pharmacokinetic Parameters of Bupropion

Parameter	Bupropion	
	Bupropion HBr XL 1 x 522 mg tablet	Bupropion HBr XL 3 x 174 mg tablets
Geometric Mean (% CV)		
AUC ₀₋₂₄ (ng-h/mL)	1655 (32.4%)	1677 (33.0%)
C _{max,ss} (ng/mL)	165 (37.2%)	159 (32.0%)
C _{min,ss} (ng/mL)	28.8 (44.6%)	28.9 (41.4%)
Median Tmax (Min - Max)		
T _{max,ss} (h)	4.00 (2.00 - 7.00)	5.00 (3.00 - 6.06)
Arithmetic Mean (± SD)		
AUC ₀₋₂₄ (ng-h/mL)	1730 ± 494	1763 ± 574
C _{max,ss} (ng/mL)	176 ± 63.6	167 ± 53.0
C _{min,ss} (ng/mL)	31.4 ± 13.4	31.3 ± 13.2
C _{trough} (ng/mL)	72.1 ± 20.6	73.5 ± 23.9
Fluctuation (%)	200 ± 48.6	187 ± 24.9
Swing (%)	522 ± 251	468 ± 143

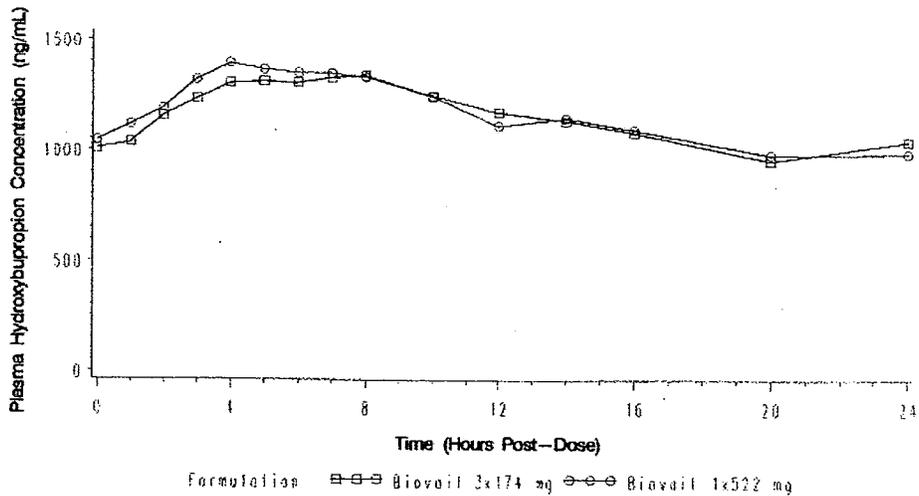
At steady state, the mean rate and extent of systemic exposure of bupropion within the 24 hours dosing interval (C_{max,ss}, AUC₀₋₂₄) were similar between Bupropion HBr XL 1 x 522 mg tablet and Bupropion HBr XL 3 x 174 mg tablets. The mean % fluctuation and the mean % swing values were 7% and 12%, respectively greater for Bupropion HBr XL 1 x 522 mg tablet compared to Bupropion HBr XL 3 x 174 mg tablets.

Table 3. Summary of Pharmacokinetic Results

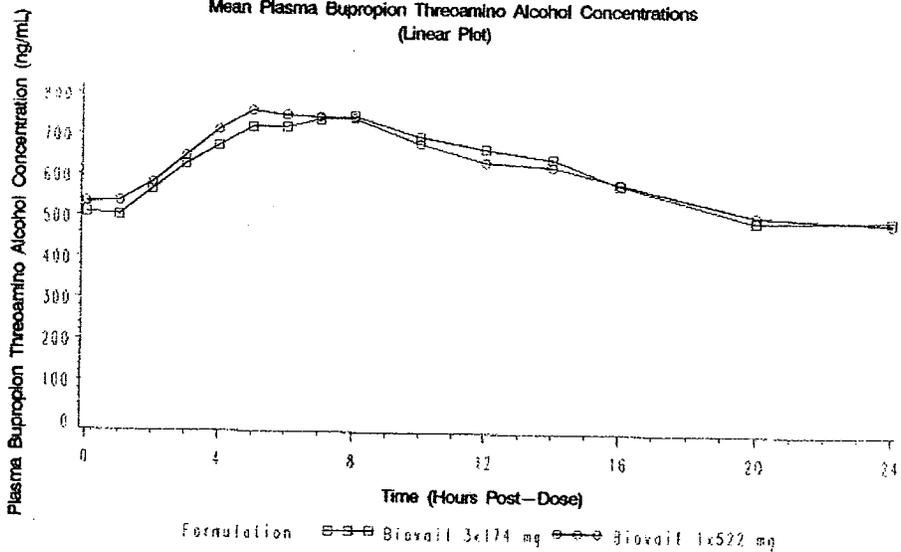
Parameter	Bupropion
	Biovail Bupropion HBr XL 1 x 522 mg tablet (A) vs. Biovail Bupropion HBr XL 3 x 174 mg tablets (B)
AUC ₀₋₂₄	97.8 % (91.4 % - 104.5 %)
C _{max,ss}	103.2 % (96.0 % - 111.0 %)
C _{min,ss}	99.0 % (90.7 % - 108.0 %)

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Project No. AA4005
 Mean Plasma Hydroxybupropion Concentrations
 (Linear Plot)



Project No. AA40055
 Mean Plasma Bupropion Threoamino Alcohol Concentrations
 (Linear Plot)



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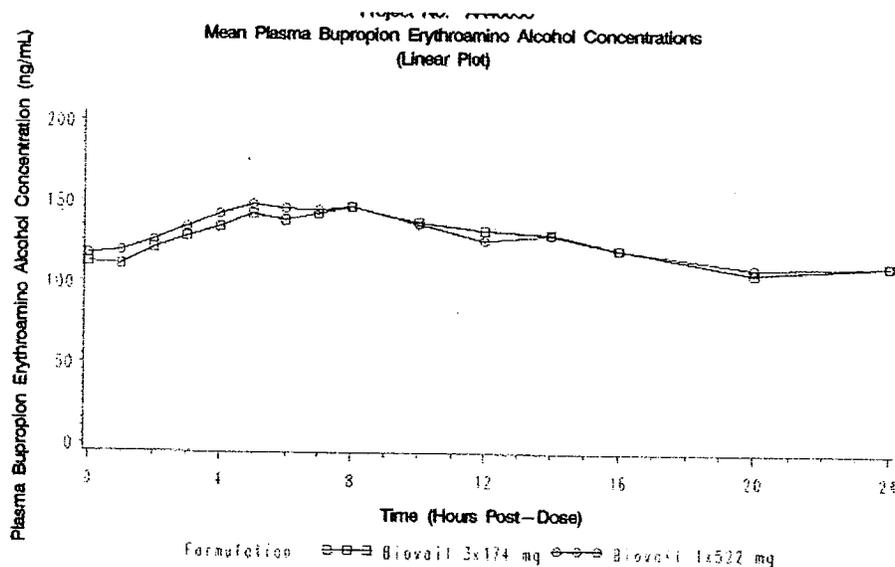


Table 4. Pharmacokinetic Parameters for Bupropion Metabolites

Parameter	Hydroxybupropion		Bupropion Threoamino Alcohol		Bupropion Erythroamino Alcohol	
	Bupropion HBr XL 1 x 522 mg	Bupropion HBr XL 3 x 174 mg	Bupropion HBr XL 1 x 522 mg	Bupropion HBr XL 3 x 174 mg	Bupropion HBr XL 1 x 522 mg	Bupropion HBr XL 3 x 174 mg
Geometric Mean (% CV)						
AUC _{0-∞} (ng·h/mL)	25158 (53.4%)	25271 (48.5%)	13802 (40.2%)	13658 (40.7%)	2857 (38.0%)	2831 (36.5%)
C _{max,ss} (ng/mL)	1338 (48.5%)	1311 (42.9%)	753 (38.3%)	731 (39.6%)	146 (35.8%)	144 (36.9%)
C _{min,ss} (ng/mL)	880 (57.7%)	943 (54.5%)	450 (48.7%)	466 (40.8%)	101 (48.2%)	105 (36.7%)
Median Tmax (Min - Max)						
T _{max,ss} (h)	5.04 (2.00 - 8.00)	7.00 (3.00 - 12.00)	6.00 (2.03 - 10.00)	7.00 (3.00 - 14.00)	6.00 (2.00 - 10.00)	8.00 (3.00 - 16.00)
Arithmetic Mean (± SD)						
AUC _{0-∞} (ng·h/mL)	27738 ± 10583	27389 ± 9385	14840 ± 5929	14730 ± 6138	3048 ± 1135	3006 ± 1075
C _{max,ss} (ng/mL)	1457 ± 530	1402 ± 446	805 ± 309	785 ± 311	156 ± 55.4	154 ± 54.9
C _{min,ss} (ng/mL)	986 ± 415	1042 ± 410	496 ± 220	504 ± 218	111 ± 46.5	7.38 ± 2.81
C _{max,ss} (ng/mL)	1156 ± 441	1141 ± 391	618 ± 247	614 ± 256	127 ± 47.3	125 ± 44.8
Fluctuation (%)	43.0 ± 17.3	34.9 ± 15.4	52.1 ± 19.0	46.7 ± 13.3	37.1 ± 17.0	33.5 ± 12.6
Swing (%)	55.1 ± 32.8	40.5 ± 20.8	71.9 ± 45.3	58.3 ± 20.3	47.3 ± 32.9	38.6 ± 16.9
M/P ratio	15.7 ± 6.82	16.0 ± 8.35	8.65 ± 2.70	8.47 ± 2.83	1.81 ± 0.599	1.77 ± 0.610

At steady state, the metabolic ratios based on the AUC_{0-∞} of hydroxybupropion, bupropion threoamino alcohol and bupropion erythroamino alcohol over bupropion were 15.7, 8.65, and 1.81, respectively, for the Biovail Bupropion HBr XL 1 x 522 mg tablet. Metabolic ratios were similar when compared to Biovail Bupropion HBr XL 3 x 174 mg tablets.

The mean % fluctuation and the mean % swing values of all bupropion metabolites were comparable following both dosage strength tablets (1 x 522 mg and 3 x 174 mg tablets).

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Table 5. Summary of Pharmacokinetic Results

Parameter	Ratios of LSM (90% Confidence Intervals)		
	Hydroxybupropion Biovail Bupropion HBr XL 1 x 522 mg (A) vs. Biovail Bupropion HBr XL 3 x 174 mg tablets (B)	Bupropion Threoamino Alcohol Biovail Bupropion HBr XL 1 x 522 mg (A) vs. Biovail Bupropion HBr XL 3 x 174 mg tablets (B)	Bupropion Erythroamino Alcohol Biovail Bupropion HBr XL 1 x 522 mg (A) vs. Biovail Bupropion HBr XL 3 x 174 mg tablets (B)
AUC _{0-∞}	99.5 % (95.3 % – 104.0 %)	100.9 % (94.1 % – 108.1 %)	100.7 % (94.6 % – 107.2 %)
C _{max,ss}	102.2 % (98.0 % – 106.6 %)	102.6 % (95.4 % – 110.3 %)	101.0 % (94.8 % – 107.6 %)
C _{min,ss}	93.7 % (87.7 % – 100.2 %)	96.6 % (88.2 % – 105.7 %)	96.4 % (88.2 % – 105.4 %)

The 90 % confidence intervals of the ratio of LSM derived from the analyses of the ln-transformed pharmacokinetic parameters AUC_{0-∞}, C_{max,ss} and C_{min,ss} for all bupropion metabolites were within 80.0-125.0%.

A statistically significant ($p < 0.1$) sequence effect was observed for AUC_{0-∞}, C_{max,ss} and C_{min,ss} for hydroxybupropion. However, this study meets the criteria for acceptability of studies with sequence effects listed in the Division of Bioequivalence guidance on statistical procedures (i.e., it is a single dose study using a two-treatment crossover design with normal healthy volunteers); the drug is not an endogenous entity; the study was based on an acceptable protocol and used a validated assay methodology (see Analytical Report); the study data were analyzed by appropriate statistical methods. Additionally, due to the fact that the margin of error (type I) was of 10%, the observed statistically significant sequence effect may fall within this 10%, which means in that case that it would erroneously suggest a sequence effect. Therefore, the observed sequence effect should not compromise the assessment of relative bioavailability.

DISCUSSION AND OVERALL CONCLUSIONS

Following repeated oral administrations of bupropion Hydrobromide XL Tablets (522 mg vs. 3 x 174 mg) in healthy volunteers, the 90 % confidence intervals of the ratios of LSM derived from the analyses of the ln transformed pharmacokinetic parameters AUC_{0-∞}, C_{max,ss} and C_{min,ss} for bupropion, hydroxybupropion, bupropion threoamino alcohol, bupropion erythroamino alcohol in plasma were within 80.0-125.0%.

In conclusion, results from the current dosage strength proportionality study demonstrated that repeated oral administrations of Biovail bupropion hydrobromide XL tablets as a single 522 mg tablet and three 174 mg tablets are equivalent under multiple dose fasting conditions.

Based upon the results of the simulations for the 174 mg and 348 mg strengths which established the similarity between the single and multiple dose

pharmacokinetics for bupropion the results of this multiple dosing only study can be used to extrapolate that the 1x522 mg strength would show BE under single dose fasting conditions. (See review NDA 22-108 Date September 18, 2007). Therefore, a single dose study will not be requested for the 522 mg study.

DISSOLUTION:

DISSOLUTION CONDITIONS:

The methodology employed for Bupropion HBr XL tablets is the same as the approved method for Wellbutrin XL Tablets.

Dissolution Medium:	0.1 NHCL
Volume:	900 ml
Sampling Times:	15 min intervals for 1 hr Hourly intervals for 18 hrs
Speed:	75 RPM
Temperature:	37C
Apparatus I:	USP Basket

522 mg Dissolution:

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Lot 06M377

Time (Hours)	Vessel #						Average	Minimum	Maximum
	1	2	3	4	5	6			
2									
4									
8									
16									

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Lot 06M378

Time (Hours)	Vessel #						Average	Minimum	Maximum
	1	2	3	4	5	6			
2									
4									
8									
16									

Lot 06M354

Time (Hours)	Vessel #						Average	Minimum	Maximum
	1	2	3	4	5	6			
2									
4									
8									
16									

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The certificates of analysis of all three batches of 522mg Bupropion HBr XL Tablets are presented in the following pages.

The Lot 06M354 is the BIO-LOT and is the same as lots 06M119P and bulk lot 06M303

Dissolution Conditions

MEDIUM: 0.1N HCl
APPARATUS: BASKET
SPEED: 75 rpm
Sampling Times: 2, 4, 8, and 16 hrs

Firms PROPOSED DISSOLUTION SPECIFICATIONS

2 HOURS	NMT	DISSOLVED
4 HOURS	—	DISSOLVED
8 HOURS	NLT	DISSOLVED
16 HOURS	NLT	DISSOLVED

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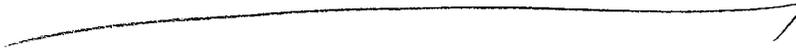
The FDA has examined the dissolution data for the 522 mg tablet in conjunction with the previous dissolution data submitted for the 174 mg and 348 mg tablets and established dissolution specifications that would be appropriate for all three strengths.

FDA PROPOSED DISSOLUTION SPECIFICATIONS		
2 HOURS	_____	DISSOLVED
4 HOURS	_____	DISSOLVED
8 HOURS	NLT —	DISSOLVED

b(4)

LABEL

b(4)



b(4)

SIGNATURES

Andre Jackson _____
Reviewer, Psychopharmacological Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FTinitialized by Raman Baweja, Ph.D. _____

Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology
cc: NDA 22-108, HFD-860(Mehta, Baweja, Jackson)

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APPENDIX
Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Bupropion Hydrobromide
PRODUCT (Brand Name):	Tradename
DOSAGE FORM:	Extended Release Tablets
DOSAGE STRENGTHS:	174 mg and 348 mg Tablets
NDA:	22-108
NDA TYPE:	New NDA
SUBMISSION DATE:	October 24, 2007
SPONSOR:	BioVail
REVIEWER	Andre Jackson

**REVIEW OF SIMULATIONS TO ESTABLISH THE RELATIONSHIP BETWEEN
SINGLE AND MULTIPLE DOSING FOR THE NEW BUPROPION
HYDROBROMIDE SALT ER FORMULATION FOR BUPROPION**

Background:

The firm has submitted three clinical pharmacology studies to characterize their new formulation. The studies were:

1. Study 3228 A Two-Way Crossover, Open-label, Single-dose, Fasting, Dosage Strength Proportionality Study of Two Strengths (2x174 mg vs. 1x 348 mg tablet) of Bupropion HBr XL tablets.
2. Study 3229 A Two-Way Crossover, Open-Label, Single-Dose, Food-Effect Study of Bupropion HBr XL 348 mg tablet. (highest strength)
3. Study 3230 A Two-Way Crossover, Open-Label, Multiple-Dose Fasting, Comparative Bioavailability study (HBr formulation vs. HCl formulation).

The recommendation from OCP related to these studies was that the relative BA study conducted in this NDA, to compare bupropion hydrobromide and bupropion hydrochloride modified release formulations, was a multiple dose study. It should be noted that a multiple dose comparison minimizes differences in formulations and therefore is not the appropriate test. In this case, where both the test (the HBr salt) and reference (HCl salt) are modified release formulations, a single dose bioequivalence study provides the most sensitive conditions for testing similarity of test and reference formulations and therefore, OCP requires a single dose, fasting bioequivalence study evaluating these two formulations in a minimum of 24 subjects.

A meeting was held to discuss the results of these studies based upon additional analysis that had been submitted by the firm to establish the relationship between the single dose and multiple dose versus the reference product Wellbutrin HCL. The firm's position was that single dose studies were predictive of

multiple dosing for this product. The new pooled data results and the questions raised based upon that data are below:

Results from the pooled data (single dose studies 3228 & 3229 in NDA 22108 vs. studies 2548 & 2571 in NDA 21515) gave the following CIs for parent:

Cmax	(81.8-97)
AUCinf (86-102)	
AUCinf T/R Ratio	=(1607.7/1704.9)=0.94
Cmax	T/R Ratio=(133.4/149)=0.89

Results for the MD study (3220) gave the following CIs for parent:

Cmax	(80.2-92)
AUCt	(84-93.9)
AUCt	T/R Ratio=(1362.44/1541.27)=0.88
Cmax	T/R Ratio=(129.86/151.03)=0.86

- Theory predicts that the range for the Cmax CI should increase from multiple to single dosing. The Cmax CI range is 15 and 12 respectively for the single and multiple dosing studies.
- This increase in the Cmax CI range based upon literature references is to be expected. However, the increase in the lower CI limit following single dosing (i.e., the pooled data) is unexpected.
- The ratio for the fraction of drug which is bioavailable decreases from single to multiple dosing, as defined by the respective T/R AUC ratios, which may be a contributing factor.
- Therefore, these results are difficult to interpret.

These apparent differences in the analyses are difficult to understand if indeed the pooled single dose data is predictive of multiple dose behavior.

It was mutually agreed that a simulation study could be used to address the issues with the following specific simulations requested from the firm:

BUPROPION SIMULATIONS:

1. Using superposition predict the steady-state concentrations for each individual subject in the fasted leg of single dose study 3229 1x348 mg Bupropion HBr treatment and the 1x348 mg Bupropion HBr fasted treatment arm of study 3228. Plot the single and predicted multiple dose profiles. Also provide a plot of the observed steady-state curves for each subject in study 3230.
2. Compare the mean profiles at steady-state separately from superposition for studies 3229 and 3228 with the results for the 1x348 mg fasted treatment arm for the Bupropion HBr in study 3230.
3. For the superimposed steady-state concentrations for each subject from #1 prepare 200 bootstrap samples which will be the test treatment. Also prepare 200 bootstrap samples for the observed Wellbutin XL formulation at steady-state (i.e., study 3230) as the reference. Calculate AUCinf and Cmax for each subject for the 200 bootstrapped test and reference samples. Analyze the data using a parallel design model and calculate the mean 90% CI for each parameter.
4. Increase the individual concentration values for each subject at each time prior to Cmax (0-6hrs) by 5% then by 10% and finally by 20%. **This can be done for either the fasted leg of single dose study 3229 1x348 mg Bupropion HBr treatment or the 1x348 mg Bupropion HBr fasted treatment arm of study 3228, if they both are superimposable with the steady-state study 3230 in step #2.**

5. Repeat steps 1-3 on each of the respective per cent changes in the time points from (0-6 hrs). This step should be completed (i.e., each study has had the absorption concentrations increased by 5-20% for each individual subject). When this is completed then the mean curves in # 6 can be estimated.

6. **Summarize** and provide mean curves for Bupropion HBr (i.e., increased by 5%, 10% and 20%) and compare with the mean steady-state curve for the fasting 348 mg arm of study 3230 for Wellbutrin XL. **Summarize the 90% CI** for each of the simulated Bupropion HBr (i.e., increased by 5%, 10% and 20% respectively) as test vs. Wellbutrin XL (ref) 300 mg collected in study 3230.

7. Based upon the simulated single dose curves i.e., 5%, 10% and 20% determine which per cent change in absorption single dose plasma concentrations from 0-6 hrs would result in steady-state ratios close to the observed 0.89 test/reference ratio in study 3230.

Results:

Figure 1: Comparison of simulated (Study 3229) and observed (Study 3230) plasma bupropion concentrations

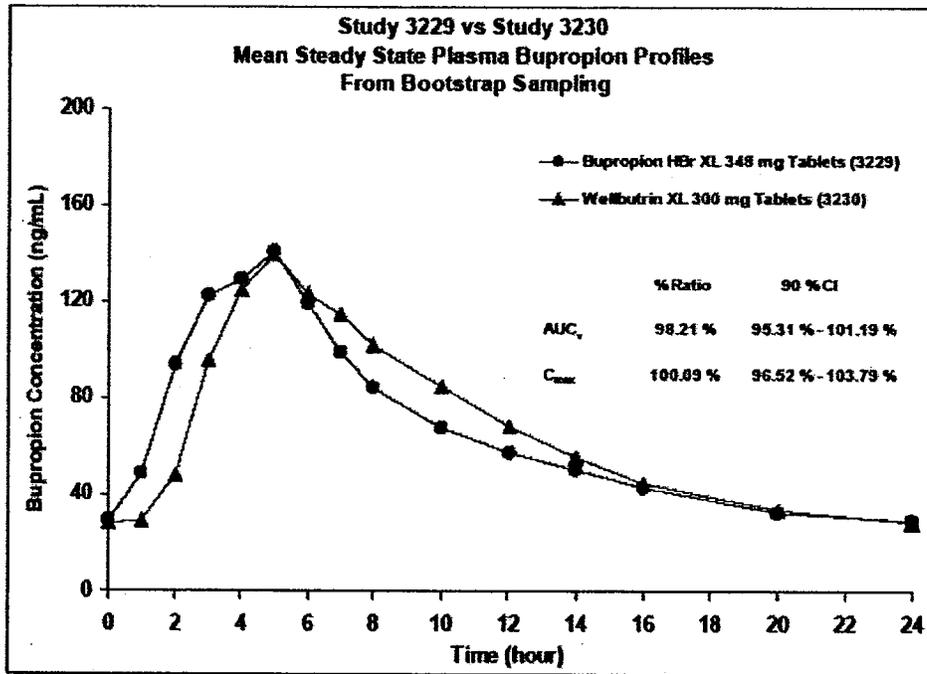


Figure 2: Comparison of simulated (Study 3228) and observed (Study 3230) plasma bupropion concentrations

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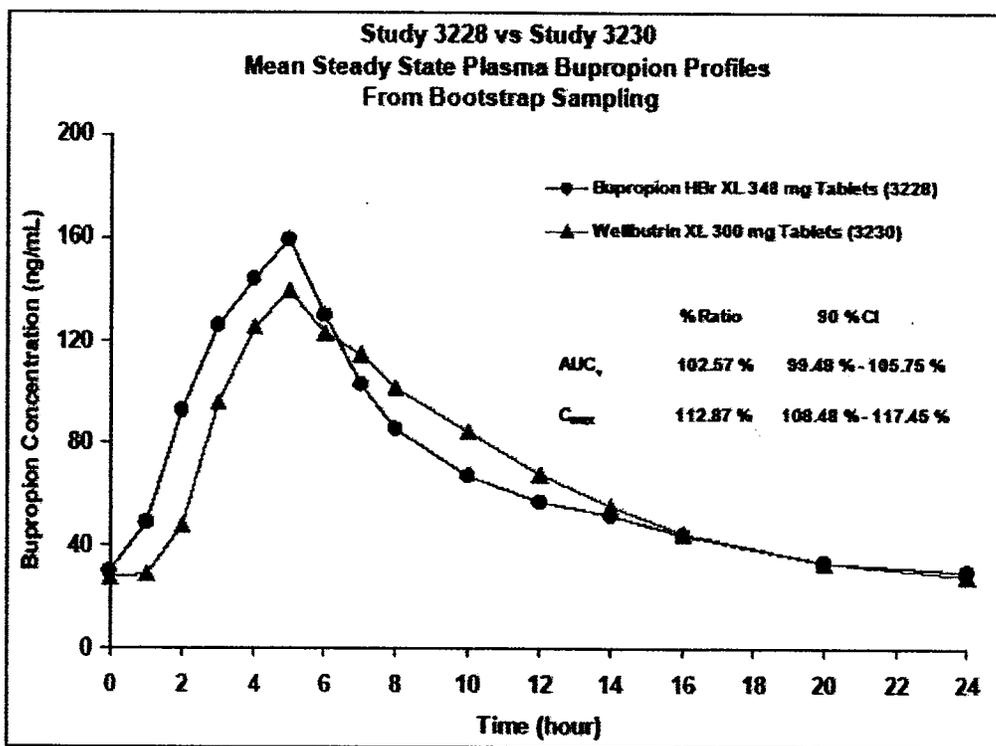


Table 1: Mean PK Parameter and Summary Statistics For Bupropion HBr XL 348 mg Tablets (Study 3229) With a 20% Increase in Concentration up to C_{max} Versus Wellbutrin XL 300 mg Tablets (Study 3230) Based on Bootstrap Sampling

	Study 3229	Study 3230	Bupropion HBr XL 348 mg Tablets vs Wellbutrin XL 300 mg Tablets	
	Bupropion HBr XL 348 mg Tablets (n=48)	Wellbutrin XL 300 mg Tablets (n=38)		
	Mean±SD Geometric Mean	Mean±SD Geometric Mean	Ratio of Geometric Means	90 % Geometric Confidence Intervals
AUC _t (ng*hr/mL)	1631.57 ± 158.53 1624.10 (9.72 %)	1581.39 ± 107.35 1577.97 (6.79 %)	102.92 %	99.83 % - 106.12 %
C _{max} (ng/mL)	160.05 ± 18.88 158.97 (11.80 %)	140.56 ± 12.05 140.08 (8.57 %)	113.48 %	109.31 % - 117.81 %

Table 2: Mean PK Parameter and Summary Statistics For Bupropion HBr XL 348 mg Tablets (Study 3228) With a 20% Increase in Concentration up to C_{max} Versus Wellbutrin XL 300 mg Tablets (Study 3230) Based on Bootstrap Sampling

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	Study 3228	Study 3230	Bupropion HBr XL 348 mg Tablets vs Wellbutrin XL 300 mg Tablets	
	Bupropion HBr XL 348 mg Tablets (n=46)	Wellbutrin XL 300 mg Tablets (n=38)		
	Mean±SD Geometric Mean	Mean±SD Geometric Mean	Ratio of Geometric Means	90 % Geometric Confidence Intervals
AUC _t (ng*hr/mL)	1699.49 ± 166.00 1691.60 (9.77 %)	1581.39 ± 107.35 1577.97 (6.79 %)	107.20 %	103.94 % - 110.57 %
C _{max} (ng/mL)	179.12 ± 24.69 177.47 (13.78 %)	140.56 ± 12.05 140.08 (8.57 %)	126.69 %	121.45 % - 132.17 %

Comments:

1. The simulations done by the firm clearly showed that the single dose studies 3228 and 3229 predicted the observed multiple dose data from study 3230. The reason for the poorer predictions for the 3228 study was due to the increase in RMSE from 16% to 28% in study 3228.
2. The addition of up to 20% variability in the absorption phase resulted in only the C_{max} for the Study 3228 to exceed the limits of 80-125% for C_{max}. This is due to the larger RMSE for the 3228 Study.
3. The addition of up to 20% variability in the absorption phase did not result in the 90% CI C_{max} or AUC for the Study 3229 to exceed the limits of 80-125%.
4. The superposition results were reproduced by OCP using WinNonlin. The SAS code was checked and was appropriate for bootstrapping.
5. Based upon these results the firm will not be requested to do a single dose, fasting bioequivalence study comparing Bupropion HBr and Wellbutrin XL in a minimum of 24 subjects.

SIGNATURES

Andre Jackson _____
 Reviewer, Psychopharmacological Drug Section, DCP I
 Office of Clinical Pharmacology and Biopharmaceutics

RD/FT initialized by Raman Baweja, Ph.D. _____
 Team Leader, Psychiatry Drug Section, DCP I
 Office of Clinical Pharmacology
 cc: NDA 22-108, HFD-860(Mehta, Baweja, Jackson)
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I. Representative individual graphs for Study 3229 with a 5% increase in plasma concentrations prior to C_{max}

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Andre Jackson
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BIOPHARMACEUTICS

Raman Baweja
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BIOPHARMACEUTICS

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Bupropion Hydrobromide
PRODUCT (Brand Name):	Tradename
DOSAGE FORM:	Extended Release Tablets
DOSAGE STRENGTHS:	174 mg and 348 mg Tablets
NDA:	22-108
NDA TYPE:	New NDA
SUBMISSION DATE:	September 27, 2006
SPONSOR:	BioVail
REVIEWER	Andre Jackson

REVIEW OF A NEW BUPROPION HYDROBROMIDE SALT ER FORMULATION FOR BUPROPION

EXECUTIVE SUMMARY

Bupropion hydrochloride (HCl) is an antidepressant agent of the aminoketone class with neurochemical properties that are different from tricyclics/tetracyclics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, or other known antidepressant agents. It has been suggested that bupropion acts as a sympathomimetic amine by selectively inhibiting the reuptake of norepinephrine and dopamine. Bupropion has no clinically relevant action on serotonin and does not inhibit monoamine oxidase. The mechanism of action of bupropion appears to be mediated by its noradrenergic and/or dopaminergic action. The advantages of bupropion relative to serotonergically active drugs are the generally lower incidence of gastrointestinal side effects, and the possibly lower incidence of sexual dysfunction.

Biovail has developed a once daily, extended release (XL) tablet formulation of bupropion in the form of a hydrobromide salt. The new XL tablet contains the same amount of the active ingredient, bupropion, as in the commercially available product Wellbutrin XL® Tablets which contains bupropion as a hydrochloride (HCl) salt. A 174 mg tablet of bupropion HBr contains the same molar amount of bupropion base as a 150 mg tablet of bupropion HCl.

The in-vitro dissolution results show no potential of ethanol-induced dose dumping with the bupropion hydrobromide extended release tablets.

The following Table summarizes the MW and base equivalent relationship between Bupropion HBr and Bupropion HCL.

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

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The firm has submitted a 505(b)2 application for the approval of the new bupropion hydrobromide ER tablet. The currently approved salt form is bupropion hydrochloride XR tablet.

There were no additional clinical studies conducted.

The firm has submitted three clinical pharmacology studies to characterize their new formulation. The studies were:

1. Study 3228 A Two-Way Crossover, Open-label, Single-dose, Fasting, Dosage Strength Proportionality Study of Two Strengths (2x174 mg vs 1x 348 mg tablet) of Bupropion HBr XL tablets.

2. Study 3229 A Two-Way Crossover, Open-Label, Single-Dose, Food-Effect Study of Bupropion HBr XL 348 mg tablet. (highest strength)

3. Study 3230 A Two-Way Crossover, Open-Label, Multiple-Dose Fasting, Comparative Bioavailability study.

- The 2x174 mg vs 1x348 mg study showed dosage strength equivalence
- There was no effect of food on the absorption of the new bupropion hydrobromide ER tablet.
- The relative BA for the extent of absorption for Bupropion hydrobromide was 90% of that observed for Bupropion hydrochloride (HCl).

RECOMMENDATIONS

1. The Clinical Pharmacology and Biopharmaceutics section of NDA 22-108 is not acceptable to OCPB.

COMMENTS TO THE SPONSOR

1. DISSOLUTION

MEDIUM: 900 ml 0.1N HCl
APPARATUS I : BASKET
SPEED: 75 rpm

FDA PROPOSED DISSOLUTION SPECIFICATIONS

2 HOURS NMT — DISSOLVED
4 HOURS — DISSOLVED
8 HOURS NLT — DISSOLVED

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2. SINGLE DOSE BIOEQUIVALENCE STUDY

The relative BA study conducted in this NDA, to compare bupropion hydrobromide and bupropion hydrochloride modified release formulations, was a multiple dose study. It should be noted that a multiple dose comparison minimizes differences in formulations and therefore is not the appropriate test. In this case, where both the test (the HBr salt) and reference (HCl salt) are modified release formulations, a single dose bioequivalence study provides the most sensitive conditions for testing similarity of test and reference formulations and therefore, OCP requires a single dose, fasting bioequivalence study evaluating these two formulations in a minimum of 24 subjects. The parent and only the 4-hydroxybupropion metabolite should be measured and reported with the understanding that bioequivalence consideration will be based only on the parent drug.

COMMENTS TO THE CLINICAL DIVISION

The relative BA study conducted in this NDA, to compare bupropion hydrobromide and bupropion hydrochloride modified release formulations, was a multiple dose study. It should be noted that a multiple dose comparison minimizes differences in formulations and therefore is not the appropriate test. In this case, where both the test (the HBr salt) and reference (HCl salt) are modified release formulations, a single dose bioequivalence study provides the most sensitive conditions for testing similarity of test and reference formulations and therefore, OCP requires a single dose, fasting bioequivalence study evaluating these two formulations in a minimum of 24 subjects. The parent and only the 4-hydroxybupropion metabolite should be measured and reported with the understanding that bioequivalence consideration will be based only on the parent drug.

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QUESTION BASED REVIEW

IS THERE EQUIVALENCY BETWEEN THE 2X 174 MG ER TABLET TO THE 1X348 MG ER TABLET.?

A single dose fasting two-way crossover study was done in 48 non-smoking males and females. The dosage strength proportionality was investigated by administering a 2 x174 mg tablet dose of bupropion HBr and comparing the results to that for a 1x348 mg dose. Plasma samples were collected to 216 hrs and there was a 14 day washout between treatments.

Pharmacokinetics for Bupropion

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean \pm SD	
	2 x Bupropion HBr XL 174 mg Tablets (A) (n=46)	1 x Bupropion HBr XL 348 mg Tablet (B) (n=46)
	AUC ₀₋₄ (ng·hr/mL)	1523.91 (30.65) 1596.96 \pm 489.42
AUC _{0-inf} (ng·hr/mL)	1585.29 (30.09) 1658.90 \pm 499.09	1556.42 (34.03) 1644.75 \pm 559.69
C _{max} (ng/mL)	122.81 (32.48) 128.54 \pm 41.75	132.51 (37.22) 141.16 \pm 52.54
T _{max} (hr)*	5.00 (3.00-6.07)	5.00 (3.00-7.00)
t _{1/2} (hr)	23.65 \pm 7.36	23.84 \pm 6.90
K _a (hr ⁻¹)	3.29E-02 \pm 1.28E-02	3.17E-02 \pm 9.78E-03
MRT (hr)	23.02 \pm 5.21	22.52 \pm 5.12

* median (min - max)

Parameter	Potency Uncorrected Data		
	90% C.I.	Ratio of Means	Intra-Subject CV
AUC ₀₋₄	96.48% to 107.86%	102.02%	16.01%
AUC _{0-inf}	96.59% to 107.41%	101.85%	15.24%
C _{max}	86.68% to 99.10%	92.68%	19.29%
Parameter	Potency Corrected Data		
	90% C.I.	Ratio of Means	
AUC ₀₋₄	96.39% to 107.75%	101.91%	
AUC _{0-inf}	96.49% to 107.30%	101.75%	
C _{max}	86.59% to 98.99%	92.58%	

Table 11.2 - Pharmacokinetic Parameters for Hydroxybupropion

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean \pm SD	
	2 x Bupropion HBr XL 174 mg Tablets (A) (n=46)	1 x Bupropion HBr XL 348 mg Tablet (B) (n=46)
	AUC ₀₋₄ (ng·hr/mL)	21175.12 (50.57) 24691.89 \pm 12487.03
AUC _{0-inf} (ng·hr/mL)	21601.69 (50.27) 25050.12 \pm 12593.05	20505.06 (59.96) 24779.61 \pm 14857.90
C _{max} (ng/mL)	421.40 (46.88) 480.18 \pm 225.10	411.57 (50.75) 478.90 \pm 243.02
T _{max} (hr)*	14.00 (5.00-24.00)	8.00 (5.00-24.00)
t _{1/2} (hr)	26.51 \pm 5.77	26.05 \pm 6.24
K _a (hr ⁻¹)	2.75E-02 \pm 6.70E-03	2.83E-02 \pm 7.62E-03
MRT (hr)	43.58 \pm 8.67	42.84 \pm 9.32
M/P Ratio	15.02 \pm 9.00	15.08 \pm 11.14

* median (min - max)

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Table 11.7 – Relative Bioavailability Analysis of 2 x Bupropion HBr XL 174 mg Tablets (A) versus 1 x Bupropion HBr XL 348 mg Tablet (B) for hydroxybupropion

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC _{0-t}	98.60% to 112.69%	105.41%	19.23%
AUC _{0-inf}	98.62% to 112.54%	105.35%	19.01%
C _{max}	97.00% to 108.08%	102.39%	15.53%

Pharmacokinetic Parameters for Bupropion Erythroamino Alcohol

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Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean \pm SD	
	2 x Bupropion HBr XL 174 mg Tablets (A) (n=46)	1 x Bupropion HBr XL 348 mg Tablet (B) (n=46)
AUC ₀₋₄ (ng-hr/mL)	1624.49 (47.41) 1774.20 \pm 841.09	1556.84 (45.13) 1699.49 \pm 767.04
AUC _{0-inf} (ng-hr/mL)	1713.80 (46.12) 1864.11 \pm 859.71	1663.28 (43.67) 1804.53 \pm 788.09
C _{max} (ng/mL)	29.54 (33.12) 30.79 \pm 10.20	29.01 (33.02) 30.40 \pm 10.04
T _{max} (hr)*	14.00 (5.00-24.00)	13.00 (5.00-24.00)
t _{1/2} (hr)	32.71 \pm 7.84	32.51 \pm 8.78
K _d (hr ⁻¹)	2.24E-02 \pm 5.24E-03	2.27E-02 \pm 5.72E-03
MRT (hr)	52.66 \pm 11.42	52.28 \pm 12.78
M/P Ratio	1.16 \pm 0.68	1.13 \pm 0.50

* median (min – max)

Table 11.9 – Relative Bioavailability Analysis of 2 x Bupropion HBr XL 174 mg Tablets (A) versus 1 x Bupropion HBr XL 348 mg Tablet (B) for bupropion erythroamino alcohol

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC ₀₋₄	98.39% to 110.66%	104.35%	16.89%
AUC _{0-inf}	97.25% to 109.16%	103.04%	16.60%
C _{max}	96.15% to 107.82%	101.82%	16.46%

Table 11.3 – Pharmacokinetic Parameters for Bupropion Threoamino Alcohol

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean \pm SD	
	2 x Bupropion HBr XL 174 mg Tablets (A) (n=46)	1 x Bupropion HBr XL 348 mg Tablet (B) (n=46)
AUC ₀₋₄ (ng-hr/mL)	8720.28 (58.03) 9894.97 \pm 5741.81	8399.01 (53.61) 9441.77 \pm 5061.45
AUC _{0-inf} (ng-hr/mL)	9433.66 (59.13) 10815.80 \pm 6395.02	9012.38 (54.93) 10252.40 \pm 5631.37
C _{max} (ng/mL)	157.76 (45.91) 171.83 \pm 78.89	161.36 (40.12) 173.35 \pm 69.55
T _{max} (hr)*	8.00 (5.00-24.00)	6.00 (5.00-24.00)
t _{1/2} (hr)	56.77 \pm 20.15	53.97 \pm 17.31
K _d (hr ⁻¹)	1.35E-02 \pm 4.44E-03	1.41E-02 \pm 4.58E-03
MRT (hr)	76.90 \pm 28.13	73.60 \pm 23.99
M/P Ratio	6.65 \pm 4.37	6.43 \pm 3.94

* median (min – max)

RELATIVE BIOAVAILABILITY ASSESSMENTS FOR BUPROPION THREOAMINO ALCOH

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC _{0-∞}	98.45% to 109.49%	103.83%	15.26%
AUC ₀₋₁₂	99.20% to 110.45%	104.67%	15.42%
C _{max}	91.39% to 104.59%	97.77%	19.42%

Comment:

The results indicate that a 2x 174 mg ER tablet dose of bupropion HBr is bioequivalent to a 1 x 348 mg ER tablet dose of bupropion HBr with respect to the parent drug bupropion and metabolites, hydroxybupropion, bupropion erythroamino alcohol and bupropion threoamino alcohol for the parameters AUC and Cmax.

WHAT IS THE EFFECT OF FOOD ON THE 348 MG BUPROPION HYDROBROMIDE ER TABLET?

A single dose two-way crossover study was done in 48 non-smoking males and females under fed and fasted conditions. Subjects were dosed with bupropion HBr XL 348 mg tablet.(highest strength)

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PHARMACOKINETIC PARAMETERS FOR BUPROPION:

Pharmacokinetic Parameters	Geometric Mean (%CV)	
	Arithmetic Mean \pm SD	
	Bupropion HBr XL 348 mg Tablets (A) (Fed) (n=48)	Bupropion HBr XL 348 mg Tablets (B) (Fasted) (n=48)
AUC _{0-t} (ng·hr/mL)	1743.38 (29.91) 1813.67 \pm 542.56	1459.22 (27.36) 1514.68 \pm 414.40
AUC _{0-inf} (ng·hr/mL)	1806.08 (29.34) 1876.44 \pm 550.60	1516.77 (26.77) 1572.10 \pm 420.91
C _{max} (ng/mL)	130.36 (31.47) 136.80 \pm 43.05	121.28 (27.41) 125.91 \pm 34.52
T _{max} (hr)*	5.00 (2.00-10.00)	5.00 (3.00-7.00)
t _{1/2} (hr)	23.19 \pm 6.45	21.29 \pm 6.65
K _{e1} (hr ⁻¹)	3.27E-02 \pm 1.10E-02	3.60E-02 \pm 1.17E-02
MRT (hr)	22.36 \pm 5.92	21.20 \pm 5.56

* median (min – max)

(FED/FASTING) RELATIVE BIOAVAILABILITY ASSESSMENTS FOR BUPROPION:

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC _{0-t}	113.23% to 126.06%	119.47%	15.75%
AUC _{0-inf}	112.96% to 125.52%	119.07%	15.47%
C _{max}	98.20% to 117.64%	107.48%	26.83%

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PHARMACOKINETIC PARAMETERS FOR HYDROXYBUPROPION:

Pharmacokinetic Parameters	Geometric Mean (%CV)	
	Arithmetic Mean \pm SD	
	Bupropion HBr XL 348 mg Tablets (A) (Fed) (n=48)	Bupropion HBr XL 348 mg Tablets (B) (Fasted) (n=48)
AUC _{0-t} (ng·hr/mL)	21556.18 (54.71) 25505.66 \pm 13953.00	21143.44 (53.45) 24948.49 \pm 13334.10
AUC _{0-inf} (ng·hr/mL)	22061.74 (54.24) 25870.62 \pm 14032.96	21628.02 (52.78) 25284.90 \pm 13346.59
C _{max} (ng/mL)	457.15 (45.58) 525.08 \pm 239.34	445.93 (43.57) 507.42 \pm 221.07
T _{max} (hr)*	14.00 (7.00-36.00)	8.00 (5.00-24.02)
t _{1/2} (hr)	24.77 \pm 4.81	24.28 \pm 4.92
K _{el} (hr ⁻¹)	2.90E-02 \pm 5.59E-03	2.97E-02 \pm 5.93E-03
MRT (hr)	42.65 \pm 7.61	41.13 \pm 7.37
M/P Ratio	13.17 \pm 5.96	15.48 \pm 7.32

* median (min - max)

(FED/FASTING) RELATIVE BIOAVAILABILITY ASSESSMENTS FOR HYDROXYBUPROPION:

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC _{0-t}	95.40% to 108.96%	101.95%	19.58%
AUC _{0-inf}	95.50% to 108.95%	102.01%	19.41%
C _{max}	96.75% to 108.62%	102.52%	17.00%

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PHARMACOKINETIC PARAMETERS FOR BUPROPION THREOAMINO ALCOHOL:

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean \pm SD	
	Bupropion HBr XL 348 mg Tablets (A) (Fed) (n=48)	Bupropion HBr XL 348 mg Tablets (B) (Fasted) (n=48)
AUC _{0-t} (ng·hr/mL)	9430.21 (53.90) 10454.75 \pm 5635.07	8355.97 (53.13) 9356.36 \pm 4971.39
AUC _{0-inf} (ng·hr/mL)	9970.03 (54.94) 11148.70 \pm 6124.76	8875.08 (55.60) 10081.16 \pm 5604.76
C _{max} (ng/mL)	179.62 (43.15) 193.84 \pm 83.63	154.88 (41.45) 168.36 \pm 69.79
T _{max} (hr)*	11.00 (5.00-36.00)	7.00 (5.00-24.00)
t _{1/2} (hr)	50.49 \pm 15.20	50.82 \pm 18.50
K _d (hr ⁻¹)	1.49E-02 \pm 4.29E-03	1.51E-02 \pm 4.44E-03
MRT (hr)	69.31 \pm 20.00	70.03 \pm 23.78
M/P Ratio	5.94 \pm 2.85	6.35 \pm 3.21

* median (min – max)

(FED/FASTING) RELATIVE BIOAVAILABILITY ASSESSMENTS FOR BUPROPION THREOAMINO ALCOHOL:

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC _{0-t}	106.31% to 119.80%	112.86%	17.56%
AUC _{0-inf}	105.67% to 119.42%	112.34%	17.99%
C _{max}	107.44% to 125.18%	115.97%	22.58%

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PHARMACOKINETIC PARAMETERS FOR BUPROPION ERYTHROAMINO ALCOHOL:

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean \pm SD	
	Bupropion HBr XL 348 mg Tablets (A) (Fed) (n=48)	Bupropion HBr XL 348 mg Tablets (B) (Fasted) (n=48)
AUC _{0-t} (ng-hr/mL)	1827.80 (41.59) 1976.58 \pm 822.09	1602.42 (43.32) 1762.94 \pm 763.75
AUC _{0-inf} (ng-hr/mL)	1922.92 (40.33) 2069.29 \pm 834.50	1701.69 (41.91) 1860.34 \pm 779.59
C _{max} (ng/mL)	33.52 (29.90) 34.90 \pm 10.44	28.94 (29.09) 30.18 \pm 8.78
T _{max} (hr)*	14.00 (8.00-36.00)	14.00 (5.00-36.00)
t _{1/2} (hr)	31.81 \pm 7.32	31.09 \pm 7.84
K _d (hr ⁻¹)	2.28E-02 \pm 4.82E-03	2.36E-02 \pm 5.60E-03
MRT (hr)	53.31 \pm 11.39	51.58 \pm 11.29
M/P Ratio	1.11 \pm 0.38	1.18 \pm 0.42

* median (min - max)

(FED/FASTING) RELATIVE BIOAVAILABILITY ASSESSMENTS FOR BUPROPION ERYTHROAMINO ALCOHOL:

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC _{0-t}	106.29% to 122.40%	114.07%	20.81%
AUC _{0-inf}	105.83% to 120.66%	113.00%	19.32%
C _{max}	108.36% to 123.83%	115.84%	19.66%

COMMENTS

The 90% CI for the ratio of the means (fed bupropion/fasting bupropion) is within the acceptable limits of 80-125% for Cmax but not for AUC.

The hydroxy bupropion, and bupropion erythroamino alcohol CI values for the ratio of the (fed/fasted) studies are all within 80-125% of the reference for Cmax and AUC.

The 90% CI for the ratio of the means (fed bupropion threoamino alcohol /fasting bupropion threoamino alcohol) exceeds the 80-125% limit for Cmax.

ARE THE MULTIPLE DOSE KINETICS FOR THE BUPROPION HYDROBROMIDE SIMILAR TO THE CURRENTLY MARKETED BUPROPION HYDROCHLORIDE XL TABLET?

Study Design

The study was done as a multiple-dose two-way crossover in 48 non-smoking males and females under fasting conditions. Subjects were titrated with 150 mg Wellbutrin XL for Days 1-3. On day 4 subjects received either bupropion HBr XL 348 mg or Wellbutrin XL 300 mg tablets on days 4-13.

Blood Samples were collected on days 1, 10, 11 and 12 at time 0 and on day 13 from 0-24 hrs and there was a 14 day washout period between study treatments.

Summary PK parameters for bupropion.

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean \pm SD	
	Bupropion HBr XL 348 mg Tablets (A) (n=38)	Wellbutrin XL [®] 300 mg Tablets (B) (n=38)
AUC _t (ng·hr/mL)	1362.44 (24.53) 1409.24 \pm 345.72	1541.27 (20.43) 1575.03 \pm 321.80
C _{max} (ng/mL)	129.86 (28.44) 134.33 \pm 38.20	151.03 (27.15) 156.83 \pm 42.57
C _{min} (ng/mL)	24.72 (37.50) 26.60 \pm 9.98	26.95 (31.48) 28.32 \pm 8.92
C _{avg} (ng/mL)	56.77 (24.53) 58.72 \pm 14.41	64.22 (20.43) 65.63 \pm 13.41
T _{max} (hr)*	4.01 (2.00 - 7.00)	4.50 (3.00 - 7.00)
Degree of Fluctuation (%)	187.51 \pm 53.50	195.47 \pm 47.80
Degree of Swing (%)	475.44 \pm 280.21	499.74 \pm 228.53
MRT (hr)	9.12 \pm 0.72	9.76 \pm 0.69

* median (min - max)

Summary PK parameters for hydroxybupropion

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean \pm SD	
	Bupropion HBr XL 348 mg Tablets (A) (n=38)	Wellbutrin XL [®] 300 mg Tablets (B) (n=38)
AUC _t (ng·hr/mL)	21815.79 (29.60) 22879.88 \pm 6771.48	25099.08 (29.19) 26180.58 \pm 7642.05
C _{max} (ng/mL)	1158.54 (28.08) 1208.14 \pm 339.24	1344.33 (29.42) 1403.10 \pm 412.83
C _{min} (ng/mL)	762.55 (34.99) 814.63 \pm 285.05	895.28 (32.81) 944.00 \pm 309.69
C _{avg} (ng/mL)	908.99 (26.0) 953.33 \pm 282.14	1045.80 (29.19) 1090.86 \pm 318.42
T _{max} (hr)*	6.00 (3.00-10.00)	7.00 (4.00-10.02)
Degree of Fluctuation (%)	43.46 \pm 16.88	43.12 \pm 17.82
Degree of Swing (%)	53.97 \pm 25.74	52.19 \pm 26.83
MRT (hr)	11.32 \pm 0.31	11.51 \pm 0.29
M/P Ratio	15.57 \pm 4.20	15.97 \pm 4.84

* median (min - max)

Summary of pk parameters for bupropion threoamino alcohol

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean \pm SD	
	Bupropion HBr XL 348 mg Tablets (A) (n=38)	Wellbutrin XL [®] 300 mg Tablets (B) (n=38)
AUC _t (ng-hr/mL)	8842.06 (37.35) 9446.28 \pm 3528.05	9768.54 (27.53) 10112.95 \pm 2783.98
C _{max} (ng/mL)	486.58 (34.68) 514.82 \pm 178.53	541.95 (26.73) 560.74 \pm 149.88
C _{min} (ng/mL)	282.78 (47.91) 312.46 \pm 149.70	318.60 (34.19) 335.65 \pm 114.75
C _{avg} (ng/mL)	368.42 (37.35) 393.60 \pm 147.00	407.02 (27.53) 421.37 \pm 116.00
T _{max} (hr)*	6.00 (3.00 - 10.00)	7.00 (5.00 - 14.00)
Degree of Fluctuation (%)	55.17 \pm 18.45	55.08 \pm 19.06
Degree of Swing (%)	74.98 \pm 32.28	72.78 \pm 31.30
MRT (hr)	11.39 \pm 0.37	11.60 \pm 0.28
M/P Ratio	6.76 \pm 2.29	6.60 \pm 2.34

* median (min - max)

Summary of pk parameters for bupropion erythroamino alcohol

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean \pm SD	
	Bupropion HBr XL 348 mg Tablets (A) (n=38)	Wellbutrin XL [®] 300 mg Tablets (B) (n=38)
AUC _t (ng-hr/mL)	1922.76 (29.01) 2009.09 \pm 582.74	2091.51 (22.07) 2143.79 \pm 473.12
C _{max} (ng/mL)	99.98 (27.31) 103.93 \pm 28.38	108.26 (23.57) 111.35 \pm 26.25
C _{min} (ng/mL)	67.46 (35.71) 72.00 \pm 25.71	76.01 (25.97) 78.52 \pm 20.39
C _{avg} (ng/mL)	80.11 (29.01) 83.71 \pm 24.28	87.15 (22.07) 89.32 \pm 19.71
T _{max} (hr)*	7.00 (5.00 - 14.00)	7.00 (5.00 - 12.00)
Degree of Fluctuation (%)	40.46 \pm 16.49	37.10 \pm 14.22
Degree of Swing (%)	50.16 \pm 24.94	43.65 \pm 19.18
MRT (hr)	11.54 \pm 0.32	11.72 \pm 0.25
M/P Ratio	1.47 \pm 0.45	1.40 \pm 0.42

Summary of pk parameters Mean ("SD) Pharmacokinetic Parameters of Bupropion Erythroamino Alcohol (subjects #022 & #023 deleted; n=36)-Subjects were dropped to Inspector's comments.

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PK Parameters	Bupropion HBr XL 348 mg Tablets Lot#: 06C159P	Wellbutrin XL 300 mg Tablets Lot#: 06C090P
AUC _t (ng.hr/mL)	2022.64 ± 582.56 1936.98 (28.80)*	2137.99 ± 471.56 2085.92 (22.06)*
C _{max} (ng/mL)	104.37 ± 28.38 100.44 (27.19)*	110.09 ± 23.90 107.38 (21.71)*
C _{min} (ng/mL)	72.71 ± 25.68 68.25 (35.32)*	77.98 ± 20.20 75.51 (25.90)*
C _{avg} (ng/mL)	84.28 ± 24.27	89.08 ± 19.65
T _{max} (hr)	7.00 (5.00, 14.00)**	7.00 (5.00, 12.00)**
Degree of Fluctuation (%)	39.79 ± 16.53	36.66 ± 13.86
Degree of Swing (%)	49.12 ± 24.81	43.44 ± 19.24
MRT (hr)	11.56 ± 0.30	11.72 ± 0.24
M/P Ratio	1.45 ± 0.45	1.40 ± 0.43

* Geometric Means (%CV)

** Median (Min, Max)

Summary Statistics for Bupropion Erythroamino Alcohol (n=36)

	Bupropion HBr XL 348 mg Tablets vs Wellbutrin XL 300 mg Tablets		
	Ratio of Geometric Means (%)	90 % Geometric Confidence Interval	Intra-Subject CV (%)
AUC _t (ng.hr/mL)	93.05 %	87.81 % to 98.60 %	14.60 %
C _{max} (ng/mL)	93.64 %	88.53 % to 99.05 %	14.14 %
C _{min} (ng/mL)	90.64 %	85.03 % to 96.61 %	16.09 %

Comment:

The AUC_t, C_{min}, C_{max} and C_{avg}, values for bupropion HBr are 10-14% lower than for Wellbutrin XL HCL.

The hydroxymetabolite C_{max}, AUC_t, C_{avg}, and C_{min} were all 14% lower for the bupropion HBr compared to Wellbutrin XL HCL.

For the threoamino alcohol and the erythroamino alcohol metabolites the C_{avg}, AUC_t, C_{min} and C_{max} values were 8-10% lower for the bupropion HBr formulation.

LABEL

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 Trade Secret / Confidential

 b Draft Labeling b(4)

 Deliberative Process

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DISSOLUTION:

DISSOLUTION CONDITIONS:

The methodology employed for Bupropion HBr tablets is the same as the approved method for Wellbutrin XL Tablets.

MEDIUM: 900 ML 0.1N HCl

APPARATUS: BASKET

SPEED: 75 rpm

Sampling Times: 2, 4, 8, and 16 hrs

Bupropion HBr XL Dissolution Data – Individual Tablet Results

Percent Released at specified time points

174 mg tablets

Lot 06C611

Time (Hours)	Vessel #						Average	Minimum	Maximum
	1	2	3	4	5	6			
2									
4									
8									
16									

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Lot 06C612

Time (Hours)	Vessel #						Average	Minimum	Maximum
	1	2	3	4	5	6			
2									
4									
8									
16									

Lot 06D117

Time (Hours)	Vessel #						Average	Minimum	Maximum
	1	2	3	4	5	6			
2									
4									
8									
16									

Bupropion HBr XL Dissolution Data – Individual Tablet Results

Percent Released at specified time points
 Lot 06C468
 348 mg Tablets

Time (Hours)	Vessel #						Average	Minimum	Maximum
	1	2	3	4	5	6			
2									
4									
8									
16									

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Lot 06C469

Time (Hours)	Vessel #						Average	Minimum	Maximum
	1	2	3	4	5	6			
2									
4									
8									
16									

Lot 06C534

Time (Hours)	Vessel #						Average	Minimum	Maximum
	1	2	3	4	5	6			
2									
4									
8									
16									

Bupropion HBr XL Dissolution Data – Individual Tablet Results

BIOLOT Lot 06C159P

348 mg tablets Study 3220

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SPECIFICATIONS	INITIAL Date: Apr 2006 REGULATORY
2 Hours: NMT	
Range	
4 Hours:	
Range	
8 Hours: NLT	
Range	
16 Hours: NLT	
Range	

b(4)

b(4)

FDA PROPOSED DISSOLUTION SPECIFICATIONS
 2 HOURS NMT — DISSOLVED
 4 HOURS — DISSOLVED
 8 HOURS NLT — DISSOLVED

b(4)

SIGNATURES

Andre Jackson _____
 Reviewer, Psychopharmacological Drug Section, DCP I
 Office of Clinical Pharmacology and Biopharmaceutics

RD/FT initialized by Raman Baweja, Ph.D. _____

Team Leader, Psychiatry Drug Section, DCP I
 Office of Clinical Pharmacology
 cc: NDA 22-108, HFD-860(Mehta, Baweja, Jackson)

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DETAILED STUDY REPORTS

ASSAY VALIDATION

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Parameter	Bupropion	Bupropion Erythroamino Alcohol	Bupropion Threoamino Alcohol	Hydroxybupropion
Method	LC\ Mass Spectrometric \ Mass Spectrometric Detection			
Freeze-thaw	3 cycles	3 cycles	3 cycles	3 cycles
Benchtop Stability at RT	24 hrs	24 hrs	24 hrs	24 hrs
Long term at -70° C	178 days(3 and 772 ng/ml)	178 days(2 and 752 ng/ml)	178 days(2.9 and 750 ng/ml)	178 days(11 and 2942 ng/ml)
Recovery Average of Low QC, High QC	93%	94%	94%	94%

STUDY 3228 (B06-755PK-10121)A Two-Way Crossover, Open-label, Single-dose, Fasting, Dosage Strength Proportionality Study of Two Strengths of Bupropion HBr XL Tablets

OBJECTIVES

This study was designed to evaluate the dosage strength proportionality of bupropion from the following products under fasting conditions:

1. Bupropion HBr XL 174 mg Tablets (2 x 174 mg) (by or for Biovail Corporation, Canada or its subsidiaries)
2. Bupropion HBr XL 348 mg Tablets (1 x 348 mg) (by or for Biovail Corporation, Canada or its subsidiaries)

Lot #s 174 mg tablet- 06D029P
348 mg tablet 06C159P

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METHODS AND PROCEDURES

Study Design

The study followed a randomized, open-label, single-dose, two-way crossover design in 48 normal, healthy, non-smoking male and female subjects under fasting conditions.

This study was conducted to evaluate the dosage strength proportionality of bupropion between two strengths of an extended-release tablet formulation of an alternate salt of Bupropion (Bupropion Hydrobromide). A 174 mg tablet of Bupropion HBr contains the same molar amount of Bupropion (base) as a 150 mg tablet of Bupropion HCl (Wellbutrin® XL). A 348 mg tablet of Bupropion HBr contains the same molar amount of Bupropion (base) as a 300 mg tablet of Bupropion HCl (Wellbutrin® XL).

There was a 14 day washout period between study treatments.

Blood samples were collected at predose,

1,2,3,4,5,6,7,8,10,12,14,16,20,24,36,48,60,72,120,168, and 216 hours post-dose

SUBJECT DEMOGRAPHICS

NOTE: All of the subjects in this study were healthy, non-smoking males & females.

Subject No.	Race	Gender	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m ²)	Height/Weight Ratio (1/1)
001	Black	Male	25	166	65	23.6	255
002	Black	Female	21	160	69	27.0	232
003	Black	Male	30	167	66	23.7	253
004	Caucasian	Female	41	162	59	22.5	275
005	Black	Male	32	182	94	28.4	194
006	Caucasian	Female	47	164	78	29.0	210
007	Caucasian	Male	26	173	89	29.7	194
008	Hispanic	Female	46	152	65	28.1	234
009	Caucasian	Male	25	167	74	26.5	226
010	Caucasian	Female	42	163	70	26.3	233
011	Black	Male	23	182	79	23.8	236
012	Black	Female	24	168	75	26.6	224
013	Hispanic	Male	44	184	77	22.7	239
014	Black	Female	30	164	59	21.9	278
015	Caucasian	Male	43	174	68	22.5	256
016	Caucasian	Female	40	168	69	24.4	243
017	Caucasian	Male	51	165	75	27.5	220
018	Hispanic	Female	32	149	52	23.4	287
019	Caucasian	Male	42	179	69	21.5	259
020	Caucasian	Female	46	171	68	23.3	251
021	Caucasian	Male	20	186	78	22.5	238
022	Hispanic	Female	36	156	68	27.9	229
023	Asian	Male	28	169	70	24.5	241
024	Black	Female	26	157	52	21.1	302
025	Hispanic	Male	28	189	98	27.4	193
026	Caucasian	Female	48	161	71	27.4	227
027	Black	Male	40	175	82	26.8	213
028	Caucasian	Female	23	173	66	22.1	262
029	Hispanic	Male	36	166	70	25.4	237
030	Caucasian	Female	44	154	69	29.1	223
031	Caucasian	Male	26	176	62	20.0	284
032	Caucasian	Female	43	172	80	27.0	215
033	Asian	Male	40	167	78	28.0	214
034	Hispanic	Female	25	170	81	28.0	210
035	Caucasian	Male	28	166	58	21.0	286
036	Hispanic	Female	45	152	63	27.3	241

Subject No.	Race	Gender	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m ²)	Height/Weight Ratio (1)
037	Caucasian	Male	28	183	81	24.2	226
038	Hispanic	Female	43	160	58	23.0	271
039	Black	Male	27	191	97	26.6	197
*040	Black	Female	24	172	62	21.0	277
041	Hispanic	Male	37	169	77	27.0	219
042	Black	Female	23	177	69	22.0	257
043	Caucasian	Male	39	173	73	24.4	237
044	Black	Female	22	152	67	29.0	227
045	Caucasian	Male	44	173	76	25.4	228
046	Caucasian	Female	37	158	70	28.0	226
047	Asian	Male	30	174	74	24.4	235
048	Caucasian	Female	51	164	68	25.3	241

Following an overnight fast of at least 10 hours, subjects received 1 of the following treatments at 0.0 hour on Day 1 of each study period according to the randomization scheme shown in Section 16.1.7:

Treatment A: Two Bupropion HBr XL 174 mg Tablets with 240 mL of ambient temperature water (Treatment Dose = 348 mg).

Treatment B: One Bupropion HBr XL 348 mg Tablet with 240 mL of ambient temperature water (Treatment Dose = 348 mg).

PHARMACOKINETIC PARAMETERS

The pharmacokinetic parameters for bupropion, hydroxybupropion, bupropion threoamino alcohol, bupropion erythroamino alcohol and PAWC derived for both treatments were:

Primary parameters:

- AUC_{0-t} = area under the concentration-time curve from time zero to time of last measurable concentration, calculated using the linear trapezoidal rule
- $AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity
- C_{max} = maximum plasma concentration after dosing

STATISTICAL

ANOVAs were performed on the ln-transformed data for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} . ANOVAs were also performed on the untransformed data to compare the K_{el} , $t_{1/2}$, MRT, and M/P ratio. Based on the ANOVA results and the pair-wise comparisons of the ln-transformed data, the intra-subject CV, the relative ratios of the geometric means, and the 90% geometric C.I. were determined for all ln-transformed parameters. T_{max} was analyzed using nonparametric methods. The equality of treatment effect in both sequences was evaluated using Wilcoxon rank-sum tests. The mean shift between the two treatments was estimated by the median unbiased Hodges-Lehmann estimate and 90% exact C.I.

STUDY 3228

First Subject Dosed	April 15 2006
First Sample Analyzed	May 16 2006
Last Sample Analyzed	June 12 2006
Total Storage Time	60 days

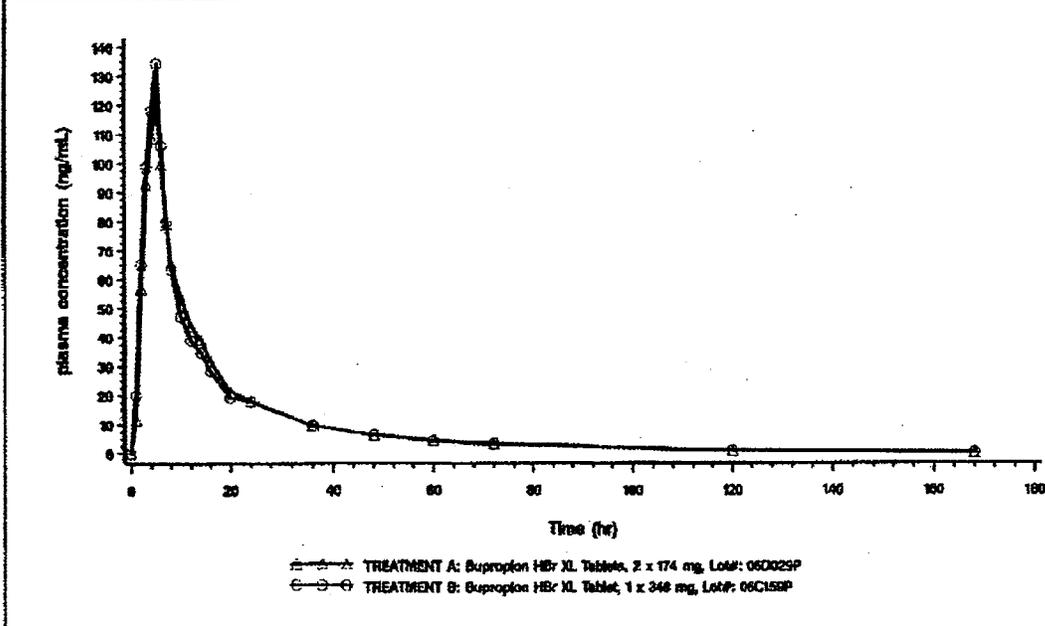
Parameter	Bupropion	Bupropion Erythroamino Alcohol	Bupropion Threoamino Alcohol	Hydroxybupropion
Method	HPLC with	HPLC with	HPLC with	HPLC with Mass

	Mass Spectrometric Detection	Mass Spectrometric Detection	Mass Spectrometric Detection	Spectrometric Detection
Sensitivity/ LOQ	1 ng/ml	1 ng/ml	1 ng/ml	4 ng/ml
Linearity (Standard curve samples)	1-1023 ng/ml	1-1023 ng/ml	1 ng/ml	4-3999 ng/ml
Quality Control (QC) Samples	3, 191, 767 ng/ml	3,191,767 ng/ml	3, 191, 767 ng/ml	11.7, 749, 2999 ng/ml
Precision of Standards (%CV)	5.5% @ 1 ng/ml 4% @ 1023 ng/ml	6.2% @ 1 ng/ml 4.0% @ 1023 ng/ml	5.3% @ 1 ng/ml 4.2% @ 1023 ng/ml	5.1% @ 3 ng/ml 4.6% @ 3999 ng/ml
Precision of QC Samples (%CV)	5.6% @ 3 ng/ml 5% @ 767 ng/ml	5.7% @ 3 ng/ml 4.5% @ 767 ng/ml	6.2% @ 3 ng/ml 4.8% @ 767 ng/ml	6.1% @ 11.7 ng/ml 4.1% @ 2999 ng/ml
Accuracy of Standards (%)	102% @ 1 ng/ml 101% @ 1023 ng/ml	108% @ 1 ng/ml 100% @ 1023 ng/ml	108% @ 1 ng/ml 99% @ 1023 ng/ml	101% @ 3 ng/ml 99% @ 3999 ng/ml
Accuracy of QC Samples (%)	99% @ 3 ng/ml 1040% @ 767 ng/ml	99% @ 3 ng/ml 102% @ 767 ng/ml	99% @ 3 ng/ml 101% @ 767 ng/ml	100% @ 11.7 ng/ml 105% @ 2999 ng/ml

RESULTS

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MEAN PLASMA BUPROPION CONCENTRATION VERSUS TIME, LINEAR SCALE (n=46):



PHARMACOKINETIC PARAMETERS FOR BUPROPION:

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	2 x Bupropion HBr XL 174 mg Tablets (A) (n=46)	1 x Bupropion HBr XL 348 mg Tablet (B) (n=46)
AUC ₀₋₁ (ng·hr/mL)	1523.91 (30.65) 1596.96 ± 489.42	1493.80 (34.76) 1581.85 ± 549.92
AUC _{0-inf} (ng·hr/mL)	1585.29 (30.09) 1658.90 ± 499.09	1556.42 (34.03) 1644.75 ± 559.69
C _{max} (ng/mL)	122.81 (32.48) 128.54 ± 41.75	132.51 (37.22) 141.16 ± 52.54
T _{max} (hr)*	5.00 (3.00-6.07)	5.00 (3.00-7.00)
t _{1/2} (hr)	23.65 ± 7.36	23.84 ± 6.90
K _d (hr ⁻¹)	3.29E-02 ± 1.28E-02	3.17E-02 ± 9.78E-03
MRT (hr)	23.02 ± 5.21	22.52 ± 5.12

* median (min - max)

RELATIVE BIOAVAILABILITY ASSESSMENTS FOR BUPROPION:

Parameter	Potency Uncorrected Data		
	90% C.I.	Ratio of Means	Intra-Subject CV
AUC ₀₋₁	96.48% to 107.86%	102.02%	16.01%
AUC _{0-inf}	96.59% to 107.41%	101.85%	15.24%
C _{max}	86.68% to 99.10%	92.68%	19.29%
Parameter	Potency Corrected Data		
	90% C.I.	Ratio of Means	
AUC ₀₋₁	96.39% to 107.75%	101.91%	
AUC _{0-inf}	96.49% to 107.30%	101.75%	
C _{max}	86.59% to 98.99%	92.58%	

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MEAN PLASMA HYDROXYBUPROPION CONCENTRATION VERSUS TIME, LINEAR SCALE
(n=46):

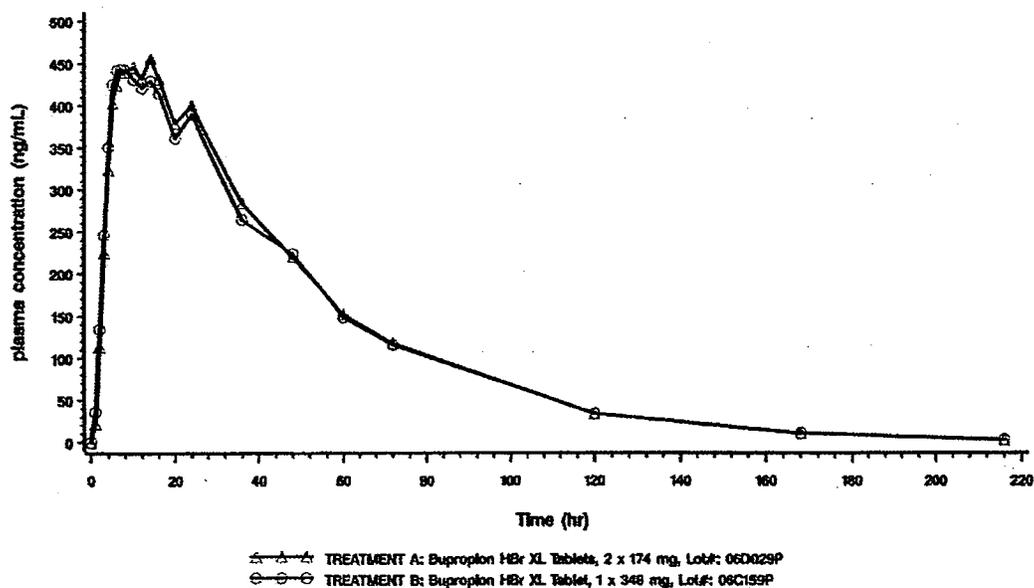


Table 11.2 - Pharmacokinetic Parameters for Hydroxybupropion

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	2 x Bupropion HBr XL 174 mg Tablets (A) (n=46)	1 x Bupropion HBr XL 348 mg Tablet (B) (n=46)
AUC _{0-∞} (ng·hr/mL)	21175.12 (50.57) 24691.89 ± 12487.03	20088.61 (60.27) 24435.37 ± 14728.10
AUC ₀₋₂₄ (ng·hr/mL)	21601.69 (50.27) 25050.12 ± 12593.05	20505.06 (59.96) 24779.61 ± 14857.90
C _{max} (ng/mL)	421.40 (46.88) 480.18 ± 225.10	411.57 (50.75) 478.90 ± 243.02
T _{max} (hr)*	14.00 (5.00-24.00)	8.00 (5.00-24.00)
t _{1/2} (hr)	26.51 ± 5.77	26.05 ± 6.24
K _e (hr ⁻¹)	2.75E-02 ± 6.70E-03	2.83E-02 ± 7.62E-03
MRT (hr)	43.98 ± 8.67	42.84 ± 9.32
M/P Ratio	15.02 ± 9.00	15.08 ± 11.14

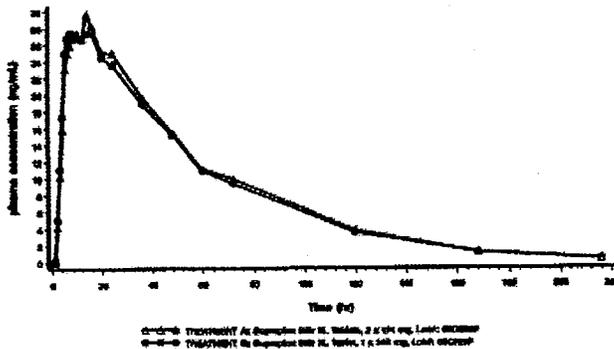
* median (min - max)

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Table 11.7 – Relative Bioavailability Analysis of 2 x Bupropion HBr XL 174 mg Tablets (A) versus 1 x Bupropion HBr XL 348 mg Tablet (B) for hydroxybupropion

Parameter	95% C.I.	Ratio of Means	Intra-Subject CV
AUC _{0-∞}	96.60% to 112.69%	105.41%	19.23%
AUC _{0-12hr}	96.62% to 112.54%	105.35%	19.01%
C _{max}	97.00% to 108.08%	102.39%	15.53%

MEAN PLASMA BUPROPION ERYTHROAMINO ALCOHOL CONCENTRATION VERSUS TIME.
LINEAR SCALE (n=46)



PHARMACOKINETIC PARAMETERS FOR BUPROPION ERYTHROAMINO ALCOHOL:

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	2 x Bupropion HBr XL 174 mg Tablets (A) (n=46)	1 x Bupropion HBr XL 348 mg Tablet (B) (n=46)
AUC _{0-∞} (ng·hr/mL)	1634.49 (47.41) 1774.20 ± 341.09	1536.84 (45.13) 1699.45 ± 767.04
AUC _{0-12hr} (ng·hr/mL)	1713.86 (46.12) 1864.11 ± 339.71	1663.28 (43.67) 1804.55 ± 788.69
C _{max} (ng/mL)	29.54 (31.12) 30.79 ± 10.20	29.01 (33.02) 30.40 ± 10.04
T _{max} (hr)*	14.00 (5.00-24.00)	15.00 (5.00-24.00)
t _{1/2} (hr)	32.71 ± 7.34	32.51 ± 8.78
K _{el} (hr ⁻¹)	2.24E-02 ± 1.34E-03	2.27E-02 ± 5.72E-03
MRT (hr)	52.66 ± 11.42	52.24 ± 12.78
M/P Ratio	1.16 ± 0.64	1.13 ± 0.50

* median (min - max)

RELATIVE BIOAVAILABILITY ASSESSMENTS FOR BUPROPION ERYTHROAMINO ALCOHOL:

Parameter	95% C.I.	Ratio of Means	Intra-Subject CV
AUC _{0-∞}	94.39% to 110.64%	104.33%	16.85%
AUC _{0-12hr}	97.25% to 109.16%	103.04%	16.60%
C _{max}	96.15% to 107.82%	101.82%	16.46%

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STUDY 3229 (B06-754PK-10121)

A Two-Way Crossover, Open-Label, Single-Dose, Food-Effect Study of Bupropion HBr XL

OBJECTIVES

The objective of this study was to evaluate the effect of food on the pharmacokinetics of bupropion from a novel formulation of Bupropion HBr XL 348 mg Tablets (by or for Biovail Corporation, Canada or its Subsidiaries).

METHODS AND PROCEDURES

Study Design

The study followed a randomized, open-label, single-dose, two-way crossover design in 48 normal, healthy, non-smoking male and female subjects under fed and fasted conditions.

Subjects were admitted to the clinic the day before dosing, and remained until the 24.00 hour post-dose blood draw of each period, at which time they were allowed to leave the clinic and after which they were required to return for subsequent blood draws. Following an overnight fast, subjects received 1 Bupropion HBr XL 348 mg Tablet following a high fat content meal, or under fasting conditions on Day 1 of each study period.

Treatment A: Following an overnight fast of at least 10 hours, subjects began a high fat content meal 30 minutes prior to drug administration. Subjects consumed this meal in 30 minutes or less; however, the study drug was administered 30 minutes after the start of the meal. The study drug was administered with 240 mL of ambient temperature water. No food was allowed for at least 4 hours post-dose. The standard high fat content meal consisted of the following: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes and 8 fluid ounces (\approx 240 mL) of whole milk. Subjects fasted for at least 4 hours post-dose.

Treatment B: The subjects fasted overnight for at least 10 hours before drug administration, and fasted for at least 4 hours post-dose.

At 4.5 and 9.5 hours post-dose, standardized meals and beverages were provided to the subjects. In addition, a standardized snack was provided at 13.5 hours post-dose. All meals and beverages were free of alcohol, grapefruit products, xanthines and caffeine and were identical for both study periods.

There was a 14 day washout period between study treatments.

Blood samples were collected at predose, 1,2,3,4,5,6,7,8,10,12,14,16,20,24,36,48,60,72,120,168, and 216 hours post-dose

SUBJECT DEMOGRAPHICS

NOTE: All of the subjects in this study were healthy, non-smoking males & females.

Subject No.	Race	Gender	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m ²)	Height/Weight Ratio (%)
001	Caucasian	Male	22	172	68	23.0	253
002	Asian	Female	52	151	48	21.1	315
003	Caucasian	Male	42	177	85	27.1	208
004	Asian	Female	35	154	53	22.3	291
005	Caucasian	Male	49	174	79	26.1	220
006	Caucasian	Female	50	160	72	28.1	222
007	Mulatto	Male	19	177	67	21.4	264
008	Caucasian	Female	37	169	81	28.4	209
009	Asian	Male	37	173	78	26.1	222
010	Mulatto	Female	39	166	64	23.2	259
011	Asian	Male	32	173	76	25.4	228
012	Black	Female	46	168	69	24.4	243
013	Black	Male	32	183	78	23.3	235
014	Caucasian	Female	34	160	56	21.9	286
015	Black	Male	21	170	56	19.4	304
016	Hispanic	Female	27	166	58	21.0	286
017	Hispanic	Male	26	184	83	24.5	222
018	Asian	Female	36	150	55	24.4	273
019	Caucasian	Male	23	176	79	25.5	223
020	Black	Female	28	164	69	25.7	238
021	Black	Male	33	170	64	22.1	266
022	Caucasian	Female	45	165	64	23.5	258
023	Asian	Male	36	175	77	25.1	227
024	Hispanic	Female	48	166	61	22.1	272
025	Caucasian	Male	32	173	79	26.4	219
026	Black	Female	47	171	78	26.7	219
027	Hispanic	Male	43	180	94	29.0	191
028	Caucasian	Female	46	173	79	26.4	219
029	Caucasian	Male	39	171	78	26.7	219
030	Caucasian	Female	47	163	58	21.8	281
031	Hispanic	Male	28	165	76	27.9	217
032	Caucasian	Female	30	161	55	21.2	293
033	Black	Male	35	180	90	27.8	200
034	Caucasian	Female	36	175	64	20.9	273
035	Black	Male	49	166	71	25.8	234
036	Hispanic	Female	35	157	57	23.1	275
037	Caucasian	Male	25	164	61	22.7	269

Subject No.	Race	Gender	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m ²)	Height/Weight Ratio (%)
038	Black	Female	23	166	68	24.7	244
039	Black	Male	35	169	74	25.9	228
040	Caucasian	Female	23	162	59	22.5	275
041	Caucasian	Male	38	186	83	24.0	224
042	Hispanic	Female	32	158	72	28.8	219
043	Caucasian	Male	41	187	95	27.2	197
044	Hispanic	Female	38	156	61	25.1	256
045	Hispanic	Male	31	171	75	25.6	228
046	Asian	Female	31	154	56	23.6	275
047	Caucasian	Male	50	160	70	27.3	229
048	Caucasian	Female	31	164	58	21.6	283

STATISTICAL

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ANOVAs were performed on the ln-transformed data for AUC_{0-t} , AUC_{0-inf} , and C_{max} . ANOVAs were also performed on the untransformed data to compare the K_{el} , $t_{1/2}$, MRT, and M/P ratio. Based on the ANOVA results and the pair-wise comparisons of the ln-transformed data, the intra-subject CV, the relative ratios of the geometric means, and the 90% geometric C.I. were determined for all ln-transformed parameters. T_{max} was analyzed using nonparametric methods. The equality of treatment effect in both sequences was evaluated using Wilcoxon rank-sum tests. The mean shift between the two treatments was estimated by the median unbiased Hodges-Lehmann estimate and 90% exact C.I.

PHARMACOKINETIC PARAMETERS

Primary parameters:

- AUC_{0-t} = area under the concentration-time curve from time zero to time of last measurable concentration, calculated using the linear trapezoidal rule
- AUC_{0-inf} = area under the concentration-time curve from time zero to infinity
- C_{max} = maximum plasma concentration after dosing

STUDY 3229

First Subject Dosed

April 9, 2006

First Sample Analyzed

May 3, 2006

Last Sample Analyzed

May 17, 2006

Total Storage Time

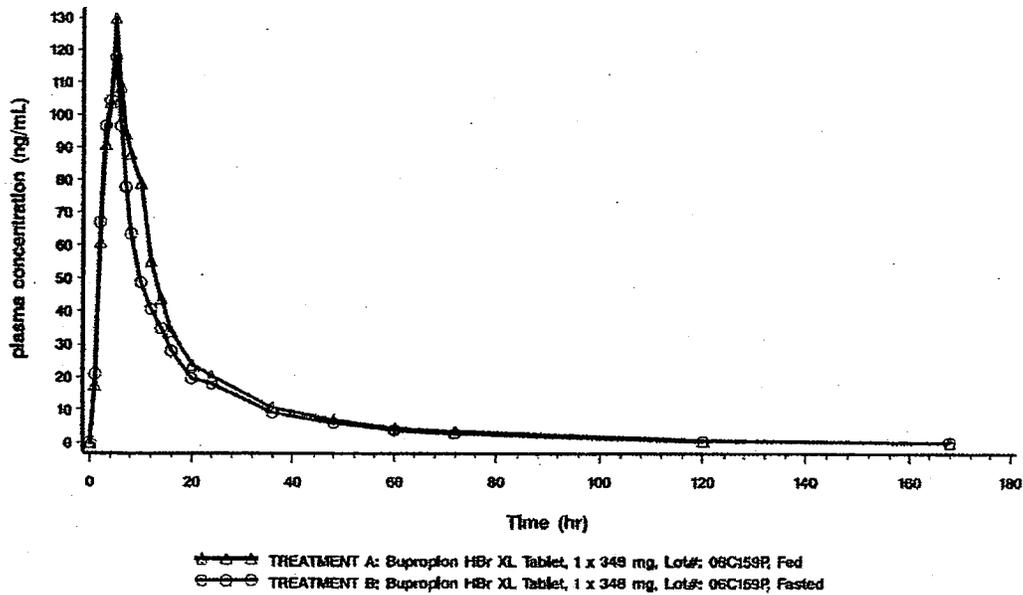
68 days

Parameter	Bupropion	Bupropion Erythroamino Alcohol	Bupropion Threoamino Alcohol	Hydroxybupropion
Method	HPLC with Mass Spectrometri c Detection	HPLC with Mass Spectrometric Detection	HPLC with Mass Spectrometri c Detection	HPLC with Mass Spectrometric Detection
Sensitivity/ LOQ	1 ng/ml	1 ng/ml	1 ng/ml	4 ng/ml
Linearity (Standard curve samples)	1-1023 ng/ml	1-1023 ng/ml	1-1023 ng/ml	4-3999 ng/ml
Quality Control (QC) Samples	3, 191, 767 ng/ml	3,191,767 ng/ml	3, 191, 767 ng/ml	11.7, 749, 2999 ng/ml
Precision	4.9% @ 1	4.9% @ 1	5.4% @ 1	5.1% @ 3 ng/ml

of Standards (%CV)	ng/ml 3.9%@ 1023 ng/ml	ng/ml 3.2%@ 1023ng/ml	ng/ml 3.7%@ 1023 ng/ml	4.8%@3999 ng/ml
Precision of QC Samples (%CV)	5.5 %@ 3 ng/ml 3.4 %@ 767 ng/ml	5.4 %@ 3 ng/ml 3.3 %@ 767 ng/ml	5.5 %@ 3 ng/ml 3.7%@ 767 ng/ml	4.4 %@ 11.7 ng/ml 5.0 %@ 2999 ng/ml
Accuracy of Standards (%)	101%@ 1 ng/ml 100%@ 1023 ng/ml	102%@ 1 ng/ml 100%@ 1023 ng/ml	101%@ 1 ng/ml 100%@ 1023 ng/ml	101%@ 3 ng/ml 99%@ 3999ng/ml
Accuracy of QC Samples (%)	99 %@ 3 ng/ml 102 %@ 767 ng/ml	98 %@ 3 ng/ml 101 %@ 767 ng/ml	99 %@ 3 ng/ml 101 %@ 767 ng/ml	100 %@ 11.7ng/ml 100 %@ 2999 ng/ml

RESULTS

MEAN PLASMA BUPROPION CONCENTRATION VERSUS TIME, LINEAR SCALE (n=48):



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PHARMACOKINETIC PARAMETERS FOR BUPROPION:

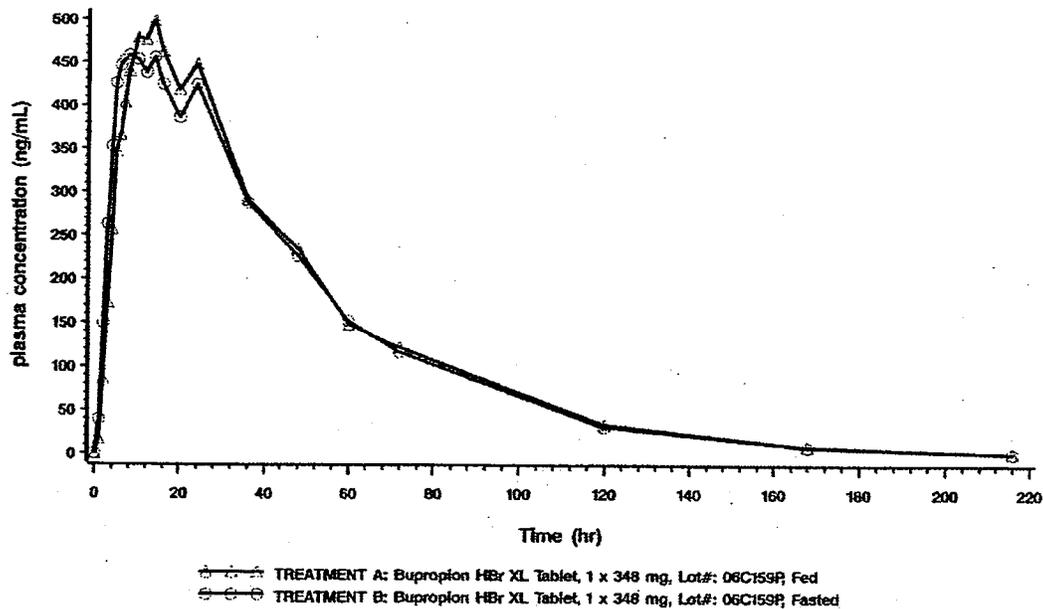
Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean \pm SD	
	Bupropion HBr XL 348 mg Tablets (A) (Fed) (n=48)	Bupropion HBr XL 348 mg Tablets (B) (Fasted) (n=48)
AUC _{0-t} (ng-hr/mL)	1743.38 (29.91) 1813.67 \pm 542.56	1459.22 (27.36) 1514.68 \pm 414.40
AUC _{0-inf} (ng-hr/mL)	1806.08 (29.34) 1876.44 \pm 550.60	1516.77 (26.77) 1572.10 \pm 420.91
C _{max} (ng/mL)	130.36 (31.47) 136.80 \pm 43.05	121.28 (27.41) 125.91 \pm 34.52
T _{max} (hr)*	5.00 (2.00-10.00)	5.00 (3.00-7.00)
t _{1/2} (hr)	23.19 \pm 6.45	21.29 \pm 6.65
K _d (hr ⁻¹)	3.27E-02 \pm 1.10E-02	3.60E-02 \pm 1.17E-02
MRT (hr)	22.36 \pm 5.92	21.20 \pm 5.56

* median (min - max)

(FED/FASTING) RELATIVE BIOAVAILABILITY ASSESSMENTS FOR BUPROPION:

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC _{0-t}	113.23% to 126.06%	119.47%	15.75%
AUC _{0-inf}	112.96% to 125.52%	119.07%	15.47%
C _{max}	98.20% to 117.64%	107.48%	26.83%

MEAN PLASMA HYDROXYBUPROPION CONCENTRATION VERSUS TIME, LINEAR SCALE (n=48):



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PHARMACOKINETIC PARAMETERS FOR HYDROXYBUPROPION:

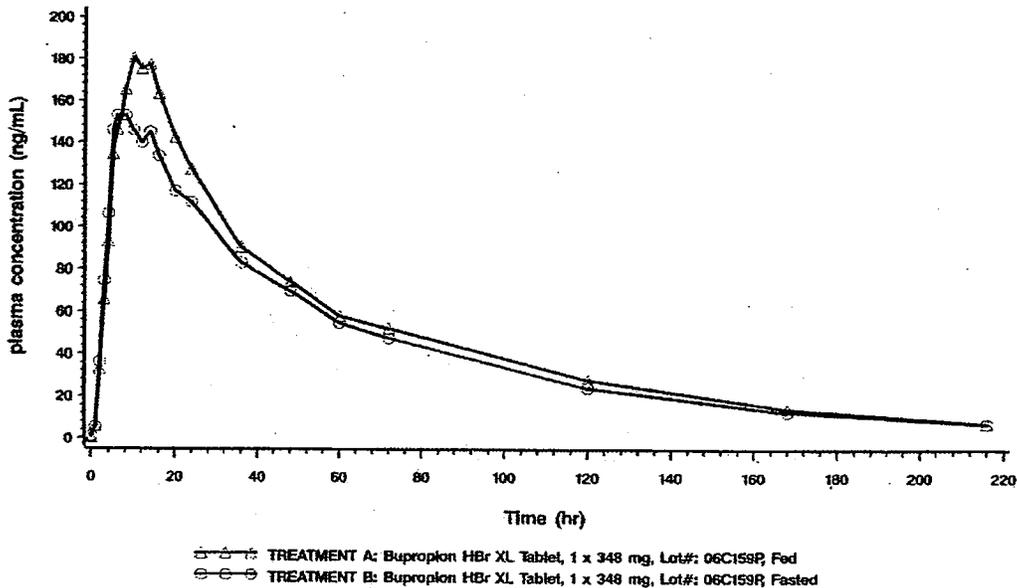
Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean \pm SD	
	Bupropion HBr XL 348 mg Tablets (A) (Fed) (n=48)	Bupropion HBr XL 348 mg Tablets (B) (Fasted) (n=48)
AUC _{0-t} (ng-hr/mL)	21556.18 (54.71) 25505.66 \pm 13953.00	21143.44 (53.45) 24948.49 \pm 13334.10
AUC _{0-inf} (ng-hr/mL)	22061.74 (54.24) 25870.62 \pm 14032.96	21628.02 (52.78) 25284.90 \pm 13346.59
C _{max} (ng/mL)	457.15 (45.58) 525.08 \pm 239.34	445.93 (43.57) 507.42 \pm 221.07
T _{max} (hr)*	14.00 (7.00-36.00)	8.00 (5.00-24.02)
t _{1/2} (hr)	24.77 \pm 4.81	24.28 \pm 4.92
K _{e1} (hr ⁻¹)	2.90E-02 \pm 5.59E-03	2.97E-02 \pm 5.93E-03
MRT (hr)	42.65 \pm 7.61	41.13 \pm 7.37
M/P Ratio	13.17 \pm 5.96	15.48 \pm 7.32

* median (min - max)

(FED/FASTING) RELATIVE BIOAVAILABILITY ASSESSMENTS FOR HYDROXYBUPROPION:

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC _{0-t}	95.40% to 108.96%	101.95%	19.58%
AUC _{0-inf}	95.50% to 108.95%	102.01%	19.41%
C _{max}	96.75% to 108.62%	102.52%	17.00%

MEAN PLASMA BUPROPION THREOAMINO ALCOHOL CONCENTRATION VERSUS TIME, LINEAR SCALE (n=48):



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PHARMACOKINETIC PARAMETERS FOR BUPROPION THREOAMINO ALCOHOL:

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean \pm SD	
	Bupropion HBr XL 348 mg Tablets (A) (Fed) (n=48)	Bupropion HBr XL 348 mg Tablets (B) (Fasted) (n=48)
AUC _{0-t} (ng-hr/mL)	9430.21 (53.90) 10454.75 \pm 5635.07	8355.97 (53.13) 9356.36 \pm 4971.39
AUC _{0-inf} (ng-hr/mL)	9970.03 (54.94) 11148.70 \pm 6124.76	8875.08 (55.60) 10081.16 \pm 5604.76
C _{max} (ng/mL)	179.62 (43.15) 193.84 \pm 83.63	154.88 (41.45) 168.36 \pm 69.79
T _{max} (hr)*	11.00 (5.00-36.00)	7.00 (5.00-24.00)
t _{1/2} (hr)	50.49 \pm 15.20	50.82 \pm 18.50
K _{el} (hr ⁻¹)	1.49E-02 \pm 4.29E-03	1.51E-02 \pm 4.44E-03
MRT (hr)	69.31 \pm 20.00	70.03 \pm 23.78
M/P Ratio	5.94 \pm 2.85	6.35 \pm 3.21

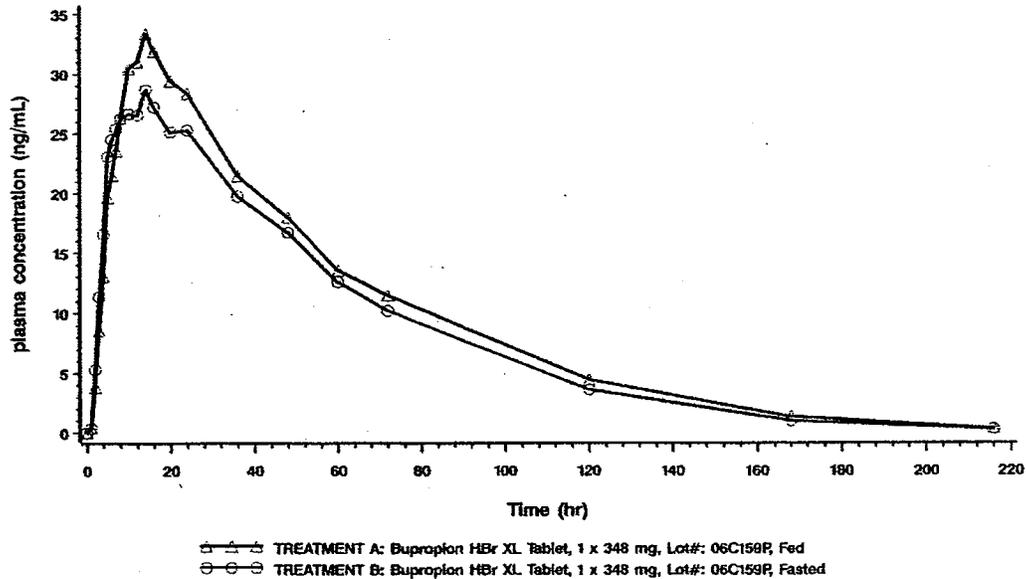
* median (min – max)

(FED/FASTING) RELATIVE BIOAVAILABILITY ASSESSMENTS FOR BUPROPION THREOAMINO ALCOHOL:

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC _{0-t}	106.31% to 119.80%	112.86%	17.56%
AUC _{0-inf}	105.67% to 119.42%	112.34%	17.99%
C _{max}	107.44% to 125.18%	115.97%	22.58%

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Mean plasma Bupropion Erythroamino alcohol concentration versus time



PHARMACOKINETIC PARAMETERS FOR BUPROPION ERYTHROAMINO ALCOHOL:

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	Bupropion HBr XL 348 mg Tablets (A) (Fed) (n=48)	Bupropion HBr XL 348 mg Tablets (B) (Fasted) (n=48)
AUC _{0-t} (ng·hr/mL)	1827.80 (41.59) 1976.58 ± 822.09	1602.42 (43.32) 1762.94 ± 763.75
AUC _{0-inf} (ng·hr/mL)	1922.92 (40.33) 2069.29 ± 834.50	1701.69 (41.91) 1860.34 ± 779.59
C _{max} (ng/mL)	33.52 (29.90) 34.90 ± 10.44	28.94 (29.09) 30.18 ± 8.78
T _{max} (hr)*	14.00 (8.00-36.00)	14.00 (5.00-36.00)
t _{1/2} (hr)	31.81 ± 7.32	31.09 ± 7.84
K _{el} (hr ⁻¹)	2.28E-02 ± 4.82E-03	2.36E-02 ± 5.60E-03
MRT (hr)	53.31 ± 11.39	51.58 ± 11.29
M/P Ratio	1.11 ± 0.38	1.18 ± 0.42

* median (min – max)

(FED/FASTING) RELATIVE BIOAVAILABILITY ASSESSMENTS FOR BUPROPION ERYTHROAMINO ALCOHOL:

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC _{0-t}	106.29% to 122.40%	114.07%	20.81%
AUC _{0-inf}	105.83% to 120.66%	113.00%	19.32%
C _{max}	108.36% to 123.83%	115.84%	19.66%

COMMENTS

1. Bupropion AUC and , bupropion threoamino alcohol Cmax values were slightly outside the 90% CI under fed condition. All other post prandial

parameters for bupropion, bupropion erythroamino alcohol, bupropion threoamino alcohol and hydroxybupropion were within the 80-125% CI range. The changes in the point estimate ratios were for bupropion AUC (19%) and for bupropion threoamino alcohol Cmax (15%). These changes are not clinically significant.

STUDY 3230 A Two-Way Crossover, Open-Label, Multiple-Dose Fasting, Comparative Bioavailability HBr

OBJECTIVES

This study was designed to evaluate the relative bioavailability of Bupropion HBr XL 348 mg Tablets compared to the reference Wellbutrin XL[®] 300 mg Tablets under steady-state, fasting conditions:

- 1) Bupropion HBr XL 348 mg Tablets (manufactured by or for Biovail Corporation, Canada or its subsidiaries)
- 2) Wellbutrin XL[®] 300 mg Tablets (manufactured by Biovail Corporation, Canada for GlaxoSmithKline, USA)

METHODS AND PROCEDURES

Study Design

The study followed a randomized, open-label, multiple-dose, two-way crossover design in 48 normal, healthy, non-smoking male and female subjects under fasting conditions.

Subjects were admitted to the clinic the day before Day 1 dosing, and remained until the morning of Day 14 (following the 24.00 hour post-dose blood draw of Day 13) for each period, at which time they were allowed to leave the clinic. Following an overnight fast of at least 10 hours, subjects received 1 Wellbutrin XL[®] 150 mg Tablet for dose titration on Days 1 to 3 of each study period. Following an overnight fast of at least 10 hours, subjects received either 1 Bupropion HBr XL 348 mg Tablet or 1 Wellbutrin XL[®] 300 mg Tablet on Days 4 to 13 of each study period.

Following an overnight fast of at least 10 hours, subjects received the following treatment at 0.00 hour on Days 1 to 3:

Dose Titration (Days 1 to 3): One Wellbutrin XL[®] 150 mg Tablet with 240 mL of ambient temperature water (Daily Dose = 150 mg).

Following an overnight fast of at least 10 hours, subjects received the following treatments at 0.00 hour on Days 4 to 13 according to the randomization scheme shown in Section 16.1.7:

Treatment A (Days 4 to 13): One Bupropion HBr XL 348 mg Tablet with 240 mL of ambient temperature water (Daily Treatment Dose = 348 mg).

Treatment B (Days 4 to 13): One Wellbutrin XL[®] 300 mg Tablet with 240 mL of ambient temperature water (Daily Treatment Dose = 300 mg).

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Wellbutrin XL[®] 150 mg Tablets
Manufactured by: Biovail Corporation, Canada for GlaxoSmithKline, USA
Lot #: 05K077P
Date of Manufacture: Sep 06/05
Expiry Date: 02/07

Treatment A:
Bupropion HBr XL 348 mg Tablets
(potency value: — of label claim)

b(4)

Lot #: 06C159P
Date of Manufacture: March 14/06
• White to off-white round shaped tablets.

Treatment B:
Wellbutrin XL[®] 300 mg Tablets
(potency value: — of label claim)
Manufacturer: Biovail Corporation, Canada for GlaxoSmithKline, USA
Lot #: 06C090P
Expiry Date: 07/07
Date of Manufacture: Feb 07/06

b(4)

Blood Samples

Days 1, 10, 11, and 12: 0.00 hour (pre-dose)
Day 13: 0.00 (pre-dose), 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00,
14.00, 16.00, 20.00, and 24.00 hours post-dose.

There were no blood samples taken on Days 2, 3, 4, 5, 6, 7, 8, and 9. All pre-dose blood samples were drawn within 10 minutes before dosing.

There was a 14 day washout period between study treatments.

SUBJECT DEMOGRAPHICS

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Subject No.	Race	Gender	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m ²)	Height/Weight Ratio
001	Hispanic	Male	47	172	81	27.4	212
*002	Black	Female	22	163	76	28.6	214
003	Hispanic	Male	35	172	75	25.4	229
004	Black	Female	26	171	66	22.6	259
005	Caucasian	Male	43	168	80	28.3	210
006	Black	Female	24	164	100	29.5	184
*007	Black	Male	34	178	86	27.1	207
008	Asian	Female	46	159	69	27.3	230
009	Caucasian	Male	46	168	72	25.5	233
010	Caucasian	Female	44	166	77	27.9	216
011	Black	Male	44	189	86	26.5	209
*012	Caucasian	Female	26	165	69	25.3	239
013	Black	Male	52	173	86	28.7	201
014	Caucasian	Female	40	181	88	26.9	206
*015	Caucasian	Male	46	185	93	27.2	199
016	Black	Female	24	161	64	24.7	252
017	Black	Male	28	171	77	26.3	222
018	Black	Female	23	161	66	25.5	244
019	Black	Male	36	181	90	27.5	201
020	Black	Female	28	155	62	25.8	250
021	Caucasian	Male	42	174	74	24.4	235
022	Caucasian	Female	34	162	59	22.5	275
023	Caucasian	Male	41	169	73	25.6	232
024	Hispanic	Female	48	162	53	20.7	306
*025	Caucasian	Male	47	174	81	26.8	215
026	Hispanic	Female	40	156	63	25.3	248
027	Hispanic	Male	27	165	74	27.2	223
028	Asian	Female	47	160	61	23.8	262
029	Hispanic	Male	50	173	75	25.1	231
030	Caucasian	Female	27	161	65	25.1	248
031	Black	Male	37	187	95	27.2	197
032	Hispanic	Female	31	153	58	24.8	264
033	Hispanic	Male	41	173	81	27.1	214
*034	Asian	Female	26	160	32	20.3	308
035	Black	Male	36	173	83	27.7	208
036	Black	Female	29	166	65	23.6	255
*037	Caucasian	Male	46	171	77	26.3	222
*038	Caucasian	Female	39	159	68	23.7	265
039	Caucasian	Male	28	172	71	24.0	242
040	Hispanic	Female	32	169	63	22.1	268
041	Hispanic	Male	39	176	85	27.4	207
042	Hispanic	Female	25	152	52	22.5	292
043	Caucasian	Male	33	179	94	29.3	190
044	Caucasian	Female	45	153	61	26.1	251
045	Asian	Male	42	168	63	22.3	267
046	Asian	Female	29	147	58	26.8	253

PHARMACOKINETIC PARAMETERS

The pharmacokinetic parameters for bupropion, bupropion erythroamino alcohol, bupropion threoamino alcohol, and hydroxybupropion derived for both treatments were:

Primary parameters:

- AUC_{τ} = area under the concentration-time curve throughout a dosing interval ($\tau = 24$)
- C_{min} = concentration at the end of a dosing interval during multiple dosing
- C_{max} = maximum plasma concentration after dosing

STATISTICAL

ANOVAs were performed on the ln-transformed data for AUC_{τ} , C_{max} , C_{avg} , and C_{min} . ANOVAs were also performed on the untransformed data to compare the MRT, M/P ratio, % Fluctuation, and % Swing. Based on the ANOVA results and the pair-wise comparisons of the ln-transformed data, the intra-subject CV, the relative ratios of the geometric means, and the 90% geometric C.I. were determined for all ln-transformed parameters (with the exception of C_{avg}). T_{max} was analyzed using nonparametric methods. The equality of treatment effect in both sequences was evaluated using Wilcoxon rank-sum tests. The mean shift between the two treatments was estimated by the median unbiased Hodges-Lehmann estimate and 90% exact C.I.

STUDY 3230

First Subject Dosed

First Sample Analyzed

Last Sample Analyzed

Total Storage Time

April 11, 2006

May 23, 2006

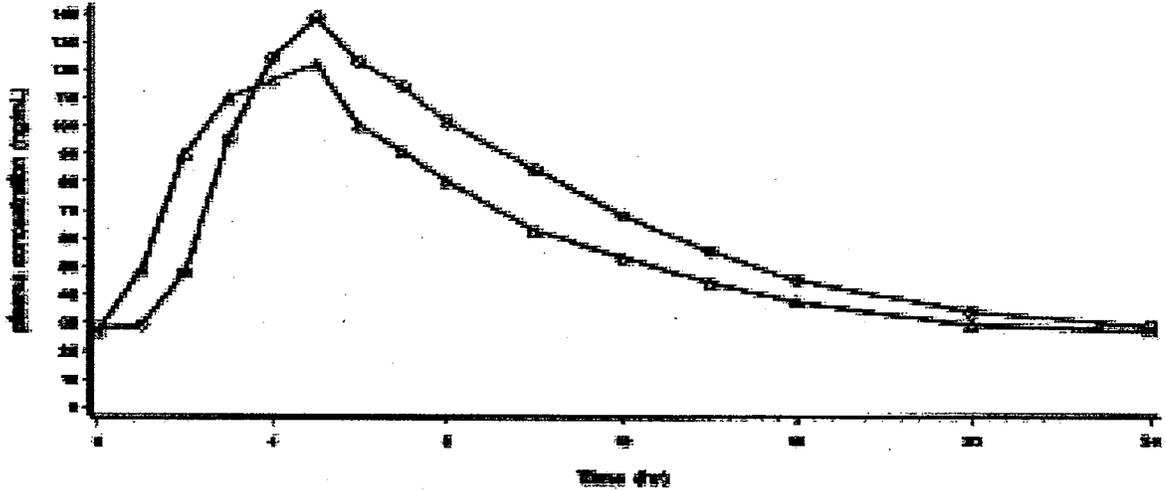
June 9, 2006

60 days

Parameter	Bupropion	Bupropion Erythroamino Alcohol	Bupropion Threoamino Alcohol	Hydroxybupropion
Method	HPLC with Mass Spectrometric Detection			
Sensitivity/LOQ	1 ng/ml	1 ng/ml	1 ng/ml	4 ng/ml
Linearity (Standard curve samples)	1-1023 ng/ml	1-1023 ng/ml	1-1023 ng/ml	4-3999 ng/ml
Quality Control (QC) Samples	3, 191, 767 ng/ml	3,191,767 ng/ml	3, 191, 767 ng/ml	11.7, 749, 2999 ng/ml
Precision of Standards (%CV)	6.4% @ 1 ng/ml 4.9% @ 1023 ng/ml	8.7% @ 1 ng/ml 5.2% @ 1023 ng/ml	7.0% @ 1 ng/ml 4.2% @ 1023 ng/ml	5.2% @ 3 ng/ml 5.6% @ 3999 ng/ml
Precision of QC Samples (%CV)	7.2% @ 3 ng/ml 7.0% @ 767 ng/ml	10% @ 3 ng/ml 6.2% @ 767 ng/ml	9.3% @ 3 ng/ml 6.0% @ 767 ng/ml	7.8% @ 11.7 ng/ml 9.9% @ 2999 ng/ml
Accuracy of Standards (%)	102% @ 1 ng/ml 100% @ 1023 ng/ml	102% @ 1 ng/ml 100% @ 1023 ng/ml	101% @ 1 ng/ml 100% @ 1023 ng/ml	102% @ 3 ng/ml 99% @ 3999 ng/ml
Accuracy of QC Samples (%)	97% @ 3 ng/ml 104% @ 767 ng/ml	98% @ 3 ng/ml 103% @ 767 ng/ml	98% @ 3 ng/ml 105% @ 767 ng/ml	100% @ 11.7 ng/ml 105% @ 2999 ng/ml

RESULTS

MEAN PLASMA BUPROPION CONCENTRATION VERSUS TIME, LINEAR SCALE (n=38):



Diamonds –Bupropion XL Treatment B
 Triangles Bupropion HBr XL Treatment A

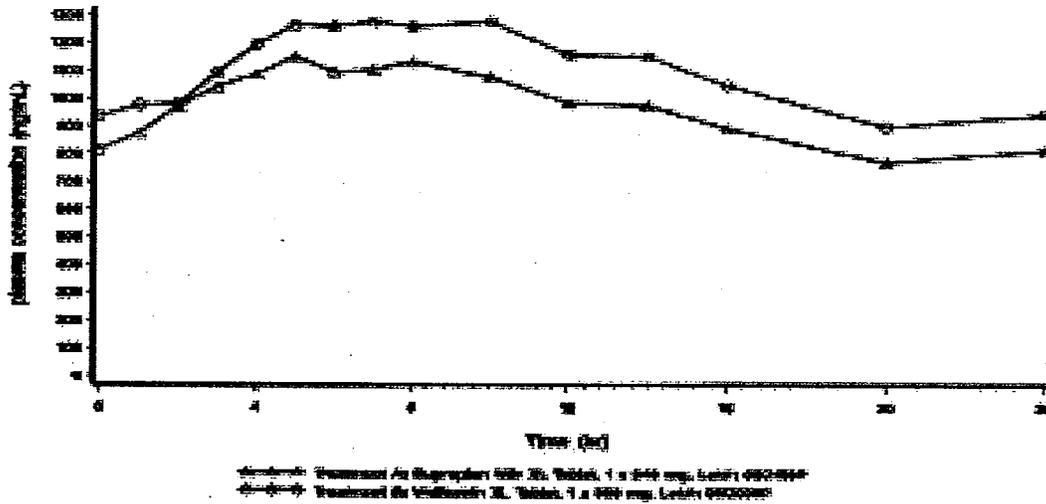
Summary statistics of pharmacokinetic parameters of bupropion at steady-state in healthy subjects.

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	Bupropion HBr XL 348 mg Tablets (A) (n=38)	Wellbutrin XL® 300 mg Tablets (B) (n=38)
AUC _t (ng·hr/mL)	1362.44 (24.53) 1409.24 ± 345.72	1541.27 (20.43) 1575.03 ± 321.80
C _{max} (ng/mL)	129.86 (28.44) 134.33 ± 38.20	151.03 (27.15) 156.83 ± 42.57
C _{min} (ng/mL)	24.72 (37.50) 26.60 ± 9.98	26.95 (31.48) 28.32 ± 8.92
C _{avg} (ng/mL)	56.77 (24.53) 58.72 ± 14.41	64.22 (20.43) 65.63 ± 13.41
T _{max} (hr)*	4.01 (2.00 - 7.00)	4.50 (3.00 - 7.00)
Degree of Fluctuation (%)	187.51 ± 53.50	195.47 ± 47.80
Degree of Swing (%)	475.44 ± 280.21	499.74 ± 228.53
MRT (hr)	9.12 ± 0.72	9.76 ± 0.69

* median (min – max)

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**MEAN PLASMA HYDROXYBUPROPION CONCENTRATION VERSUS TIME, LINEAR SCALE
(n=38)**



Triangles-Treatment A Bupropion HBr XL
 Diamonds- Treatment B Bupropion XL

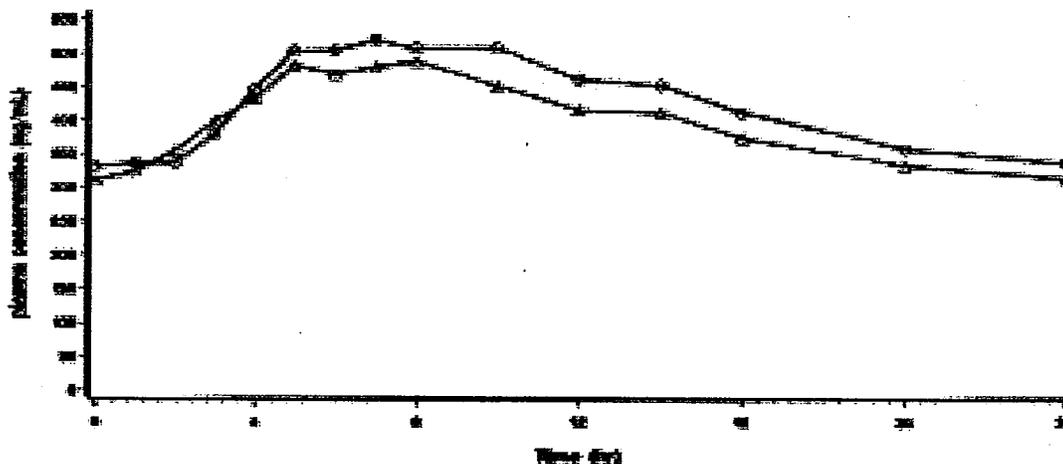
Table 11.4.2 Summary statistics of pharmacokinetic parameters of hydroxybupropion at steady state in healthy subjects (Treatment A & B)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean \pm SD	
	Bupropion HBr XL 348 mg Tablets (A) (n=38)	Wellbutrin XL [®] 300 mg Tablets (B) (n=38)
AUC ₀₋₂₄ (ng·hr/mL)	21815.79 (29.60) 22879.88 \pm 6771.48	25099.08 (29.19) 26180.58 \pm 7642.05
C _{max} (ng/mL)	1158.54 (28.08) 1208.14 \pm 339.24	1344.33 (29.42) 1403.10 \pm 412.83
C _{min} (ng/mL)	762.55 (34.99) 814.63 \pm 285.05	895.28 (32.81) 944.00 \pm 309.69
C _{avg} (ng/mL)	908.99 (26.0) 953.33 \pm 282.14	1045.80 (29.19) 1090.86 \pm 318.42
T _{max} (hr)*	6.00 (3.00-10.00)	7.00 (4.00-10.02)
Degree of Fluctuation (%)	43.46 \pm 16.88	43.12 \pm 17.82
Degree of Swing (%)	53.97 \pm 25.74	52.19 \pm 26.83
MRT (hr)	11.32 \pm 0.31	11.51 \pm 0.29
M/P Ratio	15.57 \pm 4.20	15.97 \pm 4.84

* median (min - max)

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**MEAN PLASMA BUPROPION THREOAMINO ALCOHOL CONCENTRATION VERSUS TIME
LINEAR SCALE (n=38)**



Triangles-Treatment A Bupropion HBr XL
Diamonds- Treatment B Bupropion XL

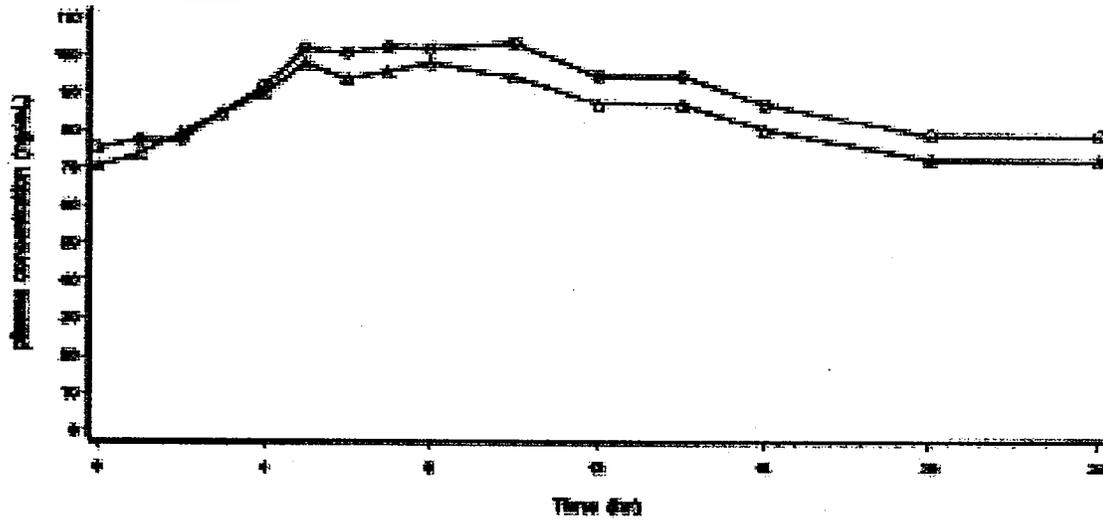
Table 11.4.3 Summary statistics of pharmacokinetic parameters of bupropion threoamino alcohol at steady state in healthy subjects (Treatment A & B)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	Bupropion HBr XL 348 mg Tablets (A) (n=38)	Wellbutrin XL [®] 300 mg Tablets (B) (n=38)
AUC _{0-∞} (ng·hr/mL)	8842.06 (37.35) 9446.28 ± 3528.05	9768.54 (27.53) 10112.95 ± 2783.98
C _{max} (ng/mL)	486.58 (34.68) 514.82 ± 178.53	541.95 (26.73) 560.74 ± 149.88
C _{min} (ng/mL)	282.78 (47.91) 312.46 ± 149.70	318.60 (34.19) 335.65 ± 114.75
C _{avg} (ng/mL)	368.42 (37.35) 393.60 ± 147.00	407.02 (27.53) 421.37 ± 116.00
T _{max} (hr)*	6.00 (3.00 - 10.00)	7.00 (5.00 - 14.00)
Degree of Fluctuation (%)	55.17 ± 18.45	55.08 ± 19.06
Degree of Swing (%)	74.98 ± 32.28	72.78 ± 31.30
MRT (hr)	11.39 ± 0.37	11.60 ± 0.28
M/P Ratio	6.76 ± 2.29	6.60 ± 2.34

* median (min - max)

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**MEAN PLASMA BUPROPION ERYTHROAMINO ALCOHOL CONCENTRATION VERSUS TIME
LINEAR SCALE (n=38)**



Triangles-Treatment A Bupropion HBr XL
Diamonds- Treatment B Bupropion XL

Table 11.4.4 Summary statistics of pharmacokinetic parameters of bupropion erythroamino alcohol at steady state in healthy subjects (Treatment A & B)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean \pm SD	
	Bupropion HBr XL 348 mg Tablets (A) (n=38)	Wellbutrin XL [®] 300 mg Tablets (B) (n=38)
AUC _t (ng-hr/mL)	1922.76 (29.01) 2009.09 \pm 582.74	2091.51 (22.07) 2143.79 \pm 473.12
C _{max} (ng/mL)	99.98 (27.31) 103.93 \pm 28.38	108.26 (23.57) 111.35 \pm 26.25
C _{min} (ng/mL)	67.46 (35.71) 72.00 \pm 25.71	76.01 (25.97) 78.52 \pm 20.39
C _{avg} (ng/mL)	80.11 (29.01) 83.71 \pm 24.28	87.15 (22.07) 89.32 \pm 19.71
T _{max} (hr) ^a	7.00 (5.00 - 14.00)	7.00 (5.00 - 12.00)
Degree of Fluctuation (%)	40.46 \pm 16.49	37.10 \pm 14.22
Degree of Swing (%)	50.16 \pm 24.94	43.65 \pm 19.18
MRT (hr)	11.54 \pm 0.32	11.72 \pm 0.25
M/P Ratio	1.47 \pm 0.45	1.40 \pm 0.42

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Table 11.4.6 Comparison of pharmacokinetic parameters of bupropion at steady state in healthy subjects (Treatment A vs. B)

Parameter	Potency Uncorrected Data		
	90% C.I.	Ratio of Means	Intra-Subject CV
AUC _{0-∞}	84.19% to 93.99%	88.93%	14.16%
C _{max}	80.20% to 92.15%	85.97%	17.97%
C _{min}	86.56% to 100.00%	93.04%	18.68%
Parameter	Potency Corrected Data		Intra-Subject CV
	90% C.I.	Ratio of Means	
AUC _{0-∞}	86.18% to 96.18%	91.04%	
AUC ₀₋₂₄	82.10% to 94.33%	88.00%	
C _{max}	88.61% to 102.37%	95.24%	

Table 11.4.7 Comparison of pharmacokinetic parameters of hydroxybupropion at steady state in healthy subjects (Treatment A vs. B)

Parameter	Potency Uncorrected Data		
	90% C.I.	Ratio of Means	Intra-Subject CV
AUC _{0-∞}	82.96% to 92.04%	87.39%	13.39%
C _{max}	81.93% to 91.10%	86.59%	13.68%
C _{min}	81.45% to 90.94%	86.06%	14.27%

Table 11.4.8 Comparison of pharmacokinetic parameters of bupropion threoamino alcohol at steady state in healthy subjects (Treatment A vs. B)

Parameter	Potency Uncorrected Data		
	90% C.I.	Ratio of Means	Intra-Subject CV
AUC _{0-∞}	85.78% to 96.23%	90.86%	14.83%
C _{max}	84.49% to 95.91%	90.02%	16.38%
C _{min}	83.54% to 95.43%	89.29%	17.21%

Table 11.4.9 Comparison of pharmacokinetic parameters of bupropion erythroamino alcohol at steady state in healthy subjects (Treatment A vs. B)

Parameter	Potency Uncorrected Data		
	90% C.I.	Ratio of Means	Intra-Subject CV
AUC _{0-∞}	87.32% to 97.69%	92.36%	14.46%
C _{max}	87.66% to 97.91%	92.64%	14.27%
C _{min}	83.81% to 95.28%	89.36%	16.57%

COMMENTS:

1. The relative BA study indicates that at comparable molar doses of 348 mg of bupropion hydrobromide and 300 mg of bupropion hydrochloride the hydrobromide salt is only 90% as available as the HCL salt. Cmax values are comparable. This decreased BA is also reflected in the ratios of the metabolites bupropion erythroamino alcohol, bupropion threoamino alcohol and hydroxybupropion of bupropion hydrobromide being approximately 90% of those for the bupropion hydrochloride.

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APPENDIX I EFFECT OF ALCOHOL ON DISSOLUTION

Confidential

Introduction

"Dose dumping" is defined as rapid drug release in a short period of time of the entire amount or a significant fraction of the drug contained in a modified release dosage form. Depending on the therapeutic indication and the therapeutic index of a drug, dose dumping can pose a significant risk to patients due to safety issues related to the high exposure.

Biovail has developed bupropion hydrobromide extended release tablets (bupropion HBr XL), 174 mg and 348 mg, modified release dosage forms. In order to assess the risk of alcohol-induced dose dumping, Biovail has evaluated bupropion HBr XL tablets by conducting *in-vitro* dissolution experiments under varying concentrations of ethanol in 0.1N HCl.

The dissolution method proposed in the NDA 22-108 submission was used for the *in-vitro* dissolution experiments, with the exception of varying the composition of the dissolution medium. The dissolution parameters are shown below.

Apparatus: USP Apparatus 1 (baskets)
 Medium: 0.1N HCl; 900 ml ✓
 Basket Speed: 75 rpm
 Wavelength: 252 nm
 Cell: 1 mm

In-Vitro Dissolution Experiments

Samples of bupropion HBr XL tablets, 174 mg and 348 mg, were tested in a range of dissolution media as shown in Table 1.

Table 1 Summary of Dissolution Experiments

Strength	Lot Number	Date of Manufacture	Media (% V/V Ethanol)
174 mg	06C611	April 2006	0.1N HCl
			0.1N HCl : Ethanol
			0.1N HCl : Ethanol
			0.1N HCl : Ethanol
348 mg	06C468	March 2006	0.1N HCl
			0.1N HCl : Ethanol
			0.1N HCl : Ethanol
			0.1N HCl : Ethanol

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Dissolution Results

Figure 1 shows the dissolution profiles, for the first 2 hours (120 minutes) of the dissolution run, of the 174 mg strength in 0.1N HCl and in 0.1N HCl with added ethanol

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Figure 2 shows comparative dissolution profiles for the 174 mg strength from 20-hour dissolution run in 0.1N HCL versus 0.1N HCl + EtOH.

Figure 3 shows the dissolution profiles, for the first 2 hours (120 minutes) of the dissolution run, of the 348 mg strength in 0.1N HCl and in 0.1N HCl with added ethanol

Figure 4 shows comparative dissolution profiles for the 348 mg strength from 20-hour dissolution run in 0.1N HCL versus 0.1N HCl + EtOH.

Table 2 through Table 2C are dissolution data for the 174 mg strength, in 0.1N HCl and in 0.1N HCl with added ethanol with time points taken every 15 minutes up to 120 minutes.

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Table 3 through Table 3C are dissolution data for the 348 mg strength, in 0.1N HCl and in 0.1N HCl with added ethanol, with time points taken every 15 minutes up to 120 minutes.

Table 4 displays results for the 174 mg strength from the dissolution run up to 20 hours in 0.1N HCl and 0.1N HCl + EtOH.

Table 5 displays results for the 348 mg strength from the dissolution run up to 20 hours in 0.1N HCl and 0.1N HCl + EtOH.

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Conclusion

The *in-vitro* dissolution results show no potential of ethanol-induced dose dumping with the bupropion hydrobromide extended release tablets.

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8 Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

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APPENDIX II-DSI REPORT

Amalia informed me this morning that you recently inquired about the inspection for NDA 22-108 (Bupropion Hydrobromide ER tablets) at Biovail Contract Research, Toronto, Canada (Biovail). Please be informed that we just completed the inspection for both the clinical and analytical portions of Study 3230 at Biovail. The following 483 items were issued to study site following the inspection:

1. The firm did not include all data in their final pharmacokinetic and statistical analyses. Specifically, data for subjects #019 and #033 were excluded when their bupropion and active metabolite levels were found to be either very low or below the limit of quantitation following drug administration. An investigation by the principal investigator (PI) failed to identify a root cause. During the interview with the PI, both subjects #019 and #033 stated they ingested the study drugs as directed and denied any noncompliance.
2. The firm failed to include in the analytical report all valid precision and accuracy (PA) data generated during a partial assay re-validation in June 2006 following completion of all sample analyses. Specifically, the precision and accuracy of the assay was re-validated by Biovail Bioanalytical Laboratory due to a deviation in the method SOP (i.e., the concentration of the

internal standard solution used in all analytical runs was 10 times higher due to a preparation error.) Four PA runs were conducted during the re-validation. PA Runs # 1, 2, and 4 yielded good results and were included in the analytical report. PA Run #3 yielded poor results and was excluded without a valid reason.

3. Concentrations of the quality control samples (QCs) for Bupropion Erythoamino Alcohol (BEA; a bupropion active metabolite) used in the analytical runs are not relevant to the BEA concentrations observed in plasma samples of study subjects. For example, the mean peak concentrations (C_{max}) for BEA from study subjects following drug administration are 103+- 28.4 ng/ml for the test product and 111.4+- 26.3 ng/ml for the reference product, but the BEA QCs used to monitor performance of analytical runs are 3 ng/ml (low QC), 192 ng/ml (mid QC), and 768 ng/ml (high QC).

APPENDIX III-FDA RESPONSE TO DSI REPORT AND REQUESTED FOLLOW-UP BY FIRM

We have taken a look at the inspection report issued by the Division of Scientific investigations and we agree with the following points:

1. The OCP reviewer should decide whether the Period 2 data from subjects 019 and 033 should be excluded from the bioequivalence determination.
2. The BEA (**Bupropion Erythoamino Alcohol**) data for subjects 022 and 023 are not reliable due to the objectionable finding discussed in 483 Item 3.
3. The assay is not adequately re-validated at LLOQ (1 ng/ml) for the active metabolite, hydroxybupropion. However, this should not have a significant impact on the study results as majority of the hydroxybupropion data are higher than the LLOQ.

For item # 1 no further action is required by the firm since the OCP recommendation would be to delete these subjects and indeed in the submitted analysis they were not included.

For item # 2 an action by the firm is requested. The **Bupropion Erythoamino Alcohol (BEA)** levels should be deleted for subjects #022 and #023 and the analysis repeated.

For item # 3 no further action is required.

The sponsor submitted this analysis on June 5, 2007. See Tables on page 14. Deletion of subjects # 22 and 23 did not have any impact on the results for BEA (Bupropion Erythoamino Alcohol)

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Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

Information		Information	
NDA Number	22-108	Brand Name	
OCPB Division (I, II, III)	I	Generic Name	Bupropion Hydrobromide ER
Medical Division	Psychiatry	Drug Class	
OCPB Reviewer	Andre Jackson	Indication(s)	Depression
OCPB Team Leader	Raman Baweja	Dosage Form	Tablets
		Dosing Regimen	Once/day
Date of Submission	September 27, 2006	Route of Administration	Oral
Estimated Due Date of OCPB Review	June 9, 2007	Sponsor	Biovail
PDUFA Due Date	July 28, 2007	Priority Classification	IS
Division Due Date	June 26, 2007		

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Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x	1		Study 3228 (B06-755PK-10121) A Two-Way Crossover, Open-label, Single-dose, Fasting, Dosage Strength Proportionality Study of Two Strengths of Bupropion HBr XL Tablets (2 x 174 mg Versus 1 X 348 mg) in Normal, Healthy, Non-Smoking Male and Female Subjects
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				

In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	x	1		Influence of intrinsic and extrinsic factors on the pharmacokinetics of bupropion hbr xl tablets-Summary study report
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	1		Study 3230 A Two-Way Crossover, Open-Label, Multiple-Dose Fasting, Comparative Bioavailability HBr 348 mg Tablets versus Wellbutrin XL® 300mg Tablets in Normal, Healthy, Non-Smoking Male and Female subjects
replicate design; single / multi dose:				
Food-drug interaction studies:	x	1		Study 3229 (B06-754PK-10121) A Two-Way Crossover, Open-Label, Single-Dose, Food-Effect Study of Bupropion HBr XL 348 mg Tablets in Normal, Healthy, Non-Smoking Male and Female Subjects

Dissolution:	x	1		Method mentioned but data could not be located
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
Filability and QBR comments				
	"X" if yes	Comments		
Application fileable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)		<ol style="list-style-type: none"> 1. Does the Bupropion Hydrobromide ER tablets give comparable plasma levels as Wellbutrin XL? 2. Is there a food effect on Bupropion Hydrobromide ER tablets ? 3. Is Bupropion Hydrobromide ER tablets dose proportional over the proposed dosage range 174 mg to 348 mg in healthy adults? 		
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA HFD-850 (Electronic Entry or Lee), HFD-120 (CSO), HFD-860 (Baweja, Jackson, Mehta), CDR (Biopharm-CDR)

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

/s/

Andre Jackson
11/14/2006 03:40:19 PM
BIOPHARMACEUTICS

Raman Baweja
11/14/2006 05:15:02 PM
BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Review

IND: 73,781 (Serial No. 000)

Drug: Bupropion Hydrobromide Extended Release Tablets

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Sponsor: Bioavail Technologies

Indication: Major Depressive Disorder (MDD)

Type of Submission: 30 Day SRD

Submission Date: October 24, 2005

OCPB Consult: 11/1/05

Reviewer: Kofi A. Kumi, Ph.D.

Team Leader: Raman Baweja, Ph.D.

Background: Wellbutrin (bupropion hydrochloride) is approved for treatment of major depressive disorder (MDD). Bupropion is commercially available in the form of a hydrochloride (HCl) salt as an immediate release (Wellbutrin), a sustained release (Wellbutrin SR) and an extended release (Wellbutrin XL). The sponsor has developed a new salt of an approved drug, Wellbutrin XL (bupropion hydrochloride extended-release tablets) which is manufactured by Bioavail Corporation and marketed by GlaxoSmithKline. The sponsor states that the new bupropion salt, (hydrobromide (HBR)) has an enhanced absorption (EA) and come in tablet strengths

The sponsor states the new formulation will provide equivalent peak and systemic exposure of bupropion relative to Wellbutrin XL at a lower dose of the active ingredient

b(4)

The mean elimination half-life (\pm SD) of bupropion after chronic dosing is 21 ± 9 hours and steady state plasma concentrations are reported to be reached within 8 days. Three metabolites have been shown to be active: hydroxybupropion, threohydrobupropion and erythrohydrobupropion. In vitro findings suggest that CYP2B6 is the principal isoenzyme involved in the formation of hydroxybupropion, while CYP450 isoenzymes are not involved in the formation of threohydrobupropion. Bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme in vitro. 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. Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300 to 450 mg/day.

The sponsor plans to evaluate the new bupropion HBR (EA) formulation in three Phase 1 studies in normal volunteers in order to determine bioequivalence to the RLD. The Pharmacokinetic program include consists of a steady state fasting study, a food effect study and a single-dose dosage proportionality study. The sponsor plans to dose the subjects at or below the approved dose of bupropion, in accordance with the approved Prescribing Information for Wellbutrin XL. The proposed pharmacokinetic program is designed to demonstrate the bioequivalence between the new bupropion HBR EA and Wellbutrin XL in healthy males and females. Following a finding of bioequivalence to the RLD (Wellbutrin XL), the sponsor intends to submit an NDA under section 505(b)(2) of the Act and 21 CFR 314.54 and related regulations.

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New Protocol

Food Effect Study:

Study Title (B05-702PK-10121): A Two-Way Crossover, Open-Label, Single-Dose, Pharmacokinetic, Food Effect Study On Bupropion HBr EA 300 mg Tablets in Normal Healthy Non-Smoking Male and Female Subjects.

Objectives: To evaluate the effect of the FDA high-fat breakfast versus fasting conditions on the pharmacokinetics of bupropion from a test formulation of Bupropion HBr EA 300 mg Tablets

The synopsis of the study is attached.

Comments Specific to Protocol B05-702PK-10121

- 1) There are no comments specific to Protocol B05-702PK-10121 from a clinical pharmacology and biopharmaceutics perspective. The study can proceed from a clinical pharmacology and biopharmaceutics perspective.

Dose Proportionality Study:

Study Title (Protocol B05-704PK-10121): A two way, cross-over, open-label, single dose , fasting, dosage strength proportionality study of two strengths of Bupropion HBr EA Tablets (2 x 150 mg vs 1 x 300 mg) in normal, healthy, non-smoking male and female subjects

Objectives: To evaluate the dosage strength proportionality of two strengths of Bupropion HBr Enhanced Absorption Tablets When administered as 2 x 150-mg and 1 x 300 mg strengths under single dose fasting conditions

Comments Specific to Protocol B05-704PK-10121

- 1) Dose proportionality cannot be adequately ascertained from the study as designed. It is recommended that an appropriate dose proportionality study be conducted. The study as designed is a dose equivalency study.

General Comments:

- 1) It is recommended that the sponsor provide details of the design of the steady state multiple dose study of Bupropion HBr EA compared to a reference listed drug.
- 2) Please forward Comment #1 to the sponsor

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Kofi A. Kumi, Ph.D. _____

RD/FT Initialed by Raman Baweja, Ph.D. _____

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2. STUDY SYNOPSIS

Objectives	The objective of this study is to evaluate the effect of the Food and Drug Administration (FDA) high-fat breakfast versus fasting conditions on the pharmacokinetics of bupropion from a test formulation of Bupropion HBr EA (Enhanced Absorption) 300 mg Tablets.
Experimental Design	A randomized, two-way crossover, open-label, single-dose, food-effect design.
Subjects	Forty-eight normal, healthy, non-smoking male and female subjects.
Drug Administration	Subjects will receive one of the following treatments at 0.0 hour on Day 1 of each study period, according to a randomization scheme: Treatment A: Following an overnight fast of at least ten hours, and 30 minutes after the start of a high fat content breakfast, one Bupropion HBr EA 300 mg Tablet with 240 mL of ambient temperature water. (Treatment dose = 300 mg). Treatment B: Following an overnight fast of at least ten hours, one Bupropion HBr EA 300 mg Tablet with 240 mL of ambient temperature water. (Treatment dose = 300 mg).
Length of Study	This study consists of two 11-day periods separated by at least a two-week washout period between treatments.
Sample Collection	Twenty-two blood samples (4 mL each) will be drawn in each period according to the following schedule: 0.0 (pre-drug), 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 14.0, 16.0, 20.0, 24.0, 36.0, 48.0, 60.0, 72.0, 120.0, 168.0, and 216.0 hours post-drug administration.
Total Blood Volume	203 mL of blood will be taken from male subjects and 213 mL of blood will be taken from female subjects, including the volume for pre-study clinical blood tests, serum β -human chorionic gonadotropin (β -CG) test for female subjects at check-in for each study period, and end-of-study clinical blood tests.
Study Confinement	Subjects will be institutionalized the day prior to Day 1 dosing and will remain in the clinic up until the 24.0 hour blood sample time point for each study period at which time they may leave the clinic and return for subsequent draws.

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Subject Monitoring	<p>The Principal Investigator, or Sub-investigator (i.e., an Ontario-licensed physician), will be on-site, within the proximity of the subject confinement area, at least 30 minutes prior to the standard high fat content breakfast and for the first eight hours following drug administration. At the time of drug administration, the Principal Investigator, or Sub-investigator, shall be present in the dosing area. For the duration of the study, the subjects will be monitored by Biovail Contract Research (BCR) medical staff for adverse events (AEs). The Principal Investigator, or Sub-investigator, will be available by pager for the duration of the study. Adverse events will be monitored during each study period.</p>
Screening and Mid-Study Procedures	<p>All subjects will undergo a medical history, medication history, physical examination (including blood pressure, heart rate and temperature), electrocardiogram (ECG) and electroencephalogram (EEG) (normal EEG within one year) prior to starting the study. Selected routine clinical laboratory measurements, including screens for hepatitis C, hepatitis B-surface antigen, human immunodeficiency virus (HIV), urine drugs of abuse and urine nicotine (cotinine) will be performed during screening. In addition, a serum β-CG test will be performed for all female subjects.</p> <p>At check-in for each study period, screens for urine drugs of abuse, urine nicotine (cotinine) and alcohol (saliva or breathalyzer) will be performed on all of the subjects. In addition, a serum β-CG test will be performed for all female subjects upon check-in for each study period.</p>
End of Study Procedures	<p>The physical examination (including blood pressure and heart rate), hematology, biochemistry measurements (excluding hepatitis C, hepatitis B-surface antigen and HIV screens) and urinalysis will be repeated prior to discharge at the completion of the study.</p>
Pharmacokinetics	<p>Pharmacokinetic analysis will be conducted using non-compartmental analysis. Parameters: AUC_{0-4}, AUC_{0-12}, C_{max}, T_{max}, K_{el}, $t_{1/2}$, MRT, and metabolite/parent (MP) ratio will be calculated for bupropion, hydroxybupropion, bupropion threamino alcohol, bupropion erythramino alcohol.</p>
Statistical Analyses	<p>Descriptive statistics will be performed for plasma concentrations and for all pharmacokinetic parameters. Using General Linear Models (GLM) procedures in Statistical Analysis System (SAS), analysis of variance (ANOVA) will be performed on ln-transformed AUC_{0-4}, AUC_{0-12} and C_{max} and on untransformed</p>

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<p>Statistical Analyses (Cont'd)</p>	<p>K_{el}, MRT, MP ratio and $t_{1/2}$ at the significance level of 0.05. The intra-subject coefficient of variation (CV) will be calculated using the Mean Square Error (MSE) from the ANOVA table. The ratio of geometric means and the 90% geometric confidence interval will be calculated based on the difference in the Least Squares Means (LSM) of the ln-transformed AUC_{0-4}, AUC_{0-12} and C_{max} between the test and reference formulation.</p> <p>The pharmacologic activity-weighted composite (PAWC) at each time-point will be calculated by multiplying the molar concentration of each analyte by its relative potency and adding all four concentrations. Similar to plasma analyte concentration-time data, pharmacokinetic parameters for the PAWC will be determined and subjected to statistical analyses to compare Bupropion HBr EA 300 mg Tablets (fed) with Bupropion HBr EA 300 mg Tablets (fasted).</p> <p>The parameter T_{max} will be analyzed using nonparametric methods. The equality of treatment effect in both sequences will be evaluated using Wilcoxon rank-sum tests. The mean shift between the two treatments will be estimated by the median unbiased Hodges-Lehmann estimate and 90% exact confidence interval. The Hodges-Lehmann procedure extends the Wilcoxon rank-sum test to provide a median unbiased point estimate and an exact confidence interval for the magnitude of the shift between two populations.</p> <p>Both potency uncorrected and potency corrected data will be presented. Gender analysis will be performed if a suitable split is obtained in the subject panel.</p>
<p>Safety Data Reporting</p>	<p>The safety data will be presented in the final report.</p> <p>The current version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to code and document all Adverse Events (AEs).</p>
<p>Analytical Method</p>	<p>The plasma concentrations of bupropion, hydroxybupropion, bupropion threoamino alcohol, bupropion erythroamino alcohol will be analyzed using a validated assay method.</p>

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3. STUDY SCHEMATICS

PROCEDURE	SCREENING	STUDY PERIOD I	STUDY PERIOD II	END-OF-STUDY
Informed consent	X	X		
Medical and medication histories	X			
ECG	X			
EEG (if necessary)	X			
Blood pressure and heart rate	X			X
Physical examination	X			X
Biochemistry, hematology, urinalysis	X			
Biochemistry (excluding hepatitis B-surface antigen, hepatitis C and HIV screen), hematology, urinalysis				X
100% Urine drugs of abuse and urine nicotine (cotinine) screens	X			
100% Urine drugs of abuse, alcohol (saliva or breathalyzer), and, urine nicotine (cotinine) screens		X	X	
100% Female Subjects: Serum β -CG Test	X	X	X	
Drug administration		X	X	
Adverse events		X	X	X
Blood collection for plasma bupropion and metabolites concentration		X	X	

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2. STUDY SYNOPSIS

Objectives	The objective of this study is to evaluate the dosage strength proportionality of two strengths of Bupropion HBr Enhanced Absorption (EA) Tablets when administered as 2 x 150 mg and 1 x 300 mg strengths under single dose fasting conditions.
Experimental Design	A randomized, two-way crossover, open-label, single-dose, fasting design.
Subjects	Forty-eight normal, healthy, non-smoking male and female subjects.
Drug Administration	Subjects will receive one of the following treatments at 0.0 hour on Day 1 of each study period, according to a randomization scheme: Treatment A: Following an overnight fast of at least 10 hours, two Bupropion HBr EA 150 mg Tablets with 240 mL of ambient temperature water. (Treatment dose = 300 mg). Treatment B: Following an overnight fast of at least 10 hours, one Bupropion HBr EA 300 mg Tablet with 240 mL of ambient temperature water. (Treatment dose = 300 mg).
Length of Study	This study consists of two 11-day periods separated by at least a two-week washout period between treatments.
Sample Collection	Twenty-two blood samples (4 mL each) will be drawn in each period according to the following schedule: 0.0 (pre-dose), 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 14.0, 16.0, 20.0, 24.0, 36.0, 48.0, 60.0, 72.0, 120.0, 168.0, and 216.0 hours post-dose.
Total Blood Volume	Approximately 203 mL of blood will be taken from male subjects and approximately 213 mL of blood will be taken from female subjects, including the volume for pre-study clinical blood tests, serum β -human chorionic gonadotropin (β -CG) pregnancy test for female subjects at check-in for each study period, and post-study clinical blood tests.
Study Confinement	Subjects will be institutionalized the day prior to Day 1 dosing and will remain in the clinic up until the 24.0 hour blood sample time point for each study period at which time they may leave the clinic. Subjects are required to return for subsequent draws.

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<p>Subject Monitoring</p>	<p>The Principal Investigator, or sub-investigator (i.e., an Ontario-licensed physician), will be on-site, within the proximity of the subject confinement area, at least 30 minutes prior to dosing and for the first 8 hours following drug administration. For the duration of each study period, the subjects will be monitored by Biovail Contract Research (BCR) medical staff for adverse events (AEs). The Principal Investigator, or sub-investigator, will be available by pager for the duration of the study.</p>
<p>Screening and Mid-Study Procedures</p>	<p>All subjects will undergo a medical history, medication history, physical examination (including blood pressure, heart rate and temperature), electrocardiogram (ECG) and electroencephalogram (EEG) (normal EEG within one year) prior to starting the study. Selected routine clinical laboratory measurements, including screens for hepatitis C, hepatitis B-surface antigen, human immunodeficiency virus (HIV), urine drugs of abuse and urine nicotine (cotinine) will be performed during screening. A serum β-CG test will be performed for all female subjects.</p> <p>At check-in for each study period, screens for urine drugs of abuse, urine nicotine (cotinine) and saliva alcohol will be performed on all of the subjects. A serum β-CG test will be performed for all female subjects upon check-in for each study period.</p>
<p>Post-Study Procedures</p>	<p>The physical examination (including blood pressure and heart rate), hematology, biochemistry measurements (excluding hepatitis C, hepatitis B-surface antigen and HIV screens) and urinalysis will be repeated prior to discharge at the completion of the study.</p>
<p>Pharmacokinetics</p>	<p>Pharmacokinetic analysis will be conducted using non-compartmental analysis. Parameters: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, $t_{1/2}$, Mean Residence Time (MRT), and metabolite/parent (MP) compound ratios will be calculated for bupropion, hydroxybupropion, bupropion threoamino alcohol, bupropion erythroamino alcohol.</p> <p>The pharmacologic activity-weighted composite (PAWC) at each time-point will be calculated by multiplying the molar concentration of each analyte by its relative potency and adding all four concentrations. Similar to plasma analyte concentration-time data, pharmacokinetic parameters for the PAWC will be determined and subjected to statistical analyses to compare Bupropion HBr EA 150 mg Tablets with Bupropion HBr EA 300 mg Tablets.</p>

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<p>Statistical Analyses</p>	<p>Descriptive statistics will be performed for plasma concentrations and for all pharmacokinetic parameters. Using General Linear Models (GLM) procedures in Statistical Analysis System (SAS), analysis of variance (ANOVA) will be performed on ln-transformed AUC_{0-t}, AUC_{0-tr} and C_{max} and on untransformed K_{el}, MRT, M/P ratio and $t_{1/2}$ at the significance level of 0.05. The intra-subject coefficient of variation (CV) will be calculated using the Mean Square Error (MSE) from the ANOVA table. The ratio of geometric means and the 90% geometric confidence interval will be calculated based on the difference in the Least Squares Means (LSM) of the ln-transformed AUC_{0-t}, AUC_{0-tr} and C_{max} between the test formulations.</p> <p>The parameter T_{max} will be analyzed using nonparametric methods. The equality of treatment effect in both sequences will be evaluated using Wilcoxon rank-sum tests. The mean shift between the two treatments will be estimated by the median unbiased Hodges-Lehmann estimate and 90% exact confidence interval. The Hodges-Lehmann procedure extends the Wilcoxon rank-sum test to provide a median unbiased point estimate and an exact confidence interval for the magnitude of the shift between two populations.</p>
<p>Safety Data Reporting</p>	<p>The safety data will be presented in the final report.</p> <p>The current version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to code and document all Adverse Events (AEs).</p>
<p>Analytical Method</p>	<p>The plasma concentrations of bupropion, hydroxybupropion, bupropion threoamino alcohol, bupropion erythroamino alcohol will be analyzed using a validated assay method.</p>

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PROCEDURE	SCREENING	STUDY PERIOD I	STUDY PERIOD II	POST STUDY
Informed consent	X	X		
Medical and medication histories	X			
ECG	X			
EEG (if necessary)	X			
Blood pressure and heart rate	X			X
Physical examination	X			X
Biochemistry, hematology, urinalysis	X			
Biochemistry (excluding hepatitis B-surface antigen, hepatitis C and HIV screen), hematology, urinalysis				X
100% Urine drugs of abuse and urine nicotine (cotinine) screens	X	X	X	
100% saliva alcohol screen		X	X	
100% Female Subjects: Serum β -CG Test	X	X	X	
Drug administration		X	X	
Adverse events		X	X	X
Blood collection for plasma bupropion and metabolites concentration analyses		X	X	

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/s/

Kofi Kumi
1/23/2006 02:17:16 PM
BIOPHARMACEUTICS

Raman Baweja
1/23/2006 04:28:00 PM
BIOPHARMACEUTICS