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<b>Study No:</b> AK1BIOVAIL2548
<b>Title :</b> A two-way, crossover, open-label, single dose, food-effect, comparative bioavailability study of bupropion HCl extended release 300mg tablets in normal healthy non-smoking male and female subjects
<b>Rationale:</b> In a general trend to improve treatment convenience and patient compliance, many products are being developed for once-daily administration. Bupropion hydrochloride extended release tablets have been formulated to provide a product which is bioequivalent to bupropion immediate release and, by inference, to other approved formulations of the compound. This study sought to evaluate the effect of food on the performance of the once daily product.
<b>Phase:</b> I
<b>Study Period:</b> 26 January 2002 – 15 February 2002
<b>Study Design:</b> Two-period, randomized, single-dose, open-label, two-way crossover study
<b>Centres:</b> One centre in Canada
<b>Indication:</b> None
<b>Treatment:</b> Screening was conducted on an outpatient basis, subjects who met the inclusion/exclusion criteria were randomized according to a randomization schedule to one of two treatment sequences (AB or BA), where A and B are defined below. Subjects attended the study clinic the evening before dosing and received one of the following treatments at 0.0 h on Day 1 after an overnight fast of at least 10 h. Treatment A: one bupropion HCl extended release 300 mg tablet with 240 mL water following an overnight fast of at least 10 h. Treatment B: one bupropion HCl extended release 300 mg tablet with 240 mL water within 5 minutes following the complete ingestion of a high-fat content breakfast. Blood samples were collected from each of the subjects for 120 h following the single dose. After a 2-week washout period subjects underwent a second treatment sequence with the alternate treatment regimen.
<b>Objectives:</b> The objective of this study was to evaluate the effect of food on the rate and extent of absorption of a once daily formulation of bupropion hydrochloride (HCl) extended release tablets (300 mg) under single-dose conditions.
<b>Statistical Methods:</b> Information on adverse events (AEs) reported by subjects was listed and summarized. For pharmacokinetic data an analysis of variance (ANOVA) was performed on log-transformed AUC <sub>last</sub> , AUC <sub>inf</sub> , and C <sub>max</sub> . The ANOVA used a mixed-effects model with subject (sequence) as a random effect. The fixed effects were sequence, period, and treatment. To evaluate the effect of food on the pharmacokinetics of newly formulated once daily bupropion HCl 300mg extended release tablets, the 90% confidence interval for the ratio of means for the test treatment (bupropion HCl 300 mg extended release tablet in the fed state) to the reference treatment (bupropion HCl 300 mg extended release tablet in the fasted state) for AUC <sub>last</sub> , AUC <sub>inf</sub> , and C <sub>max</sub> was calculated. For lack of food effect to be concluded, the 90% confidence intervals (CIs) for the ratio of means for AUC <sub>last</sub> , AUC <sub>inf</sub> , and C <sub>max</sub> were to fall within 0.80 to 1.25. Descriptive statistics were calculated for all pharmacokinetic parameters including AUC <sub>last</sub> , AUC <sub>inf</sub> , C <sub>max</sub> , t <sub>max</sub> , t <sub>1/2</sub> , MRT, and M/P ratios, C <sub>last</sub> , and t <sub>last</sub> . With: AUC <sub>last</sub> : area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration, AUC <sub>inf</sub> : area under the plasma concentration-time curve from time zero extrapolated to the infinite time, C <sub>max</sub> : maximum observed plasma concentration, t <sub>max</sub> : time to reach C <sub>max</sub> , t <sub>1/2</sub> : apparent terminal half-life, MRT: mean residence time, M/P ratio: metabolite to parent ratio based on AUC <sub>inf</sub> C <sub>last</sub> : last observed plasma concentration t <sub>last</sub> : time of the last observed plasma concentration.
<b>Study Population:</b> Normal, healthy, non-smoking males and females with a minimum age of 18 years with a body weight not more than ±15% of the ideal weight for the subject's height and frame. Subjects were also required not to

have any known history of hypersensitivity to bupropion hydrochloride and/or related drugs any clinical laboratory or concomitant medical conditions or findings on examination, history of alcohol or drug abuse or any psychiatric or psychological disease, history of serious head injuries, seizures, any eating disorders such as bulimia or anorexia nervosa, frequent headaches or migraines.		
<b>Number of Subjects:</b>		
<b>Number of Subjects:</b>		
Planned Total N	36	
Dosed N per Treatment	34	
Completed n (%)	32 (89)	
Total Number Subjects Withdrawn N (%)	4 (11)	
Withdrawn due to Adverse Events n (%)	2 (6)	
Withdrawn due to Lack of Efficacy n (%)	0	
Withdrawn for Other Reasons n (%)	2 (6)	
<b>Demographics</b>		
N (ITT)	36	
Females: Males	10): 26	
Mean Age in Years (SD)	31.4 (6.8)	
Mean Weight in Kg (SD)	75.0 (9.1)	
White n (%)	26 (72)	
<b>Pharmacokinetics Endpoints:</b> Blood samples for PK assessment were collected for 120h after dosing. The pharmacokinetic parameters of bupropion were similar irrespective of the presence or absence of food. The pharmacokinetic parameters of the metabolites of bupropion and the pharmacological activity-weighted composite (PAWC) were also similar regardless of food intake. The results of the ANOVA to assess food effect are shown in the table below.		
<b>Bupropion Food Effects Analysis</b>		
Pharmacokinetic Parameter	Geometric Least Squares Mean Ratio (Fed/Fasted)	90% Confidence Interval
AUClast	1.10	1.04, 1.17
AUCinf	1.10	1.04, 1.16
Cmax	0.92	0.84, 1.01
<b>Hydroxybupropion Food Effects Analysis</b>		
AUClast	1.04	0.96, 1.12
AUCinf	1.05	0.97, 1.13
Cmax	1.10	1.03, 1.17
<b>Threohydrobupropion Food Effects Analysis</b>		
AUClast	1.12	1.04, 1.21
AUCinf	1.15	1.04, 1.27
Cmax	1.18	1.11, 1.25
<b>Erythrohydrobupropion Food Effects Analysis</b>		
AUClast	1.13	1.04, 1.24
AUCinf	1.15	1.05, 1.27
Cmax	1.18	1.10, 1.26
The AUClast, AUCinf, and Cmax ratios for bupropion and hydroxybupropion, together with AUClast and Cmax for threohydrobupropion and AUClast for erythrohydrobupropion were bioequivalent (0.8 – 1.25) in the presence and absence of food. The upper bound of the CI for AUCinf for threohydrobupropion (1.26) and for AUCinf and Cmax for erythrohydrobupropion (1.27 and 1.26, respectively) lay just outside up the upper bioequivalence bound of 1.25, but this was not considered clinically significant as these were marginal, particularly in the case of erythrohydrobupropion, which has only a minor contribution to the overall pharmacological activity due to its low potency. In light of the multiplicity of parameters used in the assessment of bioequivalence for extended-release bupropion tablets, the PAWC of bupropion and its metabolites, was recommended by the US Food and Drug Administration as an additional measure of bioequivalence. This parameter was used historically in the evaluation of the approval of bupropion SR since over 90% of systemic exposure to the drug involves metabolites rather than parent drug and was noted by the FDA as potentially important in evaluating the bioequivalence of bupropion. The results of bioequivalence analysis on this parameter are shown in the table below.		
<b>Pharmacological Activity-Weighted Composite Bioequivalence Analysis</b>		

Pharmacokinetic Parameter	Geometric Least Squares Mean Ratio (Fed/Fasted)	90% Confidence Interval
AUClast	1.05	0.98, 1.13
AUCinf	1.06	0.99, 1.14
Cmax	1.02	0.97, 1.08

The pharmacological activity-weighted composite of bupropion and its metabolites demonstrated that confidence intervals for AUClast, AUCinf and Cmax were within the accepted bioequivalence criteria, thereby demonstrating the absence of a food effect.

**Safety results:** Information on AEs was collected from pre-dose on the day of administration of investigational product; all AEs were followed until resolution, until the condition stabilized, until the event was otherwise explained or the subject was lost to follow-up.

Adverse Events:	Group A	Group B
N (ITT)	34	34
No. subjects with AEs n (%)	11 (32%)	7 (21%)
Most Frequent AEs		
Hypocalcemia	3 (9%)	2 (6%)
Headache	3 (9%)	1 (3%)
Serious Adverse Events:	0	0

**Publications:**  
No Publication

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