

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022497Orig1s000**

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

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## Clinical Pharmacology Review

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<b>NDA</b>	22497
<b>Submission Date:</b>	May 13, 2011
<b>Brand Name:</b>	FORFIVO XL
<b>Generic Name:</b>	Bupropion HCl
<b>Strength and Formulation:</b>	450 mg extended-release tablet
<b>Sponsor:</b>	IntelGenx Corp.
<b>Indication:</b>	Major Depressive Disorder (MDD)
<b>Submission Type:</b>	NDA Resubmission (In response to the Complete Response letter)
<b>CP Reviewer Team:</b>	Bei Yu, PhD, Ramana Uppoor, PhD.

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## 1. Executive Summary

IntelGenx Corp. (IntelGenx) is resubmitting NDA22497 to seek approval via 505(b) (2) pathway of FORFIVO XL, bupropion hydrochloride (HCl) 450 mg extended-release (ER) tablet (only one strength) in the treatment of major depressive disorder (MDD).

The NDA was first submitted in April 2009. A complete response letter was issued mainly due to a clinically important food effect of the previous formulation of FORFIVO XL, i.e., food increased mean  $C_{max}$  of bupropion by 25%, which is associated with increased risk of seizure in patients. In response to the deficiency, the sponsor has reformulated FORFIVO XL (b) (4) and conducted a new BA/BE study which is provided in the current submission.

The reference listed drug (RLD) for the application is Wellbutrin XL® (bupropion HCl) 150 mg ER tablets for once a day dosing, GlaxoSmithKline (GSK), NDA No. 21-515 that has been approved by FDA. Clinical efficacy studies were not conducted on this product.

### 1.1 Recommendations

The Office of Clinical Pharmacology (OCP/DCP I) has determined that the resubmission of NDA22497 is acceptable to support a recommendation of approval of FORFIVO XL 450 mg tablet. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP?	Comment
Overall	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	Pending labeling agreement with sponsor.
Pivotal BA/BE	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	
Labeling	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> NA	Pending satisfactory agreement with sponsor.

### Labeling Recommendations

**Detailed Labeling Recommendations (only the changed section from OCP are included here)**



3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

## 1.2 Post-Marketing Studies

There are no Phase 4 requirements or commitments.

## 1.3 Clinical Pharmacology Summary

For the treatment of major depressive disorder, Wellbutrin XL® tablets (150 mg and 300 mg) are given once daily. The labeling of Wellbutrin XL® permits administration of a maximum dose of 450 mg given as a single dose after an up-titration. The sponsor has developed FORFIVO XL (bupropion HCl ER) in only one strength of 450 mg which can be used in patients who require a dosage of 450 mg/day after up-titration or in patients who are currently being treated with other bupropion products at 450 mg/day can be switched to equivalent dose of FORFIVO XL once daily.

Bupropion is extensively hepatically metabolized with three pharmacologically active metabolites, hydroxybupropion (major metabolite), threohydrobupropion, and erythrohydrobupropion. The current submission consists of one BA/BE study to evaluate bioequivalence between 450-mg FORFIVO XL and 3 x 150-mg Wellbutrin XL®, and the food effect of FORFIVO XL. PK of bupropion and its active metabolites were evaluated in the study.

Briefly, bioequivalence was demonstrated for bupropion between the 450-mg FORFIVO XL and the approved Wellbutrin XL® given three 150-mg tablets under single dose, fasted conditions. On the other hand, food prolonged the drug absorption of bupropion by 7 hours from 5 hours to 12 hours. Food did not affect the  $C_{max}$  of bupropion; systemic exposure (AUC) of bupropion was increased by 25% when FORFIVO XL was taken with high-fat food. The PK simulation of steady-state plasma concentration-time profiles based on the single dose study indicated that at steady state the exposure of bupropion following administration of 450-mg FORFIVO XL QD under fed conditions is within the concentration ( $C_{max}$  and  $C_{min}$ ) window of bupropion after administration of Wellbutrin XL® at 3 x 150 mg daily dosing under fasted conditions. This food effect is not considered clinically significant.

## 2. Question Based Review (QBR)

### 2.1 Specific Questions

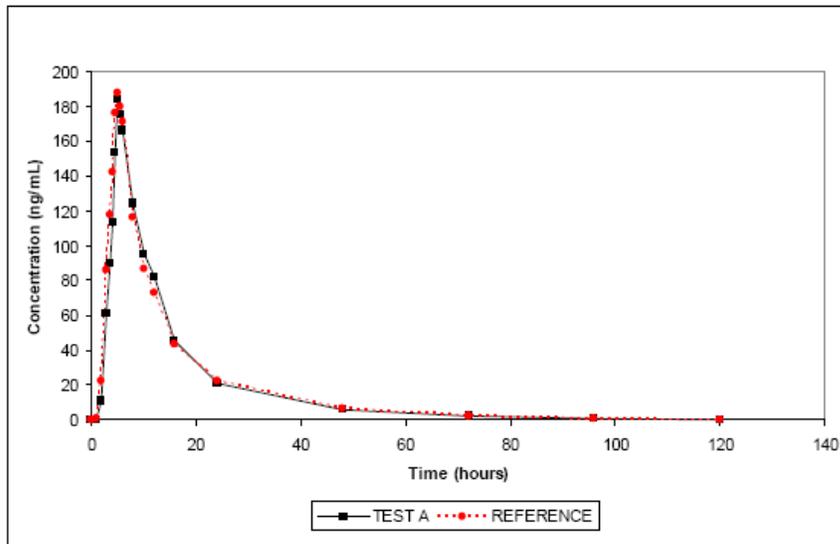
#### 2.1.1 Was an adequate link established between the currently clinically used formulation and the proposed formulation?

Yes.

The sponsor conducted a single dose, BA/BE study in which 1 x 450 mg FORFIVO XL tablet and 3 x 150 mg GSK's XL tablets were compared under fasted conditions. Thirty five male subjects completed the study (PK population).

From a biopharmaceutical perspective based on the parent drug, bupropion, bioequivalence is established between the 450-mg FORFIVO XL (bupropion HCl ER) and the approved Wellbutrin XL® given as three 150-mg tablets. In addition, equivalence is demonstrated for  $C_{max}$  and AUC for the three active metabolites (hydroxybupropion, threobupropion, and erythrobutropion).

Mean plasma bupropion concentration-time profiles after administration of 450-mg of FORFIVO XL and 3 x 150-mg Wellbutrin XL® are shown below\*:



\*TEST A: 1 x 450-mg FORFIVO XL, REFERENCE: 3 x 150 mg Wellbutrin XL®.

PK parameters for bupropion and the statistical results after administration of 450-mg FORFIVO XL or 3 x 150-mg Wellbutrin XL® are summarized in the table below:

PK Parameters	Arithmetic Means* (CV)		Geometric LS Means*		
	FORFIVO XL (fasting)	Wellbutrin XL (fasting)	FORFIVO XL (fasting)	Wellbutrin XL (fasting)	Ratio (90% CI, %)
T <sub>max</sub> **	5 (36.3)	5 (16.9)	NA	NA	NA
C <sub>max</sub>	207.46 (28.6)	215.07 (25.7)	198.65	208.15	95.44 (85.28 -106.80)
AUC <sub>t</sub>	2079.46 (31.7)	2122.49 (26.1)	1963.59	2054.36	95.58 (88.62 -103.09)
AUC <sub>inf</sub>	2147.53 (30.9)	2181.49 (26.0)	2036.36	2112.01	96.42 (90.04 -103.25)

\* Units are hr for T<sub>max</sub>, ng/mL for C<sub>max</sub>, and ng·h/mL for AUC.

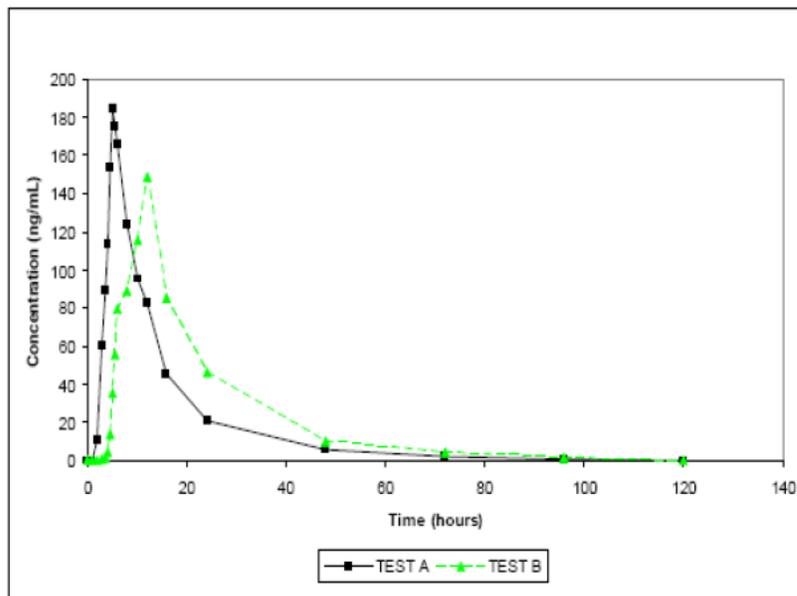
\*\* Median Value

CV: Coefficient of Variation; NA: Not Applicable.

### 2.1.2 Is there a food effect on the proposed formulation?

Food prolonged the drug absorption of bupropion by 7 hours from 5 hours to 12 hours. Food did not affect C<sub>max</sub> for bupropion, however, systemic exposure (AUC) of bupropion was increased by 25% when FORFIVO XL was taken with high-fat food. The food effect is not considered clinically significant.

In the BA/BE study, the rate and extent of absorption of bupropion from a single dose of 450-mg FORFIVO XL between fasted and fed conditions was compared. Thirty five male subjects completed the study (PK population). Mean plasma bupropion concentration-time profiles after administration of 450-mg of FORFIVO XL under fasted and fed conditions are shown below\*:



\*TEST A: 1 x 450-mg FORFIVO XL under fasted, TEST B: 1 x 450-mg FORFIVO XL under fed.

PK parameters for bupropion and the statistical results after administration of 450-mg FORFIVO XL under fasted and fed conditions are summarized in the table below:

PK Parameters	Arithmetic Means* (CV)		Geometric LS Means*		
	FORFIVO XL (fed)	FORFIVO XL (fasting)	FORFIVO XL (fed)	FORFIVO XL (fasting)	Ratio (90% CI, %)
T <sub>max</sub> **	12 (42.5)	5 (36.3)	NA	NA	NA
C <sub>max</sub>	217.23 (36.3)	207.46 (28.6)	201.27	198.65	101.32 (90.54 -113.39)
AUC <sub>t</sub>	2590.61 (26.8)	2079.46 (31.7)	2497.97	1963.59	127.21 (117.95 -137.21)
AUC <sub>inf</sub>	2646.52 (26.6)	2147.53 (30.9)	2540.22	2036.36	124.74 (116.40 -133.68)

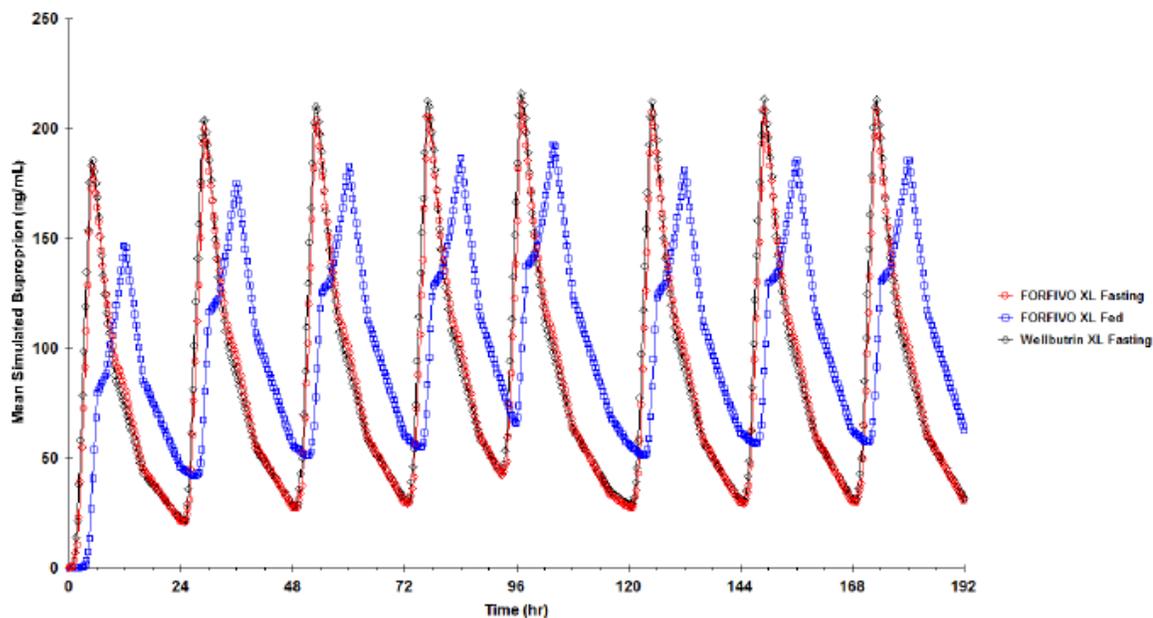
\* Units are hr for T<sub>max</sub>, ng/mL for C<sub>max</sub>, and ng·h/mL for AUC.

\*\* Median Value.

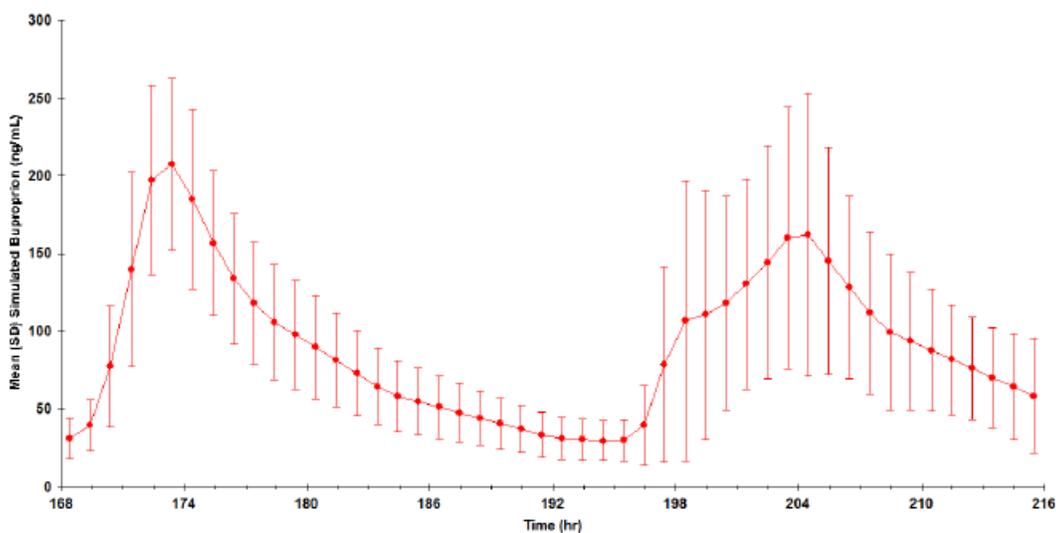
CV: Coefficient of Variation; NA: Not Applicable.

Food prolonged bupropion absorption by 7 hours from 5 hours to 12 hours, which indicates the absorption rate of bupropion from FORFIVO XL under fed conditions is slower than that under fasted conditions, i.e., it takes longer for FORFIVO XL to reach the peak concentration of bupropion under fed conditions compared to under fasted conditions. However, the systemic exposure of bupropion under fed conditions is not decreased, which is thought to be more correlated with the drug efficacy. This food effect on T<sub>max</sub> prolongation is not considered clinically significant.

To assess the effect of switching patients from Wellbutrin XL® to FORFIVO XL, the sponsor simulated steady-state plasma concentration-time profiles (after 8 daily doses) based on the data in the BA/BE study. Average simulated plasma bupropion concentrations after eight consecutive doses of each treatment are shown in the figure below:



The simulation indicates that at steady state the exposure of bupropion following administration of 450-mg FORFIVO XL QD under fed conditions is within the concentration ( $C_{max}$  and  $C_{min}$ ) window of bupropion after administration of Wellbutrin XL® at 3 x 150 mg daily dosing under fasted conditions. Additionally, the sponsor simulated mean steady state plasma bupropion concentrations after administration of Wellbutrin XL® (fasted) for 8 days with switch to FORFIVO XL (fed) on Day 9 (figure showed below) to further confirm the exposure of bupropion after dosing of FORFIVO XL does not exceed that after administration of Wellbutrin XL® (The test/ref point estimates for AUC and  $C_{max}$  were 101% and 95%, respectively; the CI for AUC and  $C_{max}$  were 90% to 113% and 83% to 108%, respectively).



### **2.1.3 Does ethanol in vitro have a dose-dumping effect on the MR product (FORFIVO XL)?**

The sponsor did not conduct an in vitro alcohol dose-dumping study for the new formulation in the current resubmission. ONDQA team reviewed the in vitro dose-dumping study with alcohol for the original (old) formulation. (b) (4)

ONDQA reviewers recommended that the new formulation would have the same or less release of drug in the presence of alcohol compared to the old formulation. OCP proposed the labeling language of alcohol-drug interaction in agreement with Clinical and ONDQA teams (based on the release data in various concentrations of alcohol (with old formulation) and the language in Wellbutrin XL® label regarding intake with alcohol, in general) which is showed below:

“...Alcohol increased the release rate of FORFIVO XL in vitro. The consumption of alcohol during treatment with FORFIVO XL should be avoided.”

### **2.1.4 Can FORFIVO XL be used in hepatic and renally impaired patients?**

Since 450 mg is the only and highest dose strength for FORFIVO XL, FORFIVO XL is not recommended in the patients with hepatic and renal impairments.

Hepatic impairment: It is recommended that Wellbutrin XL® should be used with extreme caution in patients with severe hepatic cirrhosis, and should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis). Specific recommendations are reduced frequency and/or dose is required or considered in patients with hepatic impairments. Due to a dose-dependent risk of seizure, FORFIVO XL is not recommended in the population.

Renal impairment: There is limited information on the PK of bupropion in this population. It is recommended that Wellbutrin XL® should be used with caution in patients with renal impairment and a reduced frequency and /or dose should be considered as bupropion and the metabolites of bupropion may accumulate in such patients to a greater extent than usual. Due to a dose-dependent risk of seizure, FORFIVO XL is not recommended in the population.

### **2.1.5 Are there any updated information or revision on DDI in the label of FORFIVO XL?**

Yes. Some updated information on DDI with bupropion in vivo is integrated in the label.

Ticlopidine, Clopidogrel: In a study in healthy male volunteers, 75 mg clopidogrel once daily or 250 mg ticlopidine twice daily increased  $C_{max}$  and AUC of bupropion by 40% and 60% for clopidogrel, and 38% and 85% for ticlopidine, respectively. AUC values of hydroxybupropion were reduced by 52% by clopidogrel and by 84% by ticlopidine. The effect is thought to be due to the inhibition of the CYP2B6-catalyzed bupropion hydroxylation. Due to dose-dependent risk of seizure, coadministration of FORFIVO XL with ticlopidine or clopidogrel is not recommended (Ref: [Appendix](#)).

Prasugrel: Prasugrel, a P2Y12 platelet inhibitor indicated for the reduction of thrombotic cardiovascular events, is a weak inhibitor of CYP2B6. In healthy subjects, prasugrel

increased  $C_{max}$  and AUC values of bupropion by 14% and 18%, respectively, and decreased  $C_{max}$  and AUC values of hydroxybupropion by 32% and 24%, respectively. The effect is not considered clinically significant (Ref: [Appendix](#)).

## 2.2 Standard Related Questions

### 2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

The composition of FORFIVO XL tablet is listed in the table showed below. For more information regarding chemistry/physical-chemical properties of the drug product, please refer to Dr. Pei-I Chu's review (Ref: CMC review).

Component	Grade	Function	Amount per Tablet (mg)	W/W % of Tablet
(b) (4)				
Bupropion hydrochloride	USP	Active		
Hydroxypropyl cellulose	NF			
Hydrochloric acid	NF			
(b) (4)				
Polyethylene oxide	NF			
Stearic acid	NF			
Colloidal silicon dioxide (SiO <sub>2</sub> )	NF			
Magnesium stearate	NF			
(b) (4)				
Methacrylic acid copolymer (b) (4)	NF			
Talc	USP			
Polyethylene glycol (PEG) 8000	NF			
Titanium dioxide (TiO <sub>2</sub> )	USP			
Carboxymethyl cellulose sodium (NaCMC)	NF			
(b) (4)				
Black ink			QS	--
			748.73	100%

NF National Formulary;

OS Quantity sufficient

(b) (4)

**2.2.2 What are the proposed mechanism of action and therapeutic indications?**

The mechanism of action of bupropion hydrochloride is not fully understood. It is presumed that the antidepressant effect of the drug is mediated by noradrenergic and/or dopaminergic mechanisms (Wellbutrin XL® Package Insert; Clinical Pharmacology, Pharmacodynamics).

Bupropion HCl is indicated for the treatment of major depressive disorder and as an aid to smoking cessation treatment.

**2.2.3 What are the proposed dosage and routes of administration?**

FORFIVO XL will be formulated in only one strength at 450 mg for use by oral administration.

**2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?**

Wellbutrin (bupropion HCl) IR, SR, and XL tablets. Aplenzin (bupropion hydrobromide) ER Tablets.

**2.2.5 What are the design features of the clinical pharmacology / biopharmaceutics studies and the clinical studies used to support dosing or claims?**

Key design features of the clinical pharmacology and clinical study conducted with FORFIVO XL in the current submission are summarized in the table shown below:

<b>Study Number</b>	<b>Study Design</b>	<b>Study Population</b>	<b>Treatment</b>	<b>End-point</b>
Study BPO-P0-520 (BA/BE)	Randomized, open-label, three-way crossover, fasting BE and food effect study	Healthy males	450-mg FORFIVO XL vs. 3x 150-mg Wellbutrin XL, single dose under fasted conditions;  450-mg FORFIVO XL single dose under fasted and fed conditions.	PK

**2.2.6 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

Yes. Bupropion and its three active metabolites were identified and measured.

**2.2.7 What bioanalytical methods are used to assess concentrations of the measured moieties?**

Plasma concentrations of bupropion and its three active metabolites were determined using a validated HPLC/MS/MS method. The assays are acceptable.

**2.2.8 For all moieties measured, is free, bound, or total measured?**

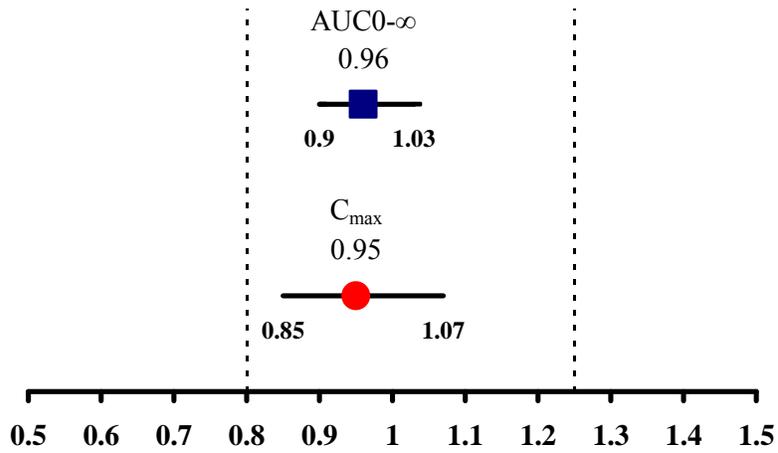
Total concentrations of bupropion and its three active metabolites were measured.

### 3. Individual Study Review

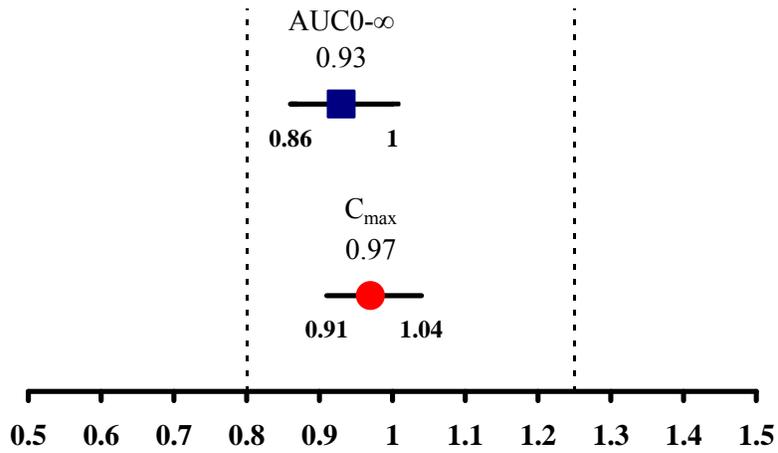
#### Biopharmaceutics- BE and Food Effect

<b>Report #</b> BPO-P0-520	<b>Study Period:</b> 10/15/2010 – 11/30/2010	<b>EDR Link:</b> <a href="#">\\FDSWA150\NONECTD\N22497\N_000\2011-05-04</a>
<b>Title</b>	Single Dose Crossover Comparative Bioavailability Study of Bupropion Hydrochloride 450 mg Extended Release Tablets and Wellbutrin XL® 150 mg Extended Release Tablets in Healthy Male Volunteers under Fasting and Fed Conditions	
<b>Study Design</b>		
<input checked="" type="checkbox"/> BE <input checked="" type="checkbox"/> Food Effect		
Single-Center Single-Dose Randomized Lab-blinded Cross-Over 3-Period 3-Cohort Healthy Male Volunteers		
<b>Screening:</b> ≤ 28 days	<b>Washout:</b> ≥ 14 days, outpatient	
<b>Period</b> 1/2/3	6 days, Inpatient stay <input checked="" type="checkbox"/> Y <input type="checkbox"/> N:	
<b>Treatments:</b> (Active Ingredient: Bupropion)		
<b>Formulation</b>	<b>Test</b> (Bupropion Hydrochloride)	<b>Reference</b> (Wellbutrin XL®)
Dosage Form/Strength	Extended Release/ 450 mg	Extended Release/ 150 mg
Dose Used in the Study	450 mg	450 mg (3 x 150 mg)
Lot #.	100015P3	10C083P
To be Marketed Formulation	Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	
Highest Strength Available	Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	
Meal used meets the FDA Guidance Recommendations: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>		
<b>Sampling Times (PK, plasma): 0, 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 48, 72, 96, and 120 hours post dose.</b>		
<b>Analytical Method:</b> The performance of the analytical method is acceptable Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>		
<b>Statistical Method:</b> ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.		
<b>Study Population :</b>		
<b>Formulation</b>	<b>Test</b> (Bupropion Hydrochloride)	<b>Reference</b> (Wellbutrin XL®)
Randomized/Completed/ PK Population/Discontinued Due to AE	36/36/35/0	36/36/35/0
Age [Median (range)]	22.5 (18-47)	22.5 (18-47)
Male/Female	Male	Male
Race (Caucasian/Black/Asian/other)	23/7/4/2	23/7/4/2
<b>Results</b>		
<b>1. Bioequivalence (Forfivo XL vs., Wellbutrin XL):</b>		

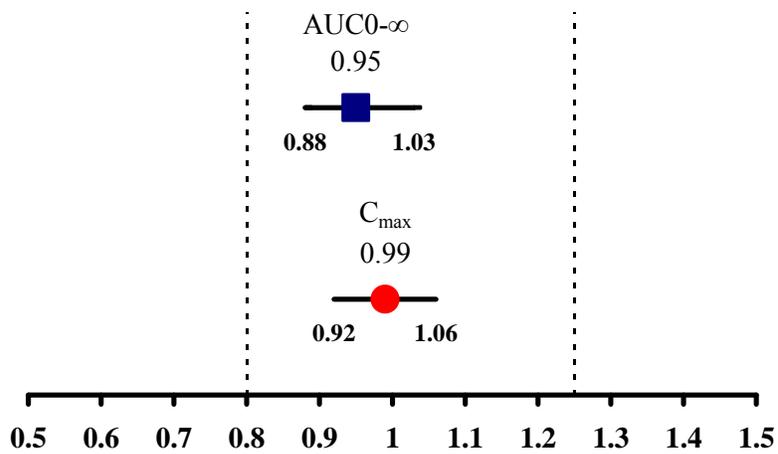
Bupropion PK



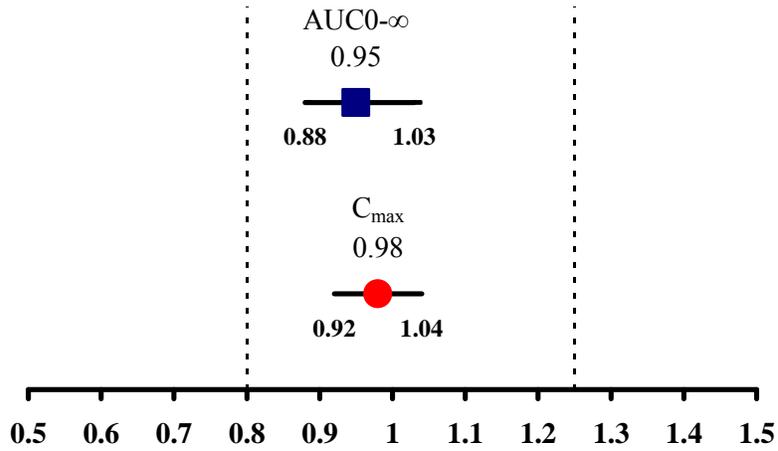
Hydroxybupropion PK



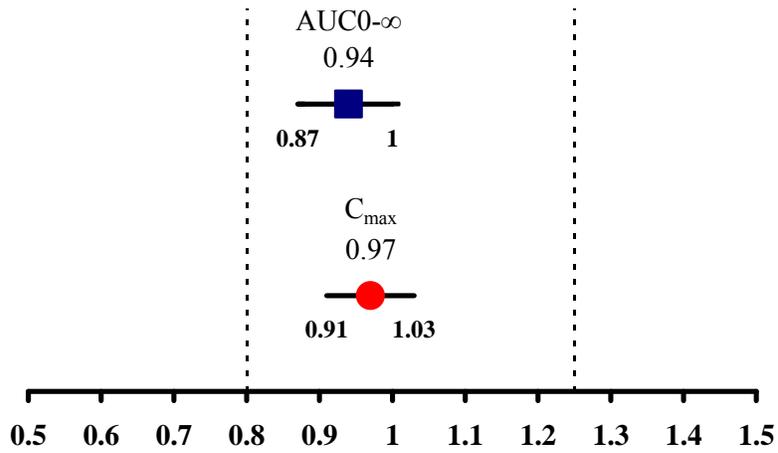
Threobupropion PK



Erythrobupropion PK

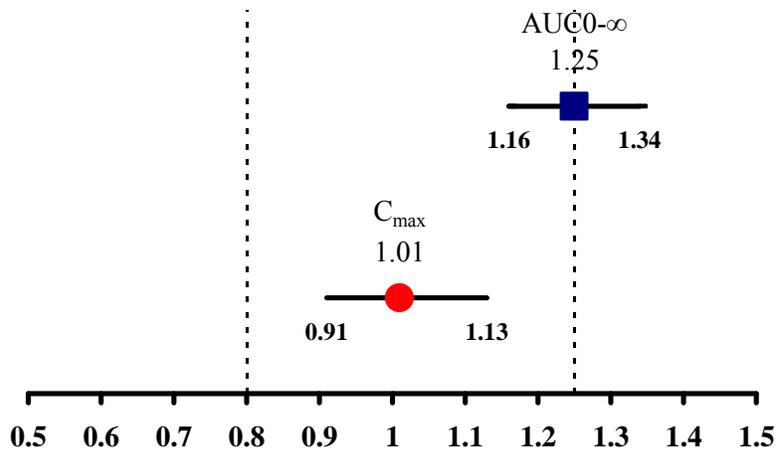


PAWC\* PK

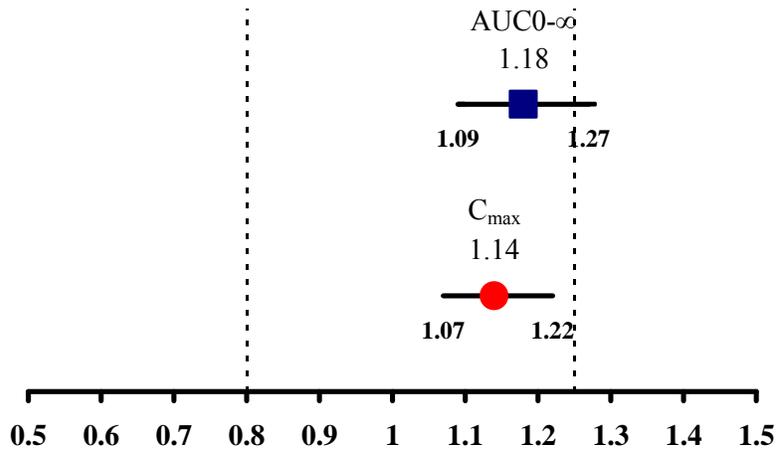


**2. Food Effect of Forfivo (Fed vs., Fasted):**

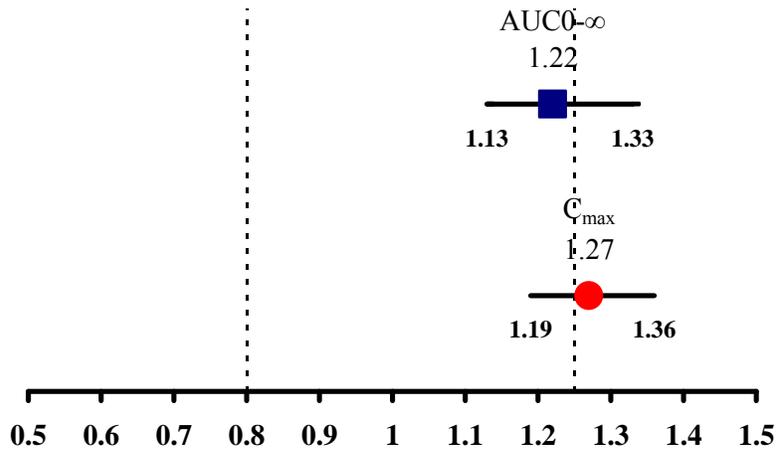
Bupropion PK



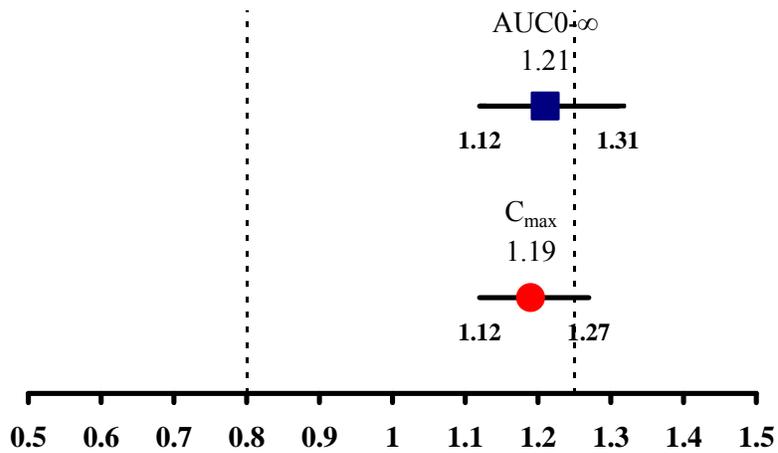
Hydroxybupropion PK



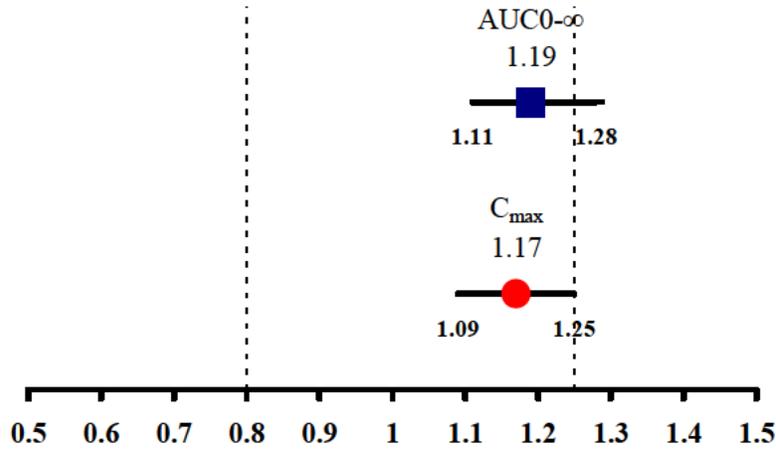
Threobupropion PK



Erythropropion PK



PAWC\* PK



\* PAWC: Pharmacologic Activity-Weighted Composite

**Site Inspected**

**Requested:** Yes   
No

**Bioanalytical Site:** (b) (4)

**Performed:** Yes  No  N/A   
The bioanalytical site inspection was canceled mainly due to a lack of serious observation based on the previous inspections.

**Clinical Site:** Cetero Research  
4801 Amber Valley Parkway  
Fargo, ND 58104, USA  
**Performed:** Yes  No  N/A   
The clinical site was inspected and no serious observation was issued.

**Safety**

Was there any death or serious adverse events?  Yes  No  NA

**Conclusion**

- BE was demonstrated for bupropion (parent moiety) between the 450-mg FORFIVO XL and the approved Wellbutrin XL® given as three 150-mg tablets under single dose, fasted conditions.
- Food prolonged the drug absorption of bupropion by 7 hours from 5 hours to 12 hours. Food did not affect C<sub>max</sub> for bupropion; systemic exposure (AUC) of bupropion was increased by 25% when FORFIVO XL was taken with high-fat food. Food increased AUC value of hydroxybupropion by 18%; food also increased C<sub>max</sub> of threo- and erythro- metabolites by 27% and 19%, respectively.

**Comments**

The food effect is not considered clinically significant.

## 4. Appendix

### 4.1 Ticlopidine and Clopidogrel

#### Abstract of the Publication

## Effect of clopidogrel and ticlopidine on cytochrome P450 2B6 activity as measured by bupropion hydroxylation

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(Clin Pharmacol Ther 2005;77:553-9.)

Miia Turpeinen, MD, Ari Tolonen, PhD, Jouko Uusitalo, MSc, Jorma Jalonen, PhD, Olavi Pelkonen, MD, PhD, and Kari Laine, MD, PhD *Oulu and Turku, Finland*

#### Study Population

Population	12 healthy volunteers
Gender	Male
Age	22 – 27 yr
Body Weight (BMI)	67 – 95 kg (21 – 26 kg/m <sup>2</sup> )
Race	No data

#### Study design and treatment

This study is an open label, crossover study:

Bupropion*	Washout (1 wk)	Combination**	Washout (2 wk)	Combination
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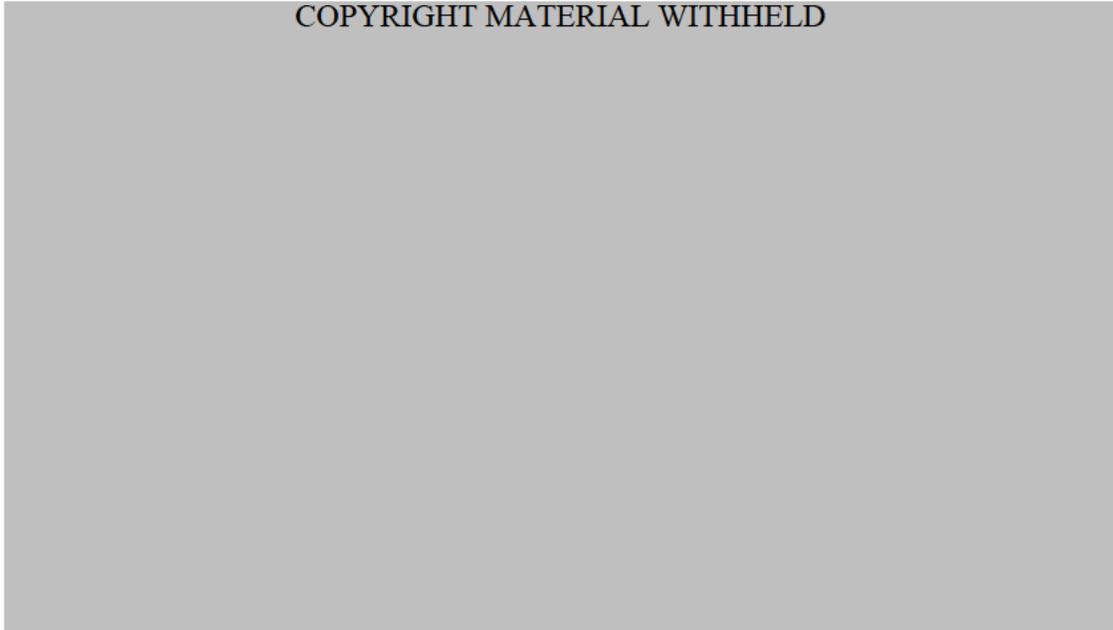
\*Bupropion (Zyban SR, 150 mg SD);

\*\* Combination of bupropion (150 mg SD on Day 4) and clopidogrel (Plavix, 75 mg QD for 4 days), or combination of bupropion (150 mg SD on Day 4) and ticlopidine (Ticlid, 250 mg BID for 4 days).

### PK Sampling Times

Blood samples to measure concentrations of bupropion and hydroxybupropion were collected at pre-dose, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours after administration of bupropion.

### PK Result



### Conclusion

Clopidogrel increased  $C_{\max}$  and AUC of bupropion by 40% and 60%, respectively; and ticlopidine increased  $C_{\max}$  and AUC of bupropion by 38% and 85%, respectively. AUC values of hydroxybupropion were reduced by 52% by clopidogrel and by 84% by ticlopidine. The effect is thought to be due to the inhibition of the CYP2B6-catalyzed bupropion hydroxylation.

## 4.2 Prasugrel

### Abstract of the Publication

# Prasugrel, a New Thienopyridine Antiplatelet Drug, Weakly Inhibits Cytochrome P450 2B6 in Humans

Nagy A. Farid, PhD, Christopher D. Payne, MS, C. Steven Ernest II, MS, Y. Grace Li, MS, Kenneth J. Winters, MD, Daniel E. Salazar, PhD, and David S. Small, PhD

Prasugrel, a thienopyridine prodrug, is hydrolyzed *in vivo* by esterases to a thiolactone followed by a single cytochrome P450 (CYP)-dependent step to an active metabolite that is a potent inhibitor of adenosine diphosphate-induced platelet aggregation. This open-label, multiple-dose, 2-period, fixed-sequence study assessed CYP2B6 inhibition by prasugrel using bupropion as a probe substrate, where its active metabolite, hydroxybupropion, is almost exclusively formed by CYP2B6. Thirty healthy subjects received a single 150-mg oral dose of sustained-release bupropion. After a 7-day washout, a 60-mg prasugrel loading dose, followed by a 10-mg daily maintenance dose for 10 days, was administered. Bupropion (150 mg) was given with prasugrel

on day 7 of this phase. Prasugrel weakly inhibited CYP2B6 activity as it increased bupropion  $C_{max}$  and  $AUC_{0-\infty}$  by 14% and 18%, respectively, and decreased hydroxybupropion  $C_{max}$  and  $AUC_{0-\infty}$  by 32% and 23%. These results are consistent with patients receiving prasugrel not requiring dose adjustments when treated with drugs primarily metabolized by CYP2B6.

**Keywords:** Bupropion; CYP2B6 inhibition; hydroxybupropion; prasugrel; thienopyridines; drug interactions

*Journal of Clinical Pharmacology*, 2008;48:53-59

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### Study Population

Population	32 healthy volunteers
Gender	Male
Age	18 – 60 yr
BMI	19 – 30 kg/m <sup>2</sup>
Race	26 (Caucasians), 2 (afro-Caribbean), and 4 (mixed).

### Study Design and Treatment

This study is an open label, multiple dose, 2 period, fixed-sequence study:

Bupropion*	Washout (≥1 wk)	Combination**
------------	-----------------	---------------

\*Bupropion SR, 150 mg SD;

\*\* Combination of bupropion SR (150 mg SD on Day 7) and Prasugrel (60 mg QD for 2 days + 10 mg QD for 10 days).

PK Sampling Times

Serial blood samples were collected for 120 hours post dose to determine plasma concentrations of bupropion and hydroxybupropion.

PK Result

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Conclusion

Prasugrel increased  $C_{\max}$  and AUC values of bupropion by 14% and 18%, respectively, and decreased  $C_{\max}$  and AUC values of hydroxybupropion by 32% and 24%, respectively\*.

\* The statement is cited from OCP reviewer's comment in NDA 22307. This information is also reflected in the approved Prasugrel label.

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BEI YU  
10/21/2011

RAMANA S UPPOOR  
10/21/2011

## ONDQA (Biopharmaceutics) Review

**NDA:** 22- 497 (Resubmission)  
**Submission Dates:** 5/4/2011; 9/20/2011  
**Product:** FORFIVO XL (Bupropion HCl 450 mg ER Tablets)  
**Applicant:** Intelgenx Corp  
**Reviewer:** Tapash K. Ghosh, Ph.D.

**Background:** Cary Pharmaceuticals, Inc initially submitted this 505(b)(2) NDA for bupropion hydrochloride 450mg extended release tablet for major depressive disorder. The first submission was not approved due to several CMC deficiencies. Intelgenx acquired NDA 22-497 from Cary and filed the resubmission on May 4, 2011.

(b)(4) is the same as the original formulation. However, the amount of (b)(4) The development of the dissolution methodology was evaluated during the 1<sup>st</sup> review cycle of the original submission. Also, during the 1<sup>st</sup> review cycle it was evaluated the *in vitro* drug – alcohol interaction study demonstrating that the presence of alcohol 20% v/v and above has the potential to cause dose dumping of Bupropion from BUP-450 tablets (b)(4) (see *Biopharmaceutics Review in DARRT dated 4/20/2010*).

**NDA Resubmission:** The Biopharmaceutics review for the resubmission focuses on the evaluation of the dissolution acceptance criteria. Note that *in vitro* drug – alcohol interaction data for the proposed new formulation of Bupropion HCl ER Tablets were not included in the resubmission.

**Recommendations:**

- The Applicant’s revised dissolution acceptance criteria using the dissolution method described in pages 4 and 5 of this review are acceptable

Dissolution Acceptance Criteria			
Acid Stage		Buffer Stage	
Time (hrs)	% Dissolved	Time (hrs)	% Dissolved
2	NMT (b)(4)	4	(b)(4)
		8	(b)(4)
		16	NLT (b)(4)

- An *in-vitro* drug alcohol interaction study was not conducted with the proposed new formulation. [REDACTED] (b) (4) [REDACTED] it is anticipated that the new formulation would have the same or less release of drug in the presence of alcohol. Therefore, Biopharmaceutics considers that a new *in-vitro* drug alcohol interaction study evaluating the new formulation is not necessary.
- The clinical/clinical pharmacology team’s proposed language for the labeling of this product, in regard to drug – alcohol interaction as described below, is acceptable by this reviewer:

*“The consumption of alcohol during treatment with FORFIVO XL should be avoided.”*

**Overall Assessment:**

From the Biopharmaceutics view point NDA 22-497 (Resubmission) for FORFIVO XL (Bupropion HCl 450 mg ER Tablets) is recommended for approval.

---

**Tapash K. Ghosh, Ph. D.**  
**Primary Biopharmaceutics Reviewer**  
**Office of New Drug Quality Assessment**

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**Angelica Dorantes, Ph. D.**  
**Biopharmaceutics Team Leader**  
**Office of New Drug Quality Assessment**

**Drug Product:**

**Proposed formulation:** The composition of the proposed formulation for the drug product is described below (Table 2.3.P.1-1). The difference between the original and the reformulated products is that the original tablets (b) (4)

**Table 2.3.P.1-1 Qualitative & Quantitative Composition of Forfivo XL Tablets Including Black Ink**

Component	Grade	Function	Amount per Tablet (mg)	W/W % of Tablet
(b) (4)				
Bupropion hydrochloride	USP	Active		(b) (4)
Hydroxypropyl cellulose	NF	(b) (4)		
Hydrochloric acid	NF			
(b) (4)				
Polyethylene oxide	NF			
Stearic acid	NF			
Colloidal silicon dioxide (SiO <sub>2</sub> )	NF			
Magnesium stearate	NF			
(b) (4)				
Methacrylic acid copolymer (b) (4)	NF			
Talc	USP			
Polyethylene glycol (PEG) 8000	NF			
Titanium dioxide (TiO <sub>2</sub> )	USP			
Carboxymethyl cellulose sodium (NaCMC)	NF			
(b) (4)				
Black ink			QS	--
			748.73	100%

NF National Formulary;  
 OS Quantity sufficient

(b) (4)

**Dissolution:**

The following table summarizes the dissolution data at release for the stability batches from the 1<sup>st</sup> cycle old formulation (b) (4)

Dissolution		Mean	SD	% CV (b) (4)
	2 hrs			
	4 hrs			
	8 hrs			
	24 hrs			

Based on the above data the Agency's proposed the following dissolution specifications in the 1<sup>st</sup> cycle review:

Time	Amount Dissolved (%)
2 hrs	NMT (b) (4)
4 hrs	(b) (4)
8 hrs	(b) (4)
16 hrs	NLT (b) (4)

In this resubmission, a minimal formulation change occurred with (b) (4)

The sponsor conducted dissolution studies using the same method with three (3) stability batches with the new formulation. The dissolution method and data are described below:



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However, based on the dissolution data from the new batches, the Agency conveyed the following information request to the sponsor on September 7, 2011.

*Based on your dissolution data submitted in this cycle from 3 batches (100012P3, 100015P3, 100016P3), the Agency proposes the following dissolution acceptance criteria:*

<b>Dissolution Acceptance Criteria</b>			
Acid Stage		Buffer Stage	
Time (hrs)	% Dissolved	Time (hrs)	% Dissolved
2	NMT (b) (4)	4	(b) (4)
		8	(b) (4)
		16	NLT (b) (4)

*Concur or describe why you can not meet the Agency's proposed dissolution acceptance criteria.*

On September 20, 2011, the sponsor responded as follows:

*As per the Agency's recommendation, the Sponsor has updated the dissolution acceptance criteria for finished product testing and stability testing of Forfivo XL tablets. Therefore, the finished product and stability specifications will be amended accordingly. The table below replaces Table 3.2.P.8-5 in Module 3, section 3.2.P.8 of the NDA 022497 resubmission and lists the product specifications with the updated dissolution information included.*

**Table 3.2.P.8-5 Finished Product and Stability Specification for the Commercial Drug Product (Forfivo XL Tablets)**

Test	Acceptance Criteria	Analytical Procedure
Dissolution	Sampling time: 2 hours 4 hours 8 hours 16 hours*	Amount dissolved (%) NMT (b) (4) (b) (4) NLT (b) (4)
		In house Method ITG-06-0003 (Current) Medium 900mL of 0.1NHCl for 2 hours then 0.05M Tris buffer pH 6.8 at 37°C. Apparatus 1 (basket) at 75 rpm

**In-vitro Drug – Alcohol Interaction:**

Based on the *in-vitro* drug alcohol interaction study conducted with the old formulation and reviewed by this reviewer during the 1st cycle, the following conclusion was made:

*The results of the drug alcohol interaction study demonstrated that the presence of alcohol 20% v/v and above has the potential to cause dose dumping of Bupropion from BUP-450 tablets possibly (b) (4)*

(b) (4) However, the clinical relevance of this increase in release on the overall safety and efficacy of the product is unknown. The Office of Clinical Pharmacology and the Clinical Division needs to look at this issue.

The sponsor did not conduct any new *in-vitro* drug alcohol interaction study with the proposed new formulation. (b) (4)

(b) (4) it is anticipated that the new formulation will possibly cause same or lesser release of drug in presence of alcohol compared to what was observed with the old formulation. Therefore, the applicant's data from the previous *in-vitro* drug alcohol interaction study will remain in effect for this new formulation.

The clinical/clinical pharmacology team proposed the following language in the label in this regard and it is acceptable by the reviewer:

### **7.7 Alcohol**

In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with bupropion. Alcohol increased release rate of FORFIVO XL *in vitro*. The consumption of alcohol during treatment with FORFIVO XL should be avoided.

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TAPASH K GHOSH  
10/18/2011

ANGELICA DORANTES  
10/18/2011

## ONDQA (Biopharmaceutics) Review

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**NDA:** 22- 497  
**Submission Dates:** 3/31/2009  
**Product:** Bupropion HCl (450 mg Extended Release Tablets)  
**Type of Submission:** Original 505 (b) (2) Application  
**Sponsor:** Cary Pharmaceuticals, Inc.  
**Reviewer:** Tapash K. Ghosh, Ph.D.

---

**Background:** Cary Pharmaceuticals, Inc. (Cary) and Intel Genx Corp., St-Laurent, Quebec, Canada, have developed an oral extended-release formulation of bupropion hydrochloride, BUP 450 XL tablets, for the treatment of major depressive disorder. BUP 450 XL is a novel extended-release tablet that contains 450 mg of bupropion (b) (4) intended to be comparable to the reference product Wellbutrin XL (GlaxoSmithKline).

In this review, development of the dissolution methodology is reviewed and comments on the proposed dissolution specifications have been made. In addition, comments have been made on the results on the in vitro drug – alcohol interaction studies.

### Recommendation:

*The sponsor's proposed current dissolution method and the proposed dissolution specifications are not acceptable by the Agency. While the overall approach for the dissolution methodology appears reasonable, before accepting the method and the specification, the sponsor needs to address the following issues:*

- Information on solubility and stability of Bupropion HCl at pH 6.8 needs to be provided to assure (b) (4) maintained during the study.*
- The sponsor needs to clarify the media to be used in the final dissolution methodology for Stage I and Stage II. (b) (4) have been used in different places. (See Appendix at the end). The sponsor is required to submit current version of the full report for dissolution Method ITG-06-0003.*

*Overall, based on the data provided and as per the Agency's IVIVC guidance, the Agency recommends the following dissolution specifications:*

Time	Amount Dissolved (%)
2 hrs	NMT (b) (4)
4 hrs	(b) (4)
8 hrs	(b) (4)
16 hrs	NLT (b) (4)

**Comments to the Clinical/Clinical Pharmacology:**

- *The results of the drug alcohol interaction study demonstrates that the presence of alcohol 20% v/v and above has the potential to cause dose dumping of Bupropion from BUP-450 tablets* [REDACTED] (b) (4)  
[REDACTED] *However, the clinical relevance of this increase in release on the overall safety and efficacy of the product is unknown. The Office of Clinical Pharmacology and the Clinical Division needs to look at this issue.*

Tapash K. Ghosh, Ph. D.  
Biopharmaceutics Primary Reviewer  
Office of New Drugs Quality Assessment

FT Initialed by Patrick Marroum, Ph. D. \_\_\_\_\_

**Composition of Bupropion HCl extended release tablet, 450mg**

A total of six lots identical with respect to their quantitative and qualitative composition were prepared in two manufacturing campaigns according to the formulation shown in the following Table.

**Components and Composition**

Component	Grade	Function	Amount per Tablet (mg)	W/W % of Tablet
(b) (4)				
Bupropion HCl	USP	Active		(b) (4)
Hydroxypropyl cellulose	NF	(b) (4)		
Hydrochloric acid	NF	(b) (4)		
Polyethylene oxide	NF			
Stearic acid	NF			
Colloidal silicon dioxide (SiO <sub>2</sub> )	NF			
Magnesium stearate	NF	(b) (4)		
Methacrylic acid copolymer (b) (4)	NF			
Talc	USP			
Polyethylene glycol (PEG) 8000	NF			
Titanium dioxide (TiO <sub>2</sub> )	USP			
Carboxymethyl cellulose sodium (NaCMC)	NF	(b) (4)		
<b>Total</b>			<b>739.00</b>	<b>100.00%</b>

NF = National Formulary; q.s. = quantity sufficient

(b) (4)

**Development of Dissolution Model**

The proposed product was developed to achieve pharmaceutical equivalence with the reference listed drug, Wellbutrin 150 mg XL tablets. In order to obtain gastric protection as observed in the reference listed drug, (b) (4)

The following Figure describes the effect of pH on the dissolution of Bupropion HCl from BUP-450 tablets:



The following table demonstrates data comparing dissolution profiles of the proposed and the reference products at different pHs:

**Summary of the Effect of pH on Dissolution of the proposed and the Reference Tablets**

Time (h)	BUP 450 XL	Wellbutrin XL 150 mg
0		
1		
2		
4		
6		
8		
10		
12		
14		
16		
18		
20		
22		
24		

(b) (4)

**Reviewer's Comments:** *It is to be noted that except at pH 6.8, dissolution profiles between the proposed and the reference products at pHs (b) (4) are very different. That emphasizes that though both products are Buprenorphine XL products, their mechanism of release are different which may be attributed to the differences in the formulation.*

### **Optimization of Dissolution Model**



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**Reviewers Comments:**

While the overall approach for the dissolution methodology appears reasonable, before accepting the method and the specification, the sponsor needs to address the following issues:

- Information on solubility and stability of Bupropion HCl at pH 6.8 needs to be provided to assure (b) (4) maintained during the study.
- The sponsor needs to clarify the mediums to be used in the final dissolution methodology for Stage I and Stage II. For Stage I, (b) (4) have been used in different places. (See Appendix at the end). The sponsor is required to submit current version of the full report for dissolution Method ITG-06-0003.

Overall, based on the data provided and as per the Agency’s IVIVC guidance, the Agency recommends the following dissolution specifications:

**The Agency’s proposed specifications:**

Time	Amount Dissolved (%)
2 hrs	NMT (b) (4)
4 hrs	(b) (4)
8 hrs	(b) (4)
16 hrs	NLT (b) (4)

### **Effect of Alcohol on the Dissolution of Bupropion HCl from BUP-450 Tablets**

The following study was conducted to determine any effect of ethyl alcohol on the dissolution of Bupropion Hydrochloride from extended-release tablets containing 450 mg of Bupropion Hydrochloride (BUP-450 tablets) as recommended in the “Draft Guidance on Bupropion Hydrochloride”.

Dissolution profiles were generated on 12 dosage units using USP Apparatus 1 (basket) at 75 rpm in 900 ml of dissolution medium as specified below. Data were collected every 15 minutes for a total of two hours.

Test 1: 0.1 N hydrochloric acid;

Test 2: 5% (v/v) of test medium replaced with Alcohol USP;

Test 3: 20% (v/v) of test medium replaced with Alcohol USP;

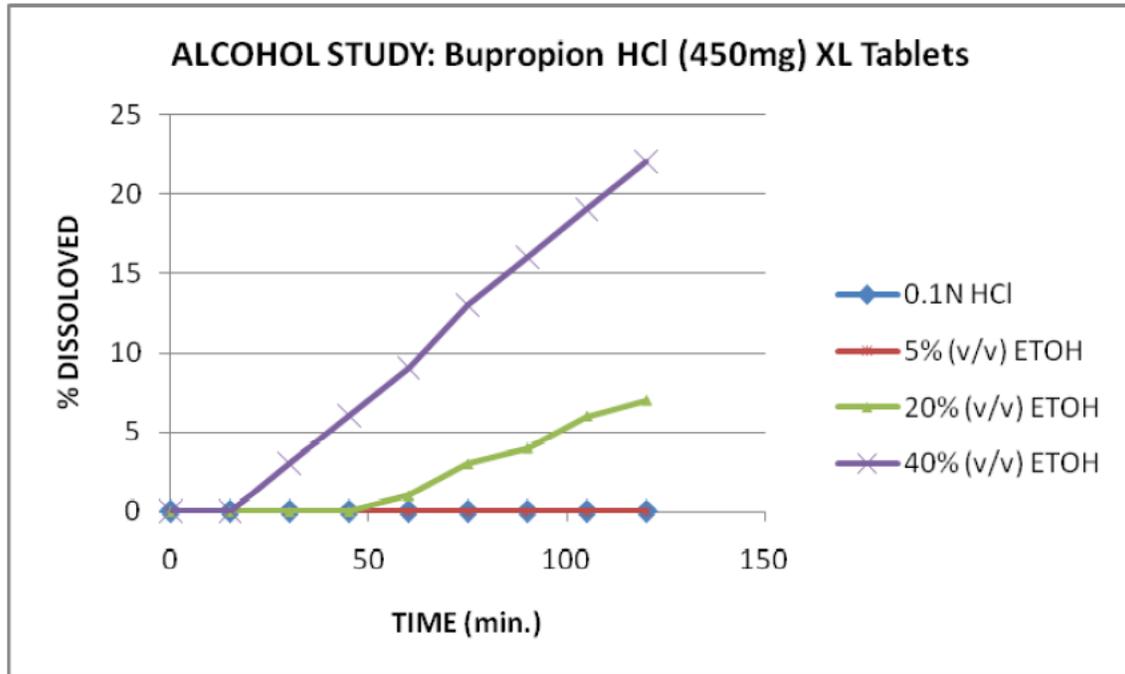
Test 4: 40% (v/v) of test medium replaced with Alcohol USP;

**Results:** The initial dissolution results, averages, minimum and maximum values, and coefficients of variation for Tests 1 – 4 are summarized in Tables 2 – 5. A summary of the results is provided in Table 1. Further on, the results are graphically displayed in Graph 1.

### **Summary of the Effect of Alcohol on Dissolution of BUP 450 XL Tablets**

Time (min.)	% Dissolved			
	Test 1 0.1N HCl	Test 2 5% (v/v) ETOH	Test 3 20% (v/v) ETOH	Test 4 40% (v/v) ETOH
0	0	0	0	0
15	0	0	0	0
30	0	0	0	3
45	0	0	0	6
60	0	0	1	9
75	0	0	3	13
90	0	0	4	16
105	0	0	6	19
120	0	0	7	22

**Graph 1:** Effect of alcohol on the dissolution of Bupropion HCl from BUP-450 tablets



**Discussion:** The results demonstrates that the presence of alcohol 20% and above has the potential to cause dose dumping of Bupropion from BUP-450 tablets (b) (4). However, the clinical relevance of this increase in release on the overall safety and efficacy of the product is unknown. The Office of Clinical Pharmacology and the Clinical Division needs to look at this issue.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22497	ORIG-1	CARY PHARMACEUTICA LS INC	BUP-450 (BUPROPION HCL)450MG ER ORAL TAB

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TAPASH K GHOSH  
04/19/2010

PATRICK J MARROUM  
04/20/2010

## Office of Clinical Pharmacology Review

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NDA number:	22-497
Submission type:	Original NDA
Submission date:	April 6, 2009
Applicant name:	Cary Pharmaceuticals, Inc.
Proposed brand name:	Forfivo XL
Generic name:	Bupropion HCl
Dosage form:	Extended-release tablet
Dosage strength (mg):	450
Proposed indication:	Major Depressive Disorder
OCP division:	DCP1
OND division:	Psychiatry
Primary reviewer:	Bei Yu, PhD
Secondary reviewer / Team leader:	Raman Baweja, PhD

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## 1. Executive Summary

Cary Pharmaceuticals, Inc. (Cary) is seeking approval via the 505(b) (2) pathway of BUP 450 XL, bupropion hydrochloride (HCl) 450 mg extended-release (ER) tablets, for use in the treatment of major depressive disorder (MDD). BUP 450 XL will be marketed in only one strength for once daily administration.

The referenced listed drug (RLD) for the application is Wellbutrin XL® (bupropion HCl) 150 mg ER tablets, GlaxoSmithKline (GSK), NDA No. 21-515 that has been approved by FDA. Wellbutrin XL® tablets are available in 150 mg and 300 mg strengths. The dosing of Wellbutrin XL® tablets above 300 mg/day is permitted in the labeling to a maximum of 450 mg/day given as a single dose (i.e., 3x150 mg, or 150 mg + 300 mg). Cary has developed BUP 450 XL 450 mg ER tablet as a new higher strength formulation.

This submission includes two clinical Phase I studies (bioequivalence and food effect studies) and one in vitro study (dose dumping with alcohol). Clinical efficacy studies were not conducted on this product.

### 1.1 Recommendation

The Office of Clinical Pharmacology (OCP/DCP1) has reviewed this original NDA 22-497.

- Bioequivalence was demonstrated for bupropion, the parent drug, between the 450-mg BUP 450 XL and the approved Wellbutrin XL® given as three 150-mg tablets under single dose, fasted conditions.
- Important Serious Clinical Safety Concerns:
  - There is a pronounced food effect for BUP 450 XL. Food increased mean  $C_{max}$  of bupropion by 25%. This increase is equivalent to a dose of about “560 mg”. For individual subjects, 67% of subjects (12 out of 18 subjects) in the food effect study showed that food increased  $C_{max}$  by >1 fold for Cary’s BUP 450 XL. In these subjects, 2 subjects showed that food increased  $C_{max}$  by >2 fold (2.19 fold and 2.75 fold); a two-fold increase of  $C_{max}$  is equivalent to a dose of “900 mg”. Further, 4 subjects showed that food increased  $C_{max}$  by >1.5 fold but < 2 fold; a 1.5-fold increase of  $C_{max}$  is equivalent to a dose of “675 mg”. Finally, three subjects were > 1.2 fold and < 1.5 fold; a 1.2-fold increase of  $C_{max}$  is equivalent to a dose of “540 mg”.

The estimated seizure incidence is known to increase almost tenfold between 450 and 600 mg/day for IR formulation. Thus, the therapeutic index of the drug, bupropion, is narrow above the recommended dose. This increase in bupropion  $C_{max}$  is a very serious safety concern as there is a serious risk of increase in seizures.

- The sponsor, Cary Pharmaceuticals, Inc., has developed BUP 450 XL (bupropion HCl ER) in only one strength of 450 mg which will serve as the highest dose for once daily administration. The currently approved GSK's Wellbutrin IR or Wellbutrin XL<sup>®</sup> can be taken without regard to meals. Changing from the Wellbutrin IR or XL formulation to BUP 450 XL will cause prescription errors to occur because of the differences of the effect of food observed on these products, and therefore, the increased risk of seizures in patients which is a serious safety concern.
- The drug product is showing dose dumping with alcohol in vitro.
- Based on the above clinical safety concerns for Cary's BUP 450 XL, the drug should not be approved.

## **1.2 Phase 4 Requirements / Commitments**

There are no Phase 4 requirements or commitments.

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Bei Yu, PhD

Reviewer, Division of Clinical Pharmacology 1

Raman Baweja, PhD

Secondary reviewer / Team leader, Psychiatry Products

Division of Clinical Pharmacology 1

REQUIRED INTER-DIVISION Level Briefing: January 22, 2010.

### 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

For the treatment of major depressive disorder, the currently available formulations of bupropion HCl are: Wellbutrin immediate release (IR) tablet (75 mg and 100 mg) that is given three times daily; Wellbutrin sustained release (SR) tablet (50 mg, 100 mg, 150 mg, and 200 mg) that is given twice daily; and Wellbutrin XL tablet (150 mg and 300 mg) that is given once daily. It is permitted in the labeling of Wellbutrin XL to administer a maximum dose of 450 mg given as a single dose after an up-titration.

The sponsor, Cary Pharmaceuticals, Inc., has developed BUP 450 XL (bupropion HCl ER) in only one strength of 450 mg.

Bupropion is extensively hepatically metabolized. It has three pharmacologically active metabolites, hydroxybupropion, threohydrobupropion (bupropion threoamino alcohol), and erythrohydrobupropion (bupropion erythroamino alcohol) that account for over 90% of the exposure following administration of bupropion. Based on an animal study, hydroxybupropion is one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold less potent than bupropion. Recently, an animal study showed that all three active metabolites caused seizures and were more potent convulsants than the parent drug. A summary of relative AUC at steady state, relative potency, and therapeutic contribution (AUC x Potency) for bupropion and its active metabolites is shown in the table below:

Moiety	AUC	Potency	AUC x Potency
<b>Bupropion</b>	1	1	1 (11%)
<b>Hydroxybupropion</b>	13	0.5	6.5 (71%)
<b>Erythrohydrobupropion</b>	1.4	0.2	0.28 (3%)
<b>Threohydrobupropion</b>	7	0.2	1.4 (15%)
<b>Total</b>	–	–	9.18 (100%)

*Ref: Wellbutrin XL Package Insert; Clinical Pharmacology.*

In the current NDA submission for BUP 450 XL, two clinical studies (a BE study and a food effect study) were submitted. The important clinical pharmacology and biopharmaceutics findings are summarized below.

#### 1.3.1 Bioequivalence

This was a typical BE study (Study No. 3631) to compare the rate and extent of absorption of bupropion from one tablet (given as a single dose) of the test formulation of Bupropion HCl 450 mg ER (BUP 450 XL) tablets versus the rate and extent of absorption of bupropion from 3 tablets (given together as a single dose) of the reference Wellbutrin (Extended Release) XL® 150 mg tablets under fasted conditions.

From a biopharmaceutical perspective based on the parent drug, bioequivalence is established between the 450-mg BUP 450 XL and the approved Wellbutrin XL® given as three 150-mg tablets, as the 90% confidence intervals were within 80-125%; the values of  $T_{max}$  were comparable, ~5 hours.

Equivalence was demonstrated (within 90% CI) for bupropion and its two active metabolites (hydroxybupropion and erythrohydrobupropion).

One active metabolite, threohydrobupropion (bupropion threoamino alcohol), did not meet the equivalence criteria on  $AUC_{inf}$  (90% CI: 96-132%; point estimate: 1.13). The therapeutic contribution ( $AUC \times Potency$ ) from threohydrobupropion is 15%. A 13% increase of AUC leads to a ~2% increase in the therapeutic contribution from threohydrobupropion ( $15\% \times 0.13$ ). This increase is not clinically relevant.

### 1.3.2 Food Effect

The study (Study No. S08-0027) primarily compared the rate and extent of absorption of bupropion from a single dose of 450-mg BUP 450 XL between fasted and fed conditions.

Overall, food prolonged the drug absorption of bupropion by 2.5 hours from 5 hours to 7.5 hours.

Further and most importantly, food significantly increased systemic exposure of bupropion following administration of BUP 450 XL: the mean  $C_{max}$  and  $AUC_{inf}$  were increased by ~25% and ~15%, respectively. This is a serious clinical safety concern:

- a) Based on the package insert for Wellbutrin XL, bupropion is associated with a dose-related risk for seizure. For example, the IR formulation of bupropion suggested that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day. Thus, the therapeutic index of the drug, bupropion, is narrow above the recommended dose.
- b)  $C_{max}$  of bupropion was increased by 25% after administration of 450-mg BUP 450 XL under fed conditions, which is equivalent to about 112 mg *more* dose ( $450 \times 0.25$ ), i.e., the subjects were dosed more under fed conditions than under fasted conditions: 562-mg BUP 450 XL ( $450 + 112$ ) under fed conditions vs. 450-mg BUP 450 XL under fasted conditions; Additionally, based on the upper limit of 90% CI (107.5-145.5) for the increase of  $C_{max}$ , some subjects have been exposed to even much higher levels of bupropion under fed conditions, which is equivalent to the dose at 653-mg BUP 450 XL ( $450 + 450 \times 0.45$ ).
- c) In the current study, 67% of subjects (12 out of 18 subjects) showed that food increased  $C_{max}$  by >1 fold. In these 12 subjects, 2 subjects showed that food increased  $C_{max}$  by >2 fold (2.19 fold for Subject 11 and 2.75 fold for Subject 17); 4 subjects showed that food increased  $C_{max}$  by >1.5 fold but < 2 fold. Three subjects were > 1.2 fold and < 1.5 fold; remaining 3 subjects were <1.1 fold.

A two-fold increase of  $C_{max}$  is equivalent to a dose of “900 mg”, 1.5-fold increase of  $C_{max}$  is equivalent to a dose of “675 mg”, and 1.2-fold increase of  $C_{max}$  is equivalent to a dose of “540 mg”. The detailed information can be found in the Appendix following Section 5.2 (the food effect study review).

This increase in  $C_{max}$  of BUP 450 XL product is a very serious safety concern as there is a very serious risk of increase in seizures.

### **1.3.3 In Vitro Dose Dumping With Alcohol**

For 2 hours, no dissolved bupropion HCl from BUP 450 XL tablets was seen at 0% of alcohol. In the presence of 20% of alcohol, 7% of dissolved bupropion HCl from BUP 450 XL tablets was observed in two hours. In the presence of 40% of alcohol, 22% (range of 16-25%) of dissolved bupropion HCl from BUP 450 XL tablets was seen in two hours.

The drug product is showing dose dumping with alcohol. Stronger language is being stated in labeling that alcohol should not be consumed with BUP 450 XL.

## 2. Question Based Review

### 2.1 List the in vitro and in vivo Clinical Pharmacology/Biopharmaceutics studies and the clinical studies with PK and /or PD information submitted in the NDA:

Clinical PK studies:

1. Study 3631 (SD fasting BE study): A two-way crossover, open-label, single-dose, fasting bioequivalence study of bupropion HCL 450 mg ER tablets vs. Wellbutrin XL® 150 mg tablets in normal, healthy, non-smoking male and female subjects.
2. Study S08-0027 (Food effect): A food effects study of 450 mg bupropion HCL extended-release tablet (BUP-450) and 3x150 mg Wellbutrin XL® extended-release tablets in two cohorts.

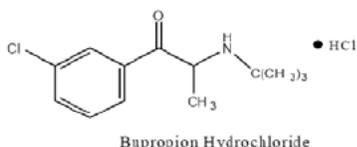
In vitro study: Effect of Alcohol on the Dissolution of Bupropion HCl from BUP-450 Tablets (dose dumping study with alcohol)

### 2.2 General Attributes of the Drug:

#### 2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

The 450-mg BUP 450 XL (bupropion hydrochloride) is an extended-release tablet that contains 450 mg of bupropion <sup>(b) (4)</sup>

The general chemistry and physical-chemical properties for the BUP 450 XL are summarized below:

	Physical-chemical properties
Physical Description	White powder
Chemical Name	(±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl) amino]-1-propanone hydrochloride
Molecular Formula	C <sub>13</sub> H <sub>18</sub> ClNO • HCl
Molecular Weight	276.21
Structural Formula	 <p>Bupropion Hydrochloride</p>
Solubility	Soluble in water, 0.1 N HCl and alcohol
pKa	7.9

The composition of the 450-mg BUP 450 XL tablet including inactive ingredients, is shown in the table below:

Component	Grade	Function	Amount per Tablet (mg)	W/W % of Tablet
(b) (4)				
Bupropion hydrochloride	USP	Active	(b) (4)	
Hydroxypropyl cellulose	NF	(b) (4)		
Hydrochloric acid	NF	(b) (4)		
(b) (4)				
Polyethylene oxide	NF			
Stearic acid	NF			
Colloidal silicon dioxide (SiO <sub>2</sub> )	NF			
Magnesium stearate	NF	(b) (4)		
(b) (4)				
Methacrylic acid copolymer (b) (4)	NF			
Talc	USP			
Polyethylene glycol (PEG) 8000	NF			
Titanium dioxide (TiO <sub>2</sub> )	USP			
Carboxymethyl cellulose sodium (NaCMC)	NF			
(b) (4)				
			740.27	100%

NF = National Formulary; q.s. = quantity sufficient

(b) (4)

**2.2.2 What are the proposed mechanism of action and therapeutic indications?**

The mechanism of action of bupropion hydrochloride is not fully understood. It is presumed that the antidepressant effect of the drug is mediated by noradrenergic and/or dopaminergic mechanisms (Wellbutrin XL Package Insert; Clinical Pharmacology, Pharmacodynamics).

Bupropion HCl is indicated for the treatment of major depressive disorder and as an aid to smoking cessation treatment.

### 2.2.3 What are the proposed dosage and routes of administration?

BUP 450 XL will be formulated in only one strength at 450 mg for use by oral administration.

### 2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

Wellbutrin (bupropion HCl) IR, SR, and XL tablets.

## 2.3 General Clinical Pharmacology

### 2.3.1 What are the design features of the clinical pharmacology / biopharmaceutics studies and the clinical studies used to support dosing or claims?

Key design features of the clinical pharmacology and clinical studies conducted with BUP 450 XL in the current submission are summarized in the table shown below:

Study Number	Study Design	Study Population	Treatment	End-point
Study 3631 (BE)	Randomized, open-label, two-way crossover, fasting BE study	Healthy males and females	450-mg BUP 450 XL vs. 3x 150-mg Wellbutrin XL, single dose under fasted conditions.	PK
Study S08-0027 (Food effect)	Randomized, open-label, crossover food effect study	Healthy males and females	450-mg BUP 450 XL, single dose under fasted and fed conditions	PK

### 2.3.2 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Bupropion and its three active metabolites were identified and measured. Please refer to Section 5. Individual Study Review for details of the bioanalytical method.

## 2.4 Intrinsic Factors

### 2.4.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure ( $AUC$ , $C_{max}$ , $C_{min}$ ) in patients with the target disease and how much of the variability is explained by the identified covariates?

The effect of intrinsic factors on exposure or response was not evaluated.

## 2.5 Extrinsic factors

### 2.5.1 Food effect

The sponsor studied the effect of food on their 450 mg bupropion ER tablets (BUP 450 XL), using the standard FDA breakfast (N=18; 7 M, 11F). Food prolonged the drug absorption of bupropion and its median  $T_{max}$  was increased from 5 hours to 7.5 hours after dosing of BUP 450 XL tablets under fed conditions. Food significantly increased

systemic exposure of bupropion following administration of BUP 450 XL: the mean  $C_{max}$  and  $AUC_{inf}$  were increased by ~25% and ~15%, respectively. This is a serious clinical safety concern:

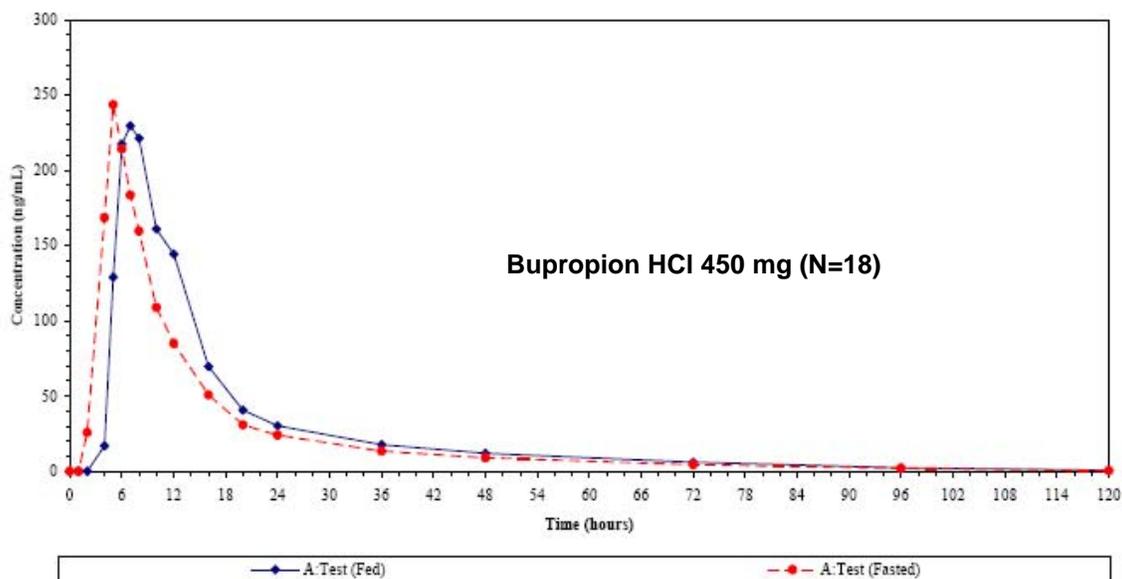
- a) Based on the package insert for Wellbutrin XL, bupropion is associated with a dose-related risk for seizure. For example, the IR formulation of bupropion suggested that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day. Thus, the therapeutic index of the drug, bupropion, is narrow above the recommended dose.
- b)  $C_{max}$  of bupropion was increased by 25% after administration of 450-mg BUP 450 XL under fed conditions, which is equivalent to about 112 mg *more* dose ( $450 \times 0.25$ ), i.e., the subjects were dosed more under fed conditions than under fasted conditions: 562-mg BUP 450 XL ( $450 + 112$ ) under fed conditions vs. 450-mg BUP 450 XL under fasted conditions; Additionally, based on the upper limit of 90% CI (107.5-145.5) for the increase of  $C_{max}$ , some subjects have been exposed to even much higher levels of bupropion under fed conditions, which is equivalent to the dose at 653-mg BUP 450 XL ( $450 + 450 \times 0.45$ ).
- c) In the current study, 67% of subjects (12 out of 18 subjects) showed that food increased  $C_{max}$  by >1 fold. In these 12 subjects, 2 subjects showed that food increased  $C_{max}$  by >2 fold (2.19 fold for Subject 11 and 2.75 fold for Subject 17); 4 subjects showed that food increased  $C_{max}$  by >1.5 fold but < 2 fold. Three subjects were > 1.2 fold and < 1.5 fold; remaining 3 subjects were <1.1 fold.

A two-fold increase of  $C_{max}$  is equivalent to a dose of “900 mg”, 1.5-fold increase of  $C_{max}$  is equivalent to a dose of “675 mg”, and 1.2-fold increase of  $C_{max}$  is equivalent to a dose of “540 mg”. The detailed information can be found in the Appendix following Section 5.2 (the food effect study review).

This increase in  $C_{max}$  of BUP 450 XL product is a very serious safety concern as there is a very serious risk of increase in seizures.

Mean plasma bupropion concentration-time profiles after administration of 450-mg BUP 450 XL under fasted and fed conditions are shown below:

**Mean Plasma Concentration (0-120 hours)**  
**Test Product A (Fed) vs. Test Product A (Fasted)**  
**Bupropion**  
**N=18**



The summary statistics of PK parameters for bupropion and the statistical results after administration of 450-mg BUP 450 XL under fasted and fed conditions are shown in the tables below:

Parameter (units)	Arithmetic Mean (% CV)	
	Median (Range) for T <sub>max</sub>	
	Fasted (N=18)	Fed (N=18)
AUC <sub>0-t</sub> (ng·hr/mL)	2591.60 (35.72)	2948.59 (32.54)
AUC <sub>0-inf</sub> (ng·hr/mL)	2708.42 (35.09)	3093.64 (31.47)
C <sub>max</sub> (ng/mL)	258.11 (23.85)	344.44 (45.50)
T <sub>max</sub> (hr)	5 (4-7)	7.5 (5-12)
T <sub>1/2</sub> (hr)	21.22 (39.15)	21.87 (38.04)

*Ref: Section 5.2 Food Effect Study.*

Ln-Transformed Data									
PK Variable	Least Squares Mean		Geometric Mean			90% Confidence Interval	P-values for Product Effects	Power of ANOVA	ANOVA % CV
	Test-Fed	Test-Fast	Test-Fed	Test-Fast	% Ratio	(Lower Limit, Upper Limit)			
C <sub>max</sub>	5.749	5.525	313.80	250.91	125.07	(107.51, 145.49)	0.0201	0.6768	26.44
AUC <sub>0-t</sub>	7.943	7.805	2815.85	2453.23	114.78	(104.64, 125.9)	0.0192	0.9767	15.99
AUC <sub>0-inf</sub>	7.995	7.851	2965.66	2568.79	115.45	(105.07, 126.86)	0.0171	0.9723	16.30

Additionally, the mean C<sub>max</sub> of threohydrobupropion was significantly increased by ~31% under fed conditions compared to that under fasted conditions. Please refer to Section 5.2 of this document.

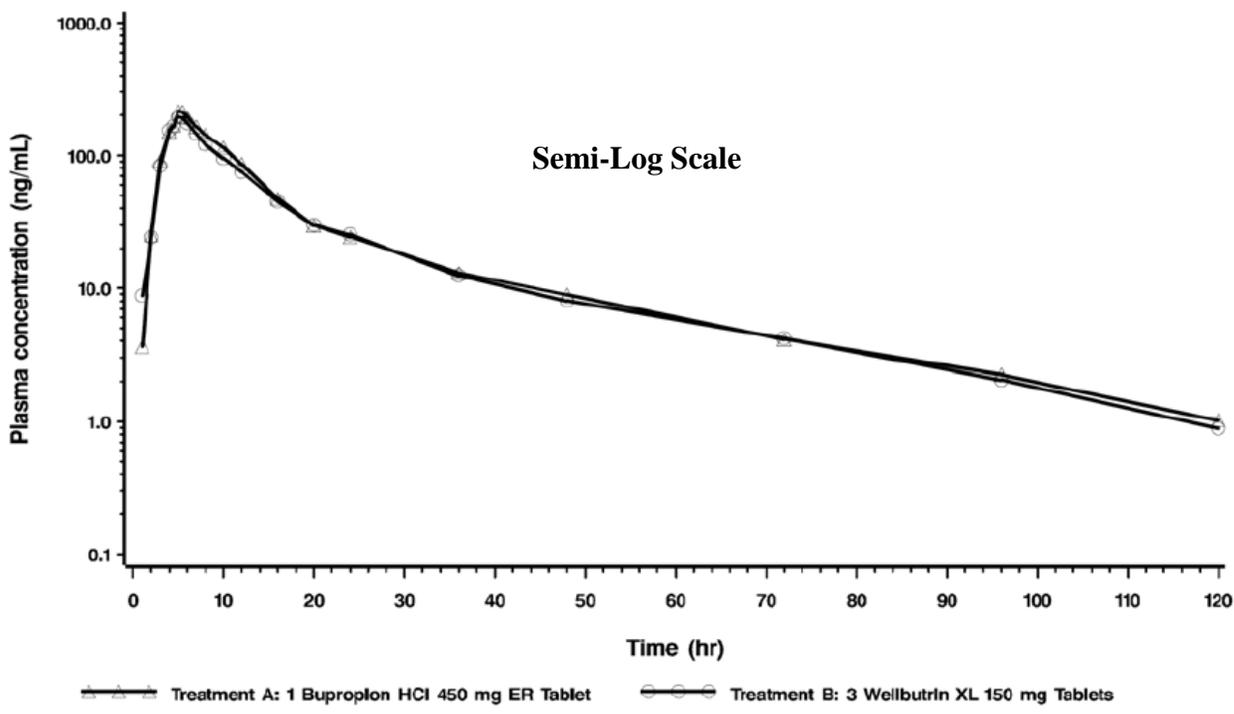
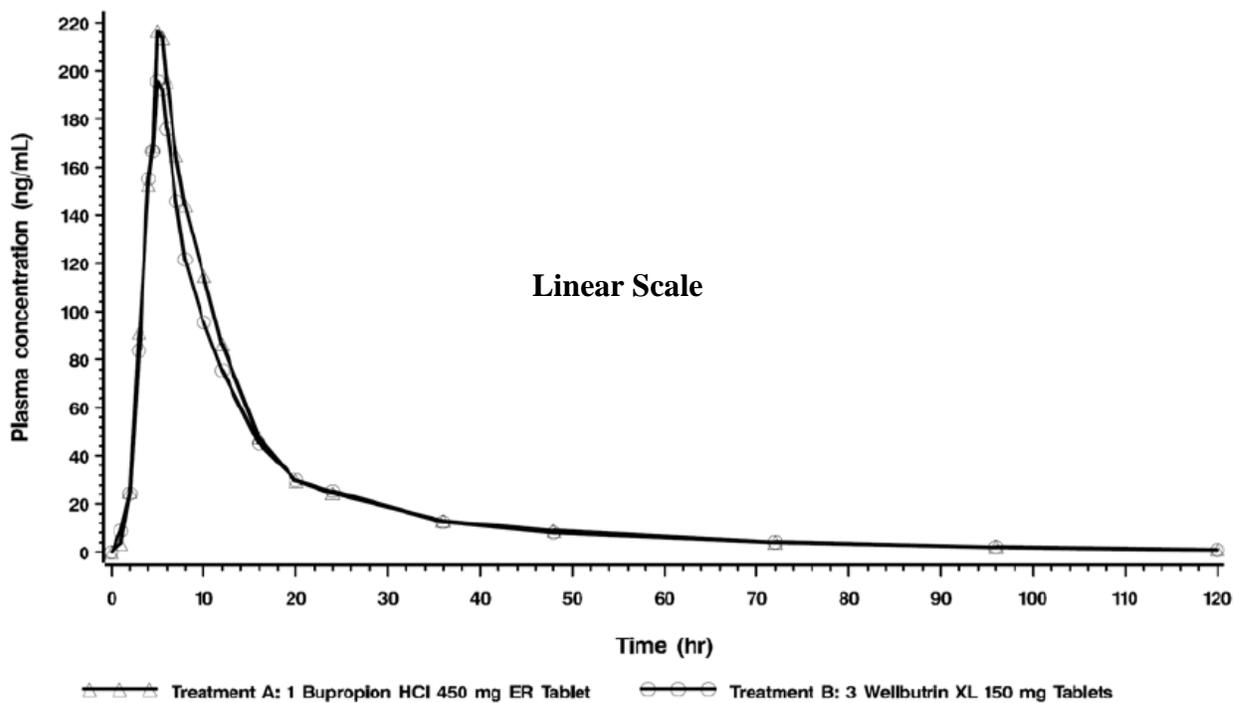
## 2.6 General Biopharmaceutics

### 2.6.1 Was an adequate link established between the currently clinically used formulation and the proposed formulation?

The currently approved tablet is GSK's Wellbutrin XL® tablets (150 mg and 300 mg), for once a day dosing. Cary Pharmaceuticals conducted a single dose, fasted BE study comparing their once a day ER tablet (BUP 450 XL) to 3 units of GSK's 150 mg XL tablets, i.e., 1 x 450 mg Cary's ER tablet vs. 3 x 150 mg GSK's XL tablets. Thirty two subjects completed the study (18 M and 14 F).

From a biopharmaceutical perspective based on the parent drug, bupropion, bioequivalence is established between the 450-mg BUP 450 XL (bupropion HCl ER) and the approved Wellbutrin XL® given as three 150-mg tablets.

Mean plasma bupropion concentration-time profiles after administration of 450-mg of BUP 450 XL and 3 x 150-mg Wellbutrin XL are shown on the next page:



PK parameters for bupropion and the statistical results after administration of 450-mg BUP 450 XL or 3 x 150-mg Wellbutrin XL are summarized in the tables below:

Tables 11.4.1, 11.4.2, 11.4.3, 11.4.4 and 11.4.5 respectively.

**Table 11.4.1 – Pharmacokinetic Parameters for Bupropion<sup>†</sup>**

Pharmacokinetic Parameters	Geometric Mean (%CV)	
	Arithmetic Mean ± SD	
	Bupropion HCl 450 mg ER Tablets (A) (n=32)	Wellbutrin XL <sup>®</sup> 150 mg Tablets (B) (n=32)
<b>AUC<sub>0-t</sub></b> (ng·hr/mL)	2393.89 (32.75) 2519.94 ± 825.30	2216.72 (32.55) 2349.56 ± 764.68
<b>AUC<sub>0-inf</sub></b> (ng·hr/mL)	2466.74 (32.00) 2591.55 ± 829.34	2274.77 (32.22) 2408.01 ± 775.97
<b>C<sub>max</sub></b> (ng/mL)	234.89 (32.79) 248.45 ± 81.47	208.87 (32.70) 220.05 ± 71.96
<b>T<sub>max</sub></b> (hr)*	5.03 (3.00-7.00)	5.00 (1.00-7.03)
<b>t<sub>1/2</sub></b> (hr)	23.85 ± 5.72	23.33 ± 5.41
<b>K<sub>el</sub></b> (hr <sup>-1</sup> )	3.19E-02 ± 1.47E-02	3.12E-02 ± 6.77E-03

\* median (min – max)

<sup>†</sup> The contents of this table correspond to Tables 14.2.1.3 and 14.2.1.4

Parameter	90% CI	Ratio of Means
AUC <sub>0-t</sub>	98.36% to 118.56%	107.99%
AUC <sub>0-inf</sub>	99.10% to 118.65%	108.44%
C <sub>max</sub>	101.54% to 124.55%	112.46%

One active metabolite, threohydrobupropion (bupropion threoamino alcohol), did not meet the criteria on AUC<sub>inf</sub>: 90% confidence interval, (96-132); point estimate, 1.13. The mean AUC was increased by ~13% for BUP 450 XL compared to the approved Wellbutrin XL.

The therapeutic contribution (AUC x Potency) from threohydrobupropion is 15%. A 13% increase of AUC leads to a ~2% increase in the therapeutic contribution from threohydrobupropion (15% x 0.13). This increase is not clinically relevant.

### 2.6.2 Are there any possibilities of error in using of Cary's BUP 450 XL?

The sponsor, Cary Pharmaceuticals, Inc., has developed BUP 450 XL (bupropion HCl ER) in only one strength of 450 mg.

The currently approved GSK's Wellbutrin IR and Wellbutrin XL<sup>®</sup> can be taken without regard to meals. Regarding Cary's BUP 450 XL, food significantly increased C<sub>max</sub> of bupropion by 25%, which is equivalent to about 112 mg *more* dose (450 x 0.25), i.e., the subjects were dosed more under fed conditions than under fasted conditions: 562-mg BUP 450 XL (450 + 112) under fed conditions vs. 450-mg BUP 450 XL under fasted conditions.

Based on the package insert for Wellbutrin, bupropion is associated with a dose-related risk for seizure. For example, the IR formulation of bupropion suggested that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day. Thus, the therapeutic index of the drug, bupropion, is narrow above the recommended dose. Therefore, Cary's BUP 450 XL should only be taken without food.

If Cary's BUP 450 XL is approved then changing from the Wellbutrin IR or XL formulation to BUP 450 XL will cause prescription errors to occur because of the differences of the effect of food observed on these products, and therefore, the increased risk of seizures in patients which is a serious safety concern.

### **2.6.3** *Does ethanol in vitro have a dose-dumping effect on the MR product?*

Dissolution profiles were generated for 12 dosage units using USP Apparatus 1 (basket) at 75 rpm in 900 ml of dissolution medium as specified below. Data were collected every 15 minutes for a total of two hours.

- Test 1: 0.1 N hydrochloric acid;
- Test 2: 5% (v/v) of test medium replaced with Alcohol USP;
- Test 3: 20% (v/v) of test medium replaced with Alcohol USP;
- Test 4: 40% (v/v) of test medium replaced with Alcohol USP;

For 2 hours, no dissolved bupropion HCl from BUP 450 XL tablets was seen at 0% of alcohol. In the presence of 20% of alcohol, 7% of dissolved bupropion HCl from BUP 450 XL tablets was observed in two hours. In the presence of 40% of alcohol, 22% (range of 16-25%) of dissolved bupropion HCl from BUP 450 XL tablets was seen in two hours.

The drug product is showing dose dumping with alcohol in vitro.

## **2.7 Analytical Section**

### **2.7.1** *What bioanalytical methods are used to assess concentrations of the measured moieties?*

Please see Section 5. Individual Study Review for details.

### **2.7.2** *For all moieties measured, is free, bound, or total measured?*

Total concentrations of bupropion and its three active metabolites were measured.

**2.7.3** *How are parent drug and active metabolites identified and what are the analytical methods used to measure them in plasma?*

Plasma concentrations of bupropion and its three active metabolites were determined using a validated HPLC/MS/MS method. The assays are acceptable. Please see Section 5. Individual Study Review for details.

**3. Detailed Labeling Recommendations (only the changed sections are included here with track changes)**

(b) (4)

## 4. Appendices

### 4.1 Package Insert for RLD (Wellbutrin XL®):



## 5. Individual Study Review

### 5.1 Study No. 3631 (Bioequivalence – 1 x 450 / 3 x 150 mg)

#### **A Two-Way Crossover, Open-Label, Single-Dose, Fasting, Bioequivalence Study of Bupropion HCl 450 mg ER Tablets Versus Wellbutrin XL® 150 mg Tablets in Normal, Healthy, Non Smoking Male and Female Subjects**

##### **Study information**

*Protocol Number:* 3631

*Investigator:*

Principal Investigator: Victor K. C. Lao, M.D.

Sub-investigators: (b) (4)

*Study site:*

(b) (4)

*Bioanalytical facility:*

(b) (4)

*Study dates:* August 25, 2008 to September 14, 2008

*Analysis dates:* September 18, 2008 to September 25, 2008

##### **Objectives**

To determine and compare the rate and extent of absorption of bupropion from one tablet (given as a single dose) of a test formulation of Bupropion HCl 450 mg ER (BUP 450 XL) tablets versus the rate and extent of absorption of bupropion from 3 tablets (given together as a single dose) of the reference Wellbutrin (Extended Release) XL ® 150 mg Tablets under fasting conditions.

##### **Study Design**

It was a randomized, open-label, single-dose, 2-way crossover design study under fasted conditions. Two treatment periods were separated by a 2-week washout period. Each of the subjects was randomized to receive the following:

*Treatment A:* 1 Bupropion HCl 450 mg ER (BUP 450 XL) Tablet with 240 mL of ambient temperature water (Treatment Dose = 450 mg).

*Treatment B:* 3 Wellbutrin XL® 150 mg Tablets with 240 mL of ambient temperature water (Treatment Dose = 450 mg).

Study Medication

*Bupropion HCl 450 mg ER Tablets (BUP 450 XL)*

Manufacturer: (b) (4)

Lot #: 08016P-01

Date of Manufacture: 2008 May 27

Re-Test Date 1: (b) (4)

Re-Test Date 2: (b) (4)

*Wellbutrin XL® 150 mg Tablets*

Manufacturer: Biovail Corp, Mississauga ON Canada

Lot #: P08B016

Expiry Date: 07/09

PK Sampling

PK blood samples were collected at 0.00 (pre-dose), 1.00, 2.00, 3.00, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 20.00, 24.00, 36.00, 48.00, 72.00, 96.00 and 120.00 hours post-dose during each study period.

PK Data Analysis

The pharmacokinetic parameters for bupropion, hydroxybupropion, bupropion threoamino alcohol, bupropion erythroamino alcohol and PAWC derived for both treatments using standard, non-compartmental methods were:

*Primary parameters:* AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, C<sub>max</sub>

*Secondary parameters:* T<sub>max</sub>, K<sub>el</sub>, t<sub>1/2</sub>

Statistical Data Analysis

ANOVAs (with the following factors: treatment, period, sequence, subject within sequence) were performed on the ln-transformed data for AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub>. ANOVAs were also performed on the untransformed data to compare the t<sub>1/2</sub> and K<sub>el</sub>. All ANOVAs were performed with the SAS GLM Procedure. T<sub>max</sub> was analyzed using nonparametric methods. The equality of treatment effect in both sequences was evaluated using Wilcoxon rank-sum tests. For all analyses, effects were considered statistically significant if the p-value associated with 'F' was less than or equal to 0.05.

Safety Assessments

Physical examination, vital signs, and clinical laboratory tests were performed and evaluated to assess subject safety. All reported adverse events and serious adverse events were collected and evaluated.

Bioanalytical Method

Using the validated method (B08 Version 18), Bupropion and its metabolites, Bupropion Erythroamino Alcohol, Bupropion Threoamino Alcohol, and Hydroxybupropion and the internal standard, (b) (4) were extracted from human plasma (0.50 mL), using sodium heparin as an anticoagulant, by SPE into an organic medium. An aliquot of this extract was injected into a HPLC system, detected using an API 3000 with HSID tandem mass spectrometer, and quantitated using a peak area ratio method.

Method sensitivity and selectivity were achieved by detecting distinct precursor to product ion mass transitions for Bupropion (240.3 →184.0), Hydroxybupropion (256.3 → 238.0), Bupropion Erythroamino Alcohol (242.4 →168.1), Bupropion Threoamino Alcohol (242.4 →168.1) and the internal standard, (b) (4), at defined retention time. The analytes were separated by reverse phase chromatography.

Evaluation of the assay, using defined acceptance criteria, was carried out by the construction of an eight (8) point calibration curve (excluding zero concentration) covering the range of 1.000 ng/mL to 1023.920 ng/mL for bupropion, 1.000 ng/mL to 1023.970 ng/mL for bupropion erythroamino alcohol, 1.000 ng/mL to 1023.970 ng/mL for bupropion threoamino alcohol, and 3.906 ng/mL to 3999.620 ng/mL for hydroxybupropion in human plasma. The slope and intercept of the calibration curves were determined through weighted linear regression analysis (1/area ratio<sup>2</sup>). Two calibration curves and duplicate QC samples (at three of four concentration levels) were analyzed along with each batch of the study samples. Peak area ratios were used to determine the concentration of the standards, quality control samples, and the unknown study samples from the calibration curves.

## Study Results

### Subject Demographics

Thirty nine subjects were dosed and 32 subjects (18 males and 14 females) completed the study. Subject disposition is summarized below:

*Table 10.1.2 – Summary of Subject Disposition<sup>†</sup>*

	Sequence		Total
	AB	BA	
Subjects randomized	20	20	40
Subjects dosed	19	20	39
Subjects completed study	16	16	32
Subjects withdrawn	3	2	5
Subjects dismissed	0	2	2
Primary reason for not completing study	Personal reasons, AEs	Administrative reasons, AEs	

A: Bupropion HCl 450 mg ER Tablets (Lot #: 08016P-01)

B: Wellbutrin XL<sup>®</sup> 150 mg Tablets (Lot #: P08B016)

<sup>†</sup> The contents of this table correspond to the randomization scheme and the removal from the study forms

In addition, subjects who did not complete the study and reasons for discontinuation is listed below:

**Table 10.1.1 – Discontinued Subjects<sup>†</sup>**

Last Dosing (Period Number)/	Subject Number/ (gender; age yrs)	Treatment Sequence	Dismissed or Withdrew	Timeframe	Reason
I	009 Male; 43	AB	Withdrew	During post-Period I Washout	Personal Reasons
I	031 Male; 28	AB	Withdrew	During post-Period I Washout	Personal Reasons
I	018 Female; 22	BA	Dismissed	During post-Period I Washout	Administrative Reason
I	029 Male; 44	BA	Withdrew	During post-Period I Washout	AEs (headache and sneezing)
I	033 Male; 54	AB	Withdrew	During post-Period I Washout	AEs (rash and itchiness over rash)
I	034 Male; 29	BA	Withdrew	During post-Period I Washout	AE (upper respiratory tract infection)
I	039 Male; 45	BA	Dismissed	During post-Period I Washout	AEs (rash and itchiness over rash)

<sup>†</sup> The contents of this table correspond to the CRFs

A: 1 Bupropion HCl 450 mg ER Tablet (Lot #: 08016P-01)

B: 3 Wellbutrin XL<sup>®</sup> 150 mg Tablets (Lot #: P08B016)

### Bioanalytical Results

Bupropion and its three active metabolites were analyzed and the procedure used was validated over the range of:

Name of Analyte(s)	Calibration Range (ng/mL)
Bupropion	1.000 to 1023.930 ± 10.0%
Bupropion Erythroamino Alcohol	1.000 to 1024.000 ± 10.0%
Bupropion Threoamino Alcohol	1.000 to 1024.000 ± 10.0%
Hydroxybupropion	3.906 to 4000.000 ± 10.0%

\*the information in the table above can be found in the bioanalytical validation report

Accuracy and precision of this method were evaluated both within run (intra-assay) and between runs (inter-assay) by the analysis of the lowest limit of quantification (LLOQ) and Quality Control samples at three different concentrations (QC HIGH, QC MED and QC LOW) in human plasma prepared in the range of the calibration/standard curve. The accuracy and precision determined, at each concentration level, were reported as percent relative error (%RE) and percent coefficient of variation (%CV), respectively.

Name of Analyte(s)	Bupropion	Hydroxybupropion
QC Intraday precision range (%)	1.6 to 5.2	2.1 to 6.0
QC Intraday accuracy range (%)	-4.1 to 4.7	-3.6 to 5.3
QC Interday precision range (%)	2.6 to 6.3	2.0 to 5.1
QC Interday accuracy range (%)	-4.2 to 2.0	-4.4 to 2.2

\*the information in the table above can be found in the bioanalytical validation report

Name of Analyte(s)	Bupropion Erythroamino Alcohol	Bupropion Threoamino Alcohol
QC Intraday precision range (%)	2.2 to 4.6	2.5 to 7.9
QC Intraday accuracy range (%)	-3.4 to 3.7	-3.5 to 4.4
QC Interday precision range (%)	2.5 to 4.1	3.5 to 9.2
QC Interday accuracy range (%)	-4.0 to 1.9	-4.3 to 1.1

\*the information in the table above can be found in the bioanalytical validation report

Procedural and Long-term stability in Matrix were determined using QC samples (QC LOW and QC HIGH) and are summarized as follows:

<b>Freeze Thaw Stability</b>	3 Cycles at $-25^{\circ}\text{C} \pm 10^{\circ}\text{C}$ and $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$
<b>In Process Stability</b>	24 Hours at $4^{\circ}\text{C} \pm 4^{\circ}\text{C}$
<b>Autosampler Re-injection Stability</b>	92 Hours at room temperature
<b>Whole Blood Stability</b>	2 Hours at $4^{\circ}\text{C} \pm 4^{\circ}\text{C}$
<b>Hemolysis Effect</b>	No significant Hemolysis Effect
<b>Matrix Effect</b>	No significant Matrix Effect
<b>Long Term Stability in Matrix</b>	510 Days at $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$ To be determined at $-25^{\circ}\text{C} \pm 10^{\circ}\text{C}$

\*the information in the table above can be found in the bioanalytical validation report

Performance measures of bupropion and its active metabolites are also summarized in the table below:

	<b>Bupropion</b>	<b>Hydroxy-bupropion</b>	<b>Threohydro-bupropion</b>	<b>Erythrohydro-bupropion</b>
Standard curve range	1 – 1023.92 ng/mL (weighted $1/x^2$ , $r^2 \geq 0.996$ )	3.91 – 3999.62 ng/mL (weighted $1/x^2$ , $r^2 \geq 0.997$ )	1 – 1023.97 ng/mL (weighted $1/x^2$ , $r^2 \geq 0.996$ )	1 – 1023.97 ng/mL (weighted $1/x^2$ , $r^2 \geq 0.996$ )
QC sample concentrations	1, 3, 192, and 767.9 ng/mL	3.9, 11.7, 749.9, and 2999.7 ng/mL	1, 3, 192, and 768.0 ng/mL	1, 3, 192, and 768 ng/mL
Precision (%)	Intra-day: 1.6-5.2 Inter-day: 2.6-6.3	Intra-day: 2.1-6.0 Inter-day: 2.0-5.1	Intra-day: 2.5-7.9 Inter-day: 3.5-9.2	Intra-day: 2.2-4.6 Inter-day: 2.5-4.1
Accuracy (%)	Intra-day: -4.1-4.7 Inter-day: -4.2-2.0	Intra-day: -3.6-5.3 Inter-day: -4.4-2.2	Intra-day: -3.5-4.4 Inter-day: -4.3-1.1	Intra-day: -3.4-3.7 Inter-day: -4.0-1.9
Internal standard	(b) (4) Lot number: 04613TD			
Reference	Bupropion	Hydroxybupropion	Threohydrobupropion	Erythrohydrobupropion

standard	Lot number: 200736 Purity: 98.9%	Lot number: 200737 Purity: 99%	Lot number: 200739 Purity: 99%	Lot number: 200738 Purity: 99%
Specificity	No interference			
Recovery	99% Internal Standard: 86%	100% Internal Standard: 86%	99.7% Internal Standard: 86%	95% Internal Standard: 86%
Matrix	Human plasma			
Stability (in human plasma)	4°C ± 4°C: 24 hours Freeze-thaw: 3 FT cycles			

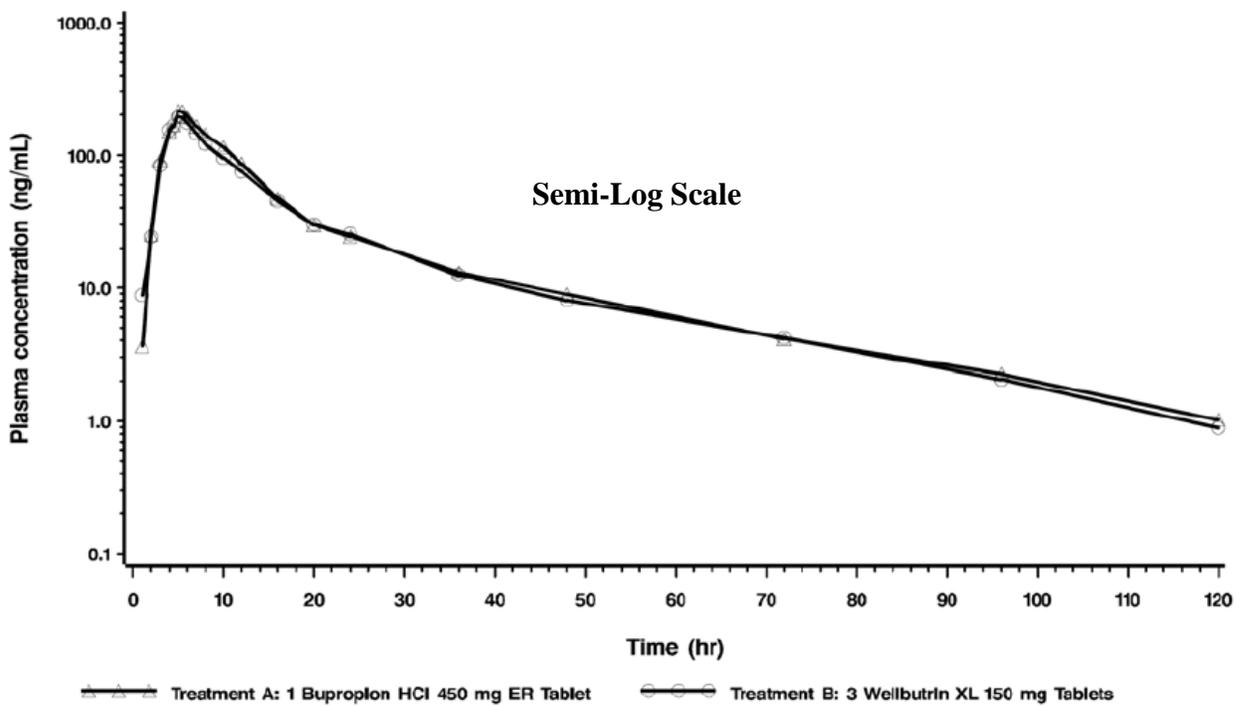
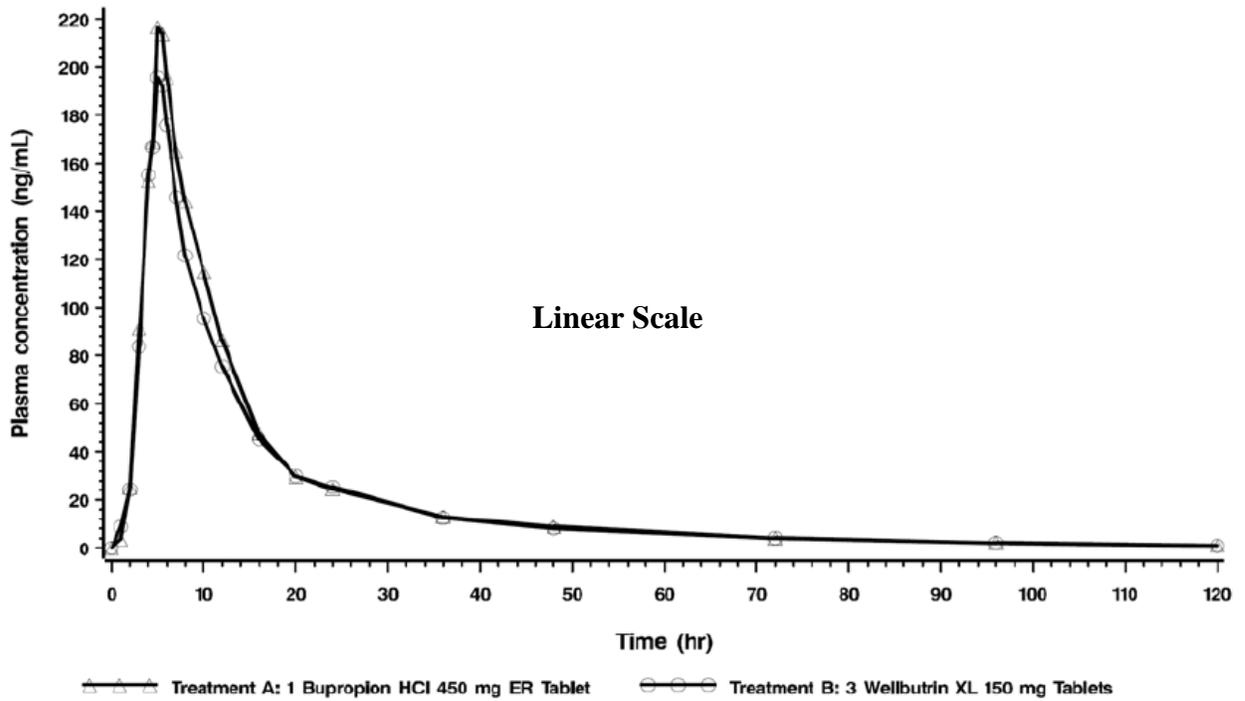
*Reviewer's comments:*

*The bioanalytical method employed in this study met the criteria set by the 'Guidance for Industry: Bioanalytical Method Development' and is acceptable.*

*PK and Statistical Results*

**(A) PK of bupropion:**

- Mean plasma bupropion concentration-time profiles and PK parameters are shown/summarized below:



TABLES 11.7.1, 11.7.2, 11.7.3, 11.7.4 and 11.7.5 respectively.

**Table 11.4.1 – Pharmacokinetic Parameters for Bupropion<sup>†</sup>**

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	Bupropion HCl 450 mg ER Tablets (A) (n=32)	Wellbutrin XL <sup>®</sup> 150 mg Tablets (B) (n=32)
<b>AUC<sub>0-t</sub></b> (ng·hr/mL)	2393.89 (32.75) 2519.94 ± 825.30	2216.72 (32.55) 2349.56 ± 764.68
<b>AUC<sub>0-inf</sub></b> (ng·hr/mL)	2466.74 (32.00) 2591.55 ± 829.34	2274.77 (32.22) 2408.01 ± 775.97
<b>C<sub>max</sub></b> (ng/mL)	234.89 (32.79) 248.45 ± 81.47	208.87 (32.70) 220.05 ± 71.96
<b>T<sub>max</sub></b> (hr)*	5.03 (3.00-7.00)	5.00 (1.00-7.03)
<b>t<sub>1/2</sub></b> (hr)	23.85 ± 5.72	23.33 ± 5.41
<b>K<sub>el</sub></b> (hr <sup>-1</sup> )	3.19E-02 ± 1.47E-02	3.12E-02 ± 6.77E-03

\* median (min – max)

<sup>†</sup> The contents of this table correspond to Tables 14.2.1.3 and 14.2.1.4

- C<sub>max</sub> for bupropion 450 mg ER (BUP 450 XL) tablets was increased by ~12% compared to 3 Wellbutrin XL 150 mg tablets. AUC for bupropion 450 mg ER tablets was increased by ~8% compared to Wellbutrin XL tablets. Mean values of T<sub>max</sub> are comparable. However, there is no statistical difference on AUC and C<sub>max</sub> between test and reference products. The statistical analysis result is shown below:

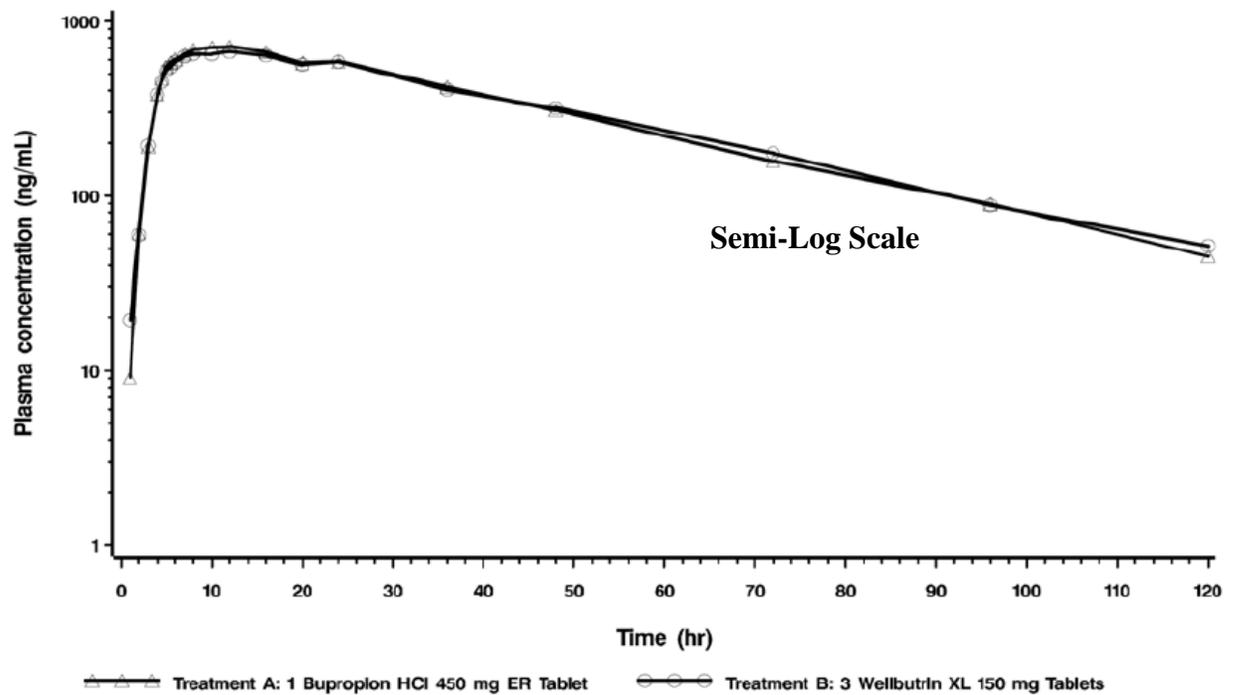
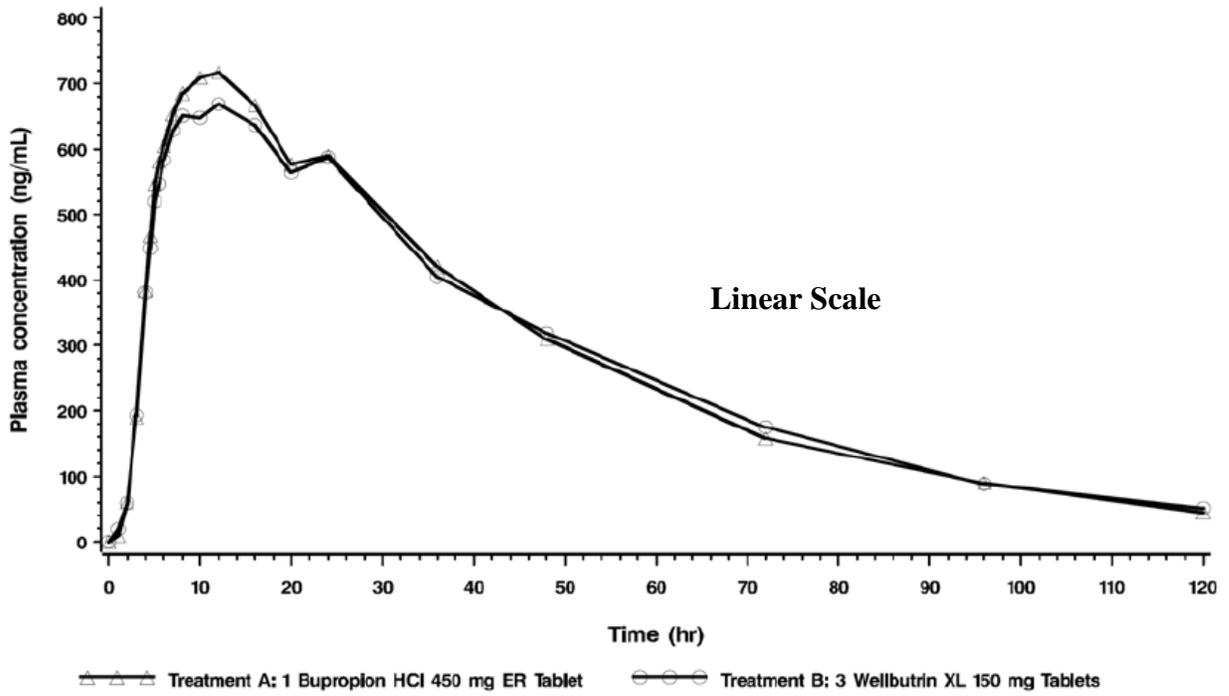
Parameter	90% CI	Ratio of Means
AUC <sub>0-t</sub>	98.36% to 118.56%	107.99%
AUC <sub>0-inf</sub>	99.10% to 118.65%	108.44%
C <sub>max</sub>	101.54% to 124.55%	112.46%

*Reviewer's comment:*

*Analysis of the data of bupropion by OCP was in agreement with that provided by the sponsor regarding the BE between test and reference drugs.*

**(B) PK of hydroxybupropion**

- Mean plasma hydroxybupropion concentration-time profiles and PK parameters are shown/summarized below:



**Table 11.4.2 – Pharmacokinetic Parameters for Hydroxybupropion<sup>‡</sup>**

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	Bupropion HCl 450 mg ER Tablets (A) (n=32)	Wellbutrin XL <sup>®</sup> 150 mg Tablets (B) (n=32)
AUC <sub>0-t</sub> (ng·hr/mL)	28991.19 (49.94) 33618.21 ± 16790.07	28214.28 (51.61) 34079.79 ± 17589.98
AUC <sub>0-inf</sub> (ng·hr/mL)	31312.90 (49.67) 36330.02 ± 18046.04 <sup>†</sup>	29799.75 (53.36) 36246.49 ± 19342.45
C <sub>max</sub> (ng/mL)	676.68 (41.99) 750.41 ± 315.09	616.94 (46.11) 711.13 ± 327.92
T <sub>max</sub> (hr)*	10.00 (4.50 - 24.00)	10.00 (5.00 - 24.03)
t <sub>1/2</sub> (hr)	25.05 ± 5.27 <sup>†</sup>	25.05 ± 6.40
K <sub>el</sub> (hr <sup>-1</sup> )	2.90E-02 ± 6.70E-03 <sup>†</sup>	2.96E-02 ± 8.32E-03

\* median (min – max); <sup>†</sup>n=31

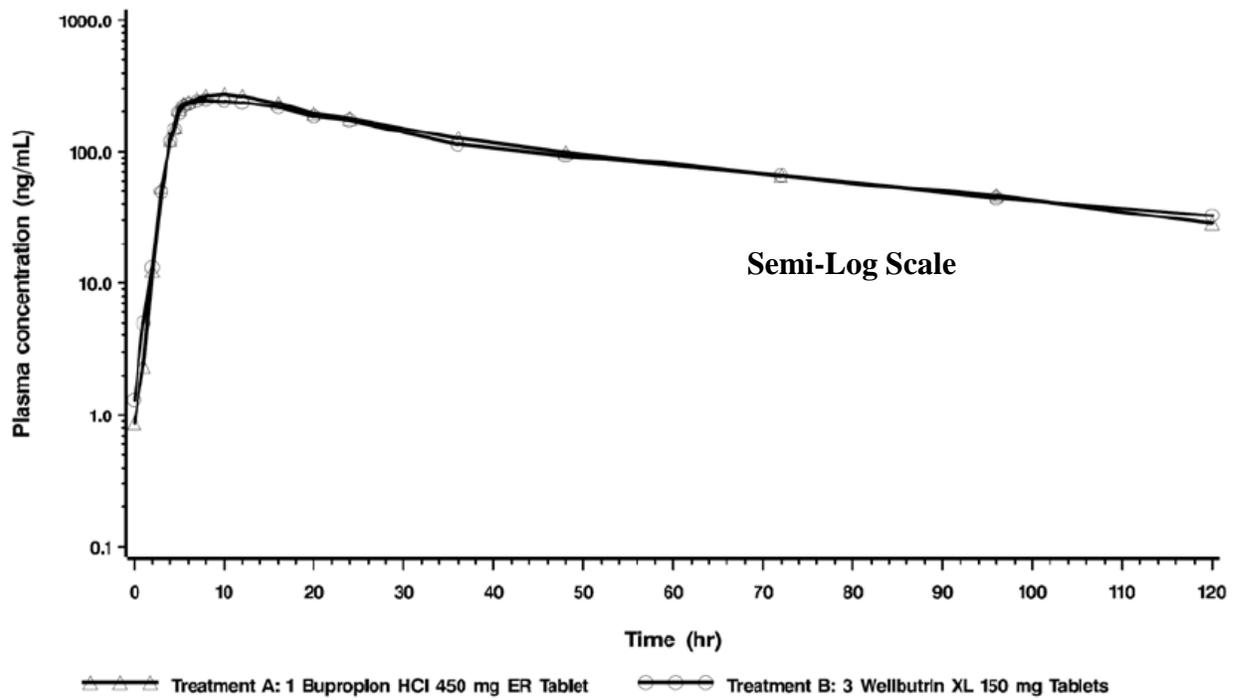
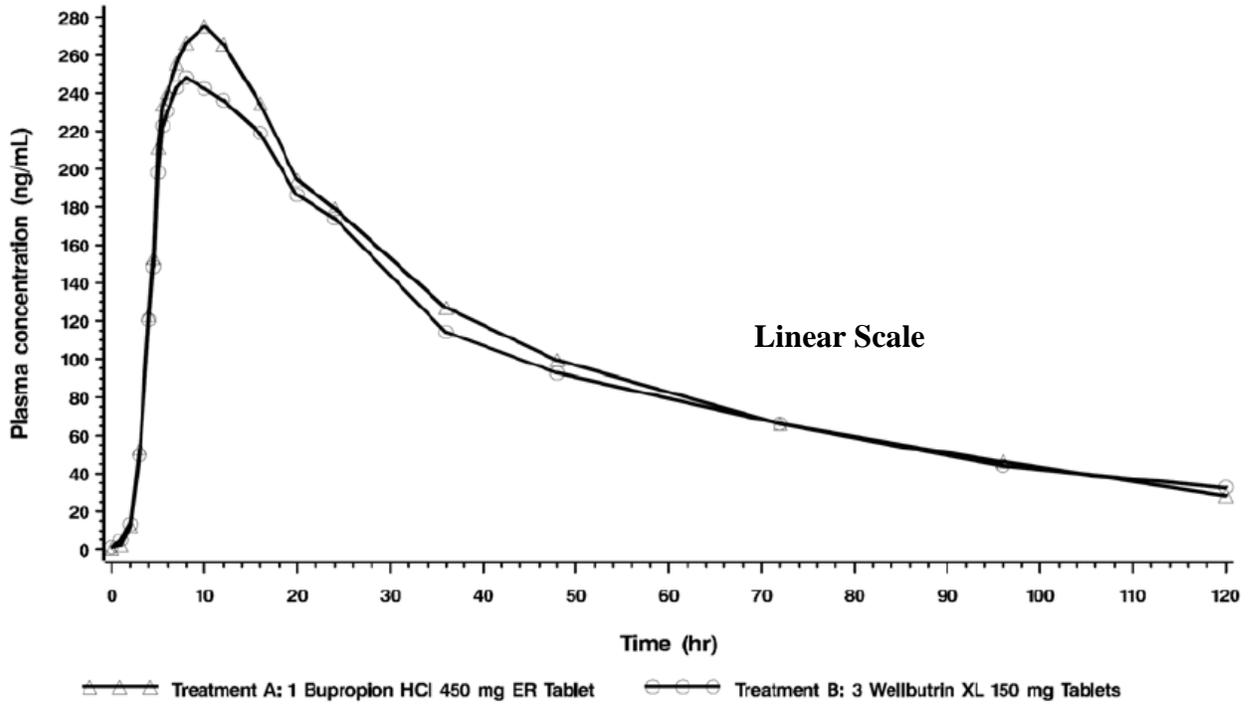
<sup>‡</sup> The contents of this table correspond to Tables 14.2.2.3 and 14.2.2.4

- C<sub>max</sub> for hydroxybupropion was increased by ~10% compared to 3 Wellbutrin XL 150 mg tablets. AUC for hydroxybupropion was increased by ~6% compared to Wellbutrin XL tablets. However, there is no statistical difference on AUC and C<sub>max</sub> between test and reference products. The statistical analysis result is shown below:

Parameter	90% CI	Ratio of Means
AUC <sub>0-t</sub>	91.64% to 115.21%	102.75%
AUC <sub>0-inf</sub>	96.57% to 116.99%	106.29%
C <sub>max</sub>	100.98% to 119.14%	109.68%

**(C) PK of bupropion threoamino alcohol**

- Mean plasma bupropion threoamino alcohol concentration-time profiles and PK parameters are shown/summarized below:



**Table 11.4.3 – Pharmacokinetic Parameters for Bupropion Threoamino Alcohol<sup>€</sup>**

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	Bupropion HCl 450 mg ER Tablets (A) (n=32)	Wellbutrin XL <sup>®</sup> 150 mg Tablets (B) (n=32)
AUC <sub>0-t</sub> (ng·hr/mL)	10855.45 (44.68) 11920.26 ± 5326.35	10477.19 (52.01) 11757.34 ± 6114.87
AUC <sub>0-inf</sub> (ng·hr/mL)	12015.76 (40.18) † 13008.79 ± 5227.28	11433.99 (61.86) ‡ 13316.14 ± 8237.72
C <sub>max</sub> (ng/mL)	289.54 (30.34) 302.07 ± 91.64	256.72 (36.01) 272.27 ± 98.04
T <sub>max</sub> (hr)*	9.00 (5.00 - 16.00)	8.00 (5.00 - 16.00)
t <sub>1/2</sub> (hr)	35.98 ± 8.18 †	37.77 ± 9.95 ‡
K <sub>el</sub> (hr <sup>-1</sup> )	2.02E-02 ± 4.44E-03 †	1.98E-02 ± 5.86E-03 ‡

\* median (min – max); † n = 21; ‡ n=23

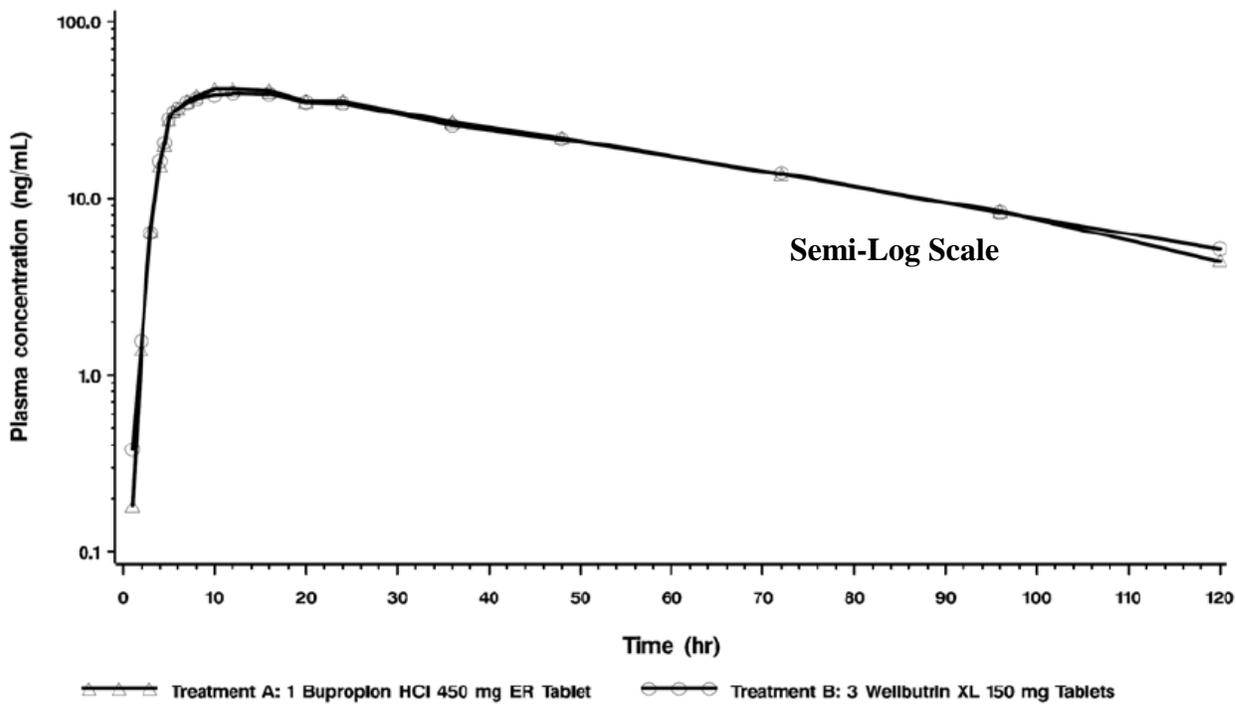
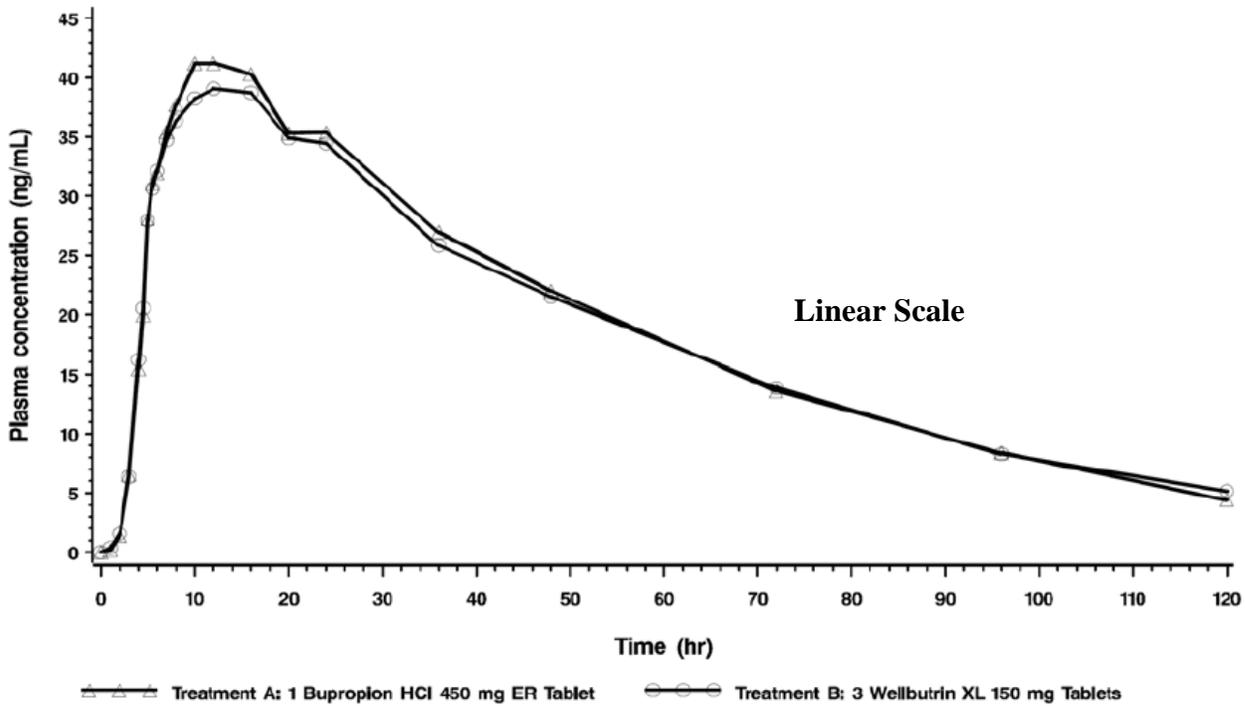
<sup>€</sup> The contents of this table correspond to Tables 14.2.3.3 and 14.2.3.4

- C<sub>max</sub> for bupropion threoamino alcohol was increased by ~13% compared to 3 Wellbutrin XL 150 mg tablets. AUC for bupropion threoamino alcohol was significantly increased by ~13% compared to Wellbutrin XL tablets. The statistical analysis result is shown below:

Parameter	90% CI	Ratio of Means
AUC <sub>0-t</sub>	92.02% to 116.67%	103.61%
AUC <sub>0-inf</sub>	96.13% to 132.03%	112.66%
C <sub>max</sub>	103.35% to 123.08%	112.79%

**(D) PK of bupropion erythroamino alcohol**

- Mean plasma bupropion erythroamino alcohol concentration-time profiles and PK parameters are shown/summarized below:



*Table 11.4.4 – Pharmacokinetic Parameters for Bupropion Erythroamino Alcohol*

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	Bupropion HCl 450 mg ER Tablets (A) (n=32)	Wellbutrin XL <sup>®</sup> 150 mg Tablets (B) (n=32)
AUC <sub>0-t</sub> (ng·hr/mL)	2072.29 (36.18) 2224.51 ± 804.90	2038.79 (43.05) 2246.21 ± 966.89
AUC <sub>0-inf</sub> (ng·hr/mL)	2252.13 (36.20) † 2402.64 ± 869.74	2193.79 (46.34) ‡ 2441.79 ± 1131.42
C <sub>max</sub> (ng/mL)	42.54 (25.58) 43.93 ± 11.24	40.32 (29.40) 42.20 ± 12.41
T <sub>max</sub> (hr)*	10.01 (6.00 - 20.00)	11.02 (5.00 - 24.05)
t <sub>1/2</sub> (hr)	30.83 ± 8.53 †	31.93 ± 8.63 ‡
K <sub>el</sub> (hr <sup>-1</sup> )	2.42E-02 ± 6.72E-03 †	2.35E-02 ± 7.21E-03 ‡

\* median (min – max); †n = 28; ‡n=31

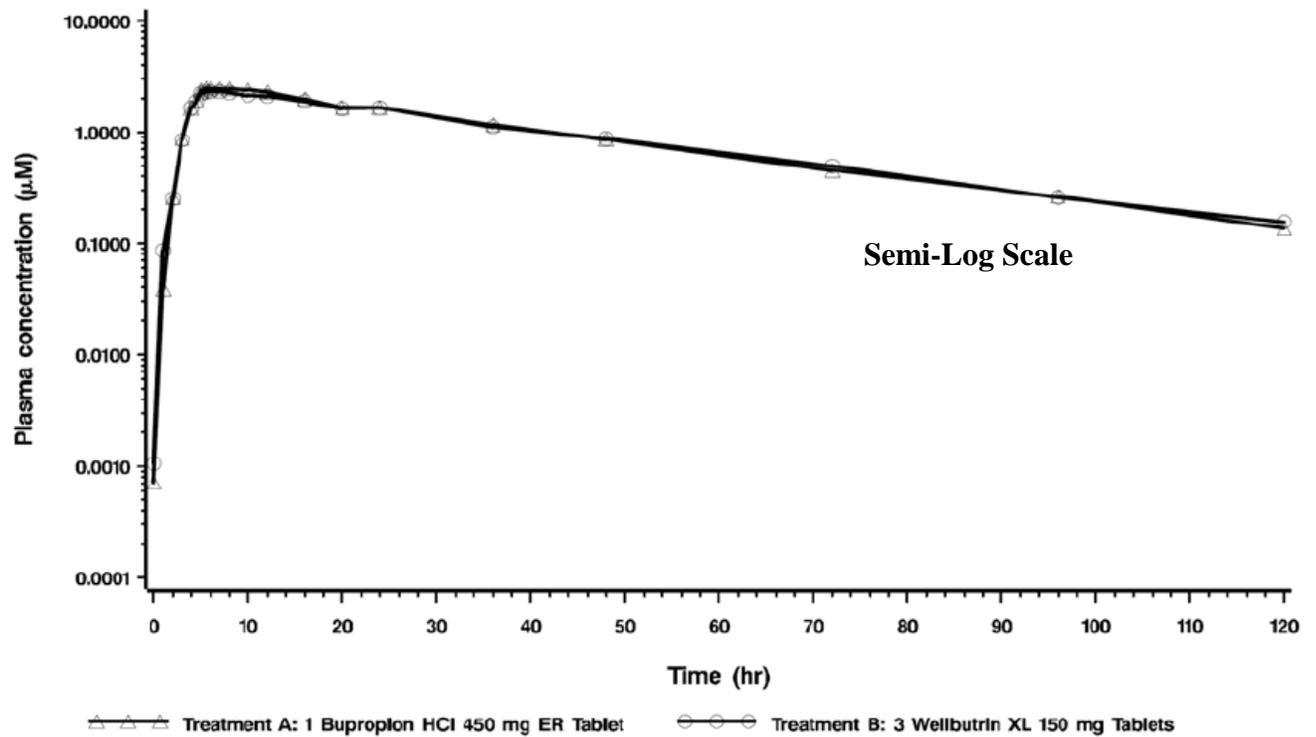
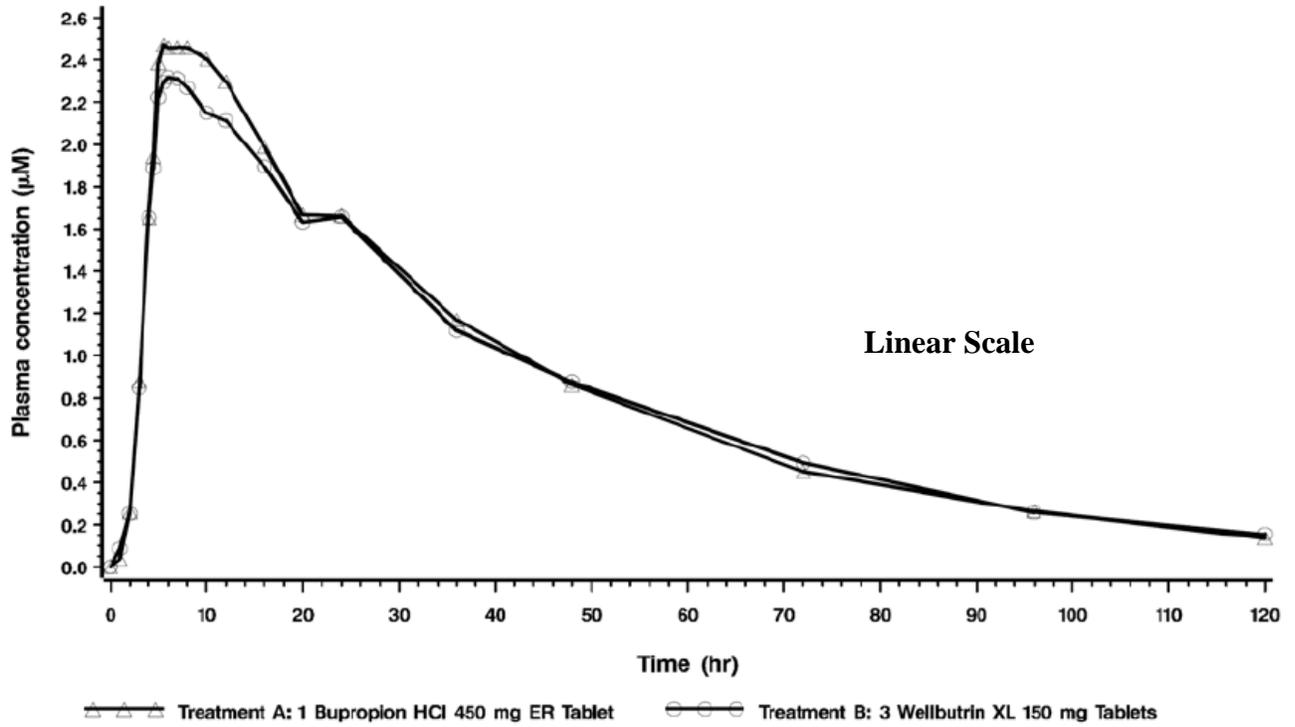
€ The contents of this table correspond to Tables 14.2.4.3 and 14.2.4.4

- C<sub>max</sub> for bupropion erythroamino alcohol was increased by ~6% compared to 3 Wellbutrin XL 150 mg tablets. AUC for bupropion threoamino alcohol was increased by ~8% compared to Wellbutrin XL tablets. However, there is no statistical difference on AUC and C<sub>max</sub> between test and reference products. The statistical analysis result is shown below:

Parameter	90% CI	Ratio of Means
AUC <sub>0-t</sub>	89.57% to 115.35%	101.64%
AUC <sub>0-inf</sub>	96.26% to 120.04%	107.50%
C <sub>max</sub>	96.68% to 115.12%	105.50%

**(E) PK of PAWC (Pharmacologic Activity-Weighted Composite)**

- Mean plasma PAWC concentration-time profiles and PK parameters are shown/summarized below:



**Table 11.4.5 – Pharmacokinetic Parameters for PAWC<sup>€</sup>**

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD	
	Bupropion HCl 450 mg ER Tablets (A) (n=32)	Wellbutrin XL <sup>®</sup> 150 mg Tablets (B) (n=32)
AUC <sub>0-t</sub> (µM.hr)	91.20 (43.07) 101.13 ± 43.56	88.05 (46.21) 101.41 ± 46.86
AUC <sub>0-inf</sub> (µM.hr)	98.75 (43.39) † 109.70 ± 47.60	92.98 (48.38) 108.11 ± 52.31
C <sub>max</sub> (µM)	2.64 (30.70) 2.77 ± 0.85	2.42 (32.98) 2.58 ± 0.85
T <sub>max</sub> (hr)*	5.75 (4.00 - 12.03)	5.81 (4.00 - 12.00)
t <sub>1/2</sub> (hr)	26.77 ± 5.44 †	26.20 ± 6.31
K <sub>el</sub> (hr <sup>-1</sup> )	2.70E-02 ± 5.94E-03 †	2.81E-02 ± 7.60E-03

\* median (min – max); † n=31

<sup>€</sup> The contents of this table correspond to Tables 14.2.4.3 and 14.2.4.4

- C<sub>max</sub> for bupropion 450 mg ER (BUP 450 XL) was increased by ~9% compared to 3 Wellbutrin XL 150 mg tablets. AUC for BUP 450 XL was increased by ~7% compared to Wellbutrin XL tablets. The statistical analysis result is shown below:

Parameter	90% CI	Ratio of Means
AUC <sub>0-t</sub>	92.77% to 115.65%	103.58%
AUC <sub>0-inf</sub>	97.32% to 118.13%	107.22%
C <sub>max</sub>	100.51% to 118.28%	109.03%

The three metabolites of bupropion have been determined to be pharmacologically active in animal studies. The relative potencies based on ED50 for bupropion, hydroxybupropion, threohydrobupropion and erythrohydrobupropion were, 1.0, 0.6, 0.2 and 0.2, respectively. The PAWC at each time-point was calculated by multiplying the molar concentration of each analyte by its relative potency and adding all four concentrations.

It should be noted that the PAWC is a value that is calculated based on relative potency determined in an animal model of antidepressant activity, and does not represent pharmacologic activity in humans.

## (F) PK Summary

Briefly, 90% CI of AUC and  $C_{\max}$  for bupropion were within 80%-125% range. For one of the active metabolites, bupropion threoamino alcohol, its 90% CI of  $AUC_{\text{inf}}$  was 96%-132%, which is out of 80%-125% range. 90% CI of AUC and  $C_{\max}$  for PAWC were within 80%-125% range.

### *Safety results*

No deaths or SAEs were reported.

Ten subjects experienced a total of 20 AEs during the study. The most frequent AEs were expressed as fractions, relative to the total number of AEs experienced after each treatment. After treatment with 1 Bupropion HCl 450 mg ER Tablet, the most frequent AE was headache (2/10). After treatment with 3 Wellbutrin XL® 150 mg Tablets, the most frequent AE was headache (3/9). No AE was reported more than once after the end-of-study exam.

Briefly, 5 subjects (14.3%) experienced AEs for Treatment A (bupropion 450 mg ER tablet) and 6 subjects (16.7%) experienced AEs for Treatment B (3 Wellbutrin XL 150 mg tablet).

### **Conclusions**

Equivalence was demonstrated for bupropion between the 450-mg BUP 450 XL (bupropion 450 mg ER) and the approved Wellbutrin XL® given as three 150-mg tablets. From a biopharmaceutical perspective based on the parent drug, equivalence is established between the 450-mg BUP 450 XL and the approved Wellbutrin XL® given as three 150-mg tablets.

One active metabolite, threohydrobupropion (bupropion threoamino alcohol), did not meet the criteria on  $AUC_{\text{inf}}$ : 90% confidence interval, (96-132); point estimate, 1.13. The mean AUC was significantly increased by ~13% for BUP 450 XL compared to the approved Wellbutrin XL®.

The safety profiles were comparable between two formulations.

## APPENDIX

An inspection of the BE study was requested by OCP I/DPP. Both clinical and analytical portions of the study were audited by Division of Scientific Investigations (DSI). Memorandum of the inspection is shown in Attachment 1. The DSI's evaluations and OCP's comments are summarized below:

1. Failure to retain the study reserve samples (test product: Bupropion HCl 450 mg ER tablets; reference product: Wellbutrin XL 150 mg tablets) used in bioequivalence Study # 3631 as required by the regulations. The reserve samples were sent back to the study co-sponsor (IntelGenx Corp., Quebec, Canada).

(b)(4) fails to meet the regulatory requirements for retention of products used in bioavailability or bioequivalence study (21 CFR 320.38 and 320.63). Per the request of co-sponsor of this NDA, (b)(4) shipped back all the reserve samples (see documents collected during the inspection in **Attachments 2, 3 and 4**).

As the test and reference products were not retained at the clinical study site, the authenticity of the products used in Study #3631 cannot be confirmed.

### *OCP Comments:*

*On March 16, 2009, approximately six months after the study, the unused study drugs were returned to the study co-sponsor. The lot numbers for both unused BUP 450 XL 450 mg ER tablets and Wellbutrin XL 150 mg tablets are matched to those in the study report, and are therefore the products used in the study.*

*Further, the samples were placed in the storage facility of co-sponsor for continuous temperature and humidity monitoring.*

*The issue is unlikely to affect the study results.*

2. Failure to perform sufficient assessments of Incurred Sample Reproducibility (ISR). Only 2.78% (39/1405) of bupropion and its metabolite samples were reanalyzed for ISR.

As cited in the above 483 observation, the SOP for ISR at the time when the study was conducted was not adequate. However, (b)(4) has now revised their SOP (effective January 2, 2009) to address the sample size issue by requiring (b)(4) of study samples to be re-assayed. Moreover, a review of the ISR data obtained by (b)(4) previously from 39 subject samples shows that the original and repeat data are similar, suggesting significant ISR problem is unlikely.

### *OCP Comments:*

*This is acceptable and is unlikely to affect the study results.*

3. Pipettes are calibrated only once every three months. There is no other procedure employed to check the accuracy of the pipettes during the entire three-month period, which would include the study period.

Per the current SOP, the performance of pipettes will not be checked at anytime other than the calibration performed once in every 3 months. During the inspection close out meeting, (b)(4) acknowledged this observation and agreed to revise the current SOP to address this issue.

*OCP Comments:*

*The issue is unlikely to affect the study results.*

4. Raw data sheets and the analytical study reports were not always documented correctly and/or accurately. For example:

- A. Corrections on raw data entry sheets were not signed and dated in several occasions.
- B. Failure to provide the reason for corrections/strike-outs in the data entry sheets.
- C. Hemolyzed samples were not mentioned or discussed in the analytical study reports, even though sample processing and study update records recorded a large number of hemolyzed study samples.

(b)(4) acknowledged their mistakes in raw data sheets and their failure to report the number of hemolyzed samples in the analytical report submitted to the FDA. DSI confirmed during the inspection that (b)(4) had conducted validation experiment using hemolyzed samples. The results showed that hemolyzed samples did not affect the precision and accuracy of the analytical method.

*OCP Comments:*

*The issue is unlikely to affect the study results.*

## 5.2. Study No. S08-0027 (Food effect study)

### A Food Effects Study of 450 mg Bupropion HCl Extended-Release Tablet (BUP-450) and 3 x 150 mg Wellbutrin XL® Extended-Release Tablets in Two Cohorts

#### Study information

*Protocol Number:* S08-0027

*Investigator:*

Principal Investigator: Jeffrey P. Ciaramita, M.D.

*Study site:*

Cetero Research  
400 Fountain Lakes Blvd.  
St. Charles, MO 63301

*Analytical facility:*

 (b) (4)

*Study dates:* March 18, 2008 to May 4, 2008 (date of first dose to date of last blood collection)

#### Objectives

To determine and compare in male and female subjects the rate and extent of absorption of bupropion from a single dose of the following products under fasting and fed conditions for:

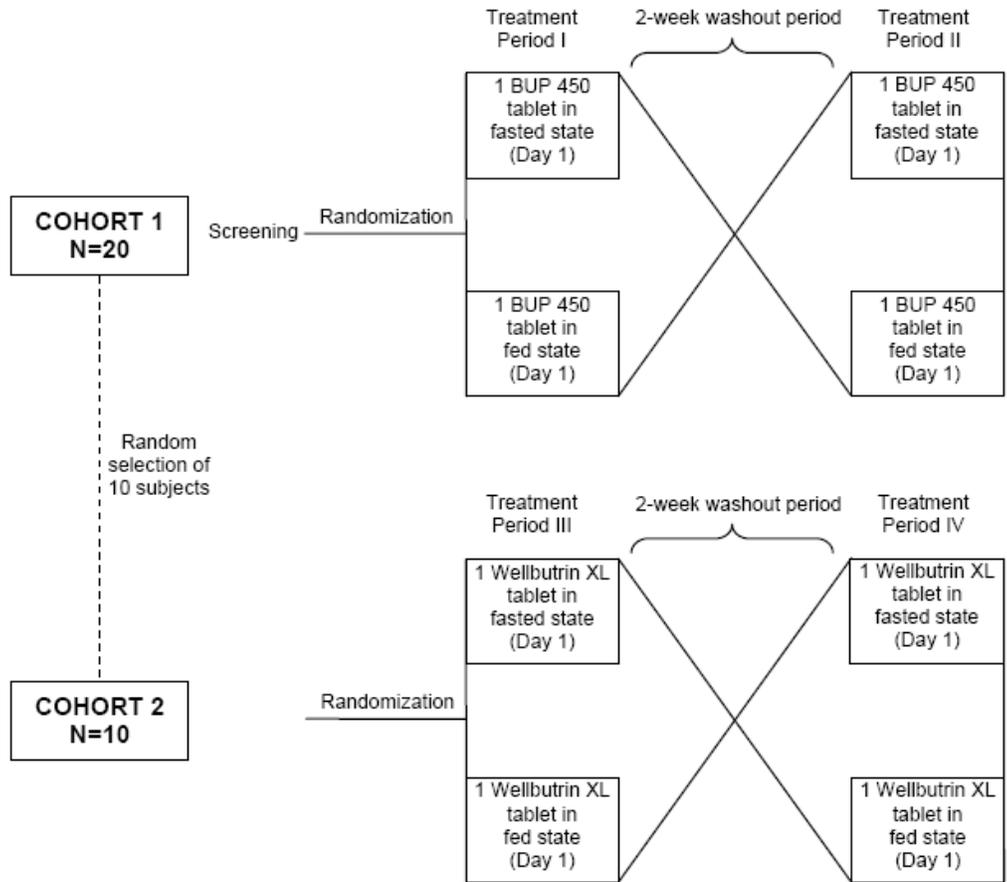
- Bupropion HCl 450 mg ER tablets (BUP-450) in a group of 20 subjects (Cohort 1);
- Wellbutrin XL® 150 mg tablets (3x150 mg) given as a single dose, in a subgroup of 10 subjects from Cohort 1 (Cohort 2).

#### Study Design

This was a randomized, single-dose, open-label, four-period, two-treatment crossover study under fasted and fed conditions comparing equal doses of a test and a reference product.

During Periods I and II, only the test product, bupropion HCl 450 mg extended-release (ER) tablet was administered. Twenty (20) subjects were randomized to receive one tablet of Bupropion HCl 450 mg ER in a fasted or fed state. Subjects dosed in the fasted state for Period I, were dosed in the fed state for Period II, and subjects dosed in the fed state for Period I were dosed in the fasted state for Period II.

After completion of Periods I and II, 10 subjects (5 males and 5 females) from Cohort 1 were randomly chosen to participate in Periods III and IV of this study. During treatment Periods III and IV only the reference product, Wellbutrin XL®, was administered. Five (5) subjects received Wellbutrin XL® (3 x 150 mg) in the fasted state and five (5) subjects received Wellbutrin XL® (3 x 150 mg) in the fed state for Period III. The subjects dosed in the fasted state for Period III were dosed in the fed state for Period IV and the subjects dosed in the fed state for Period III were dosed in the fasted state for Period IV. The dose of Wellbutrin XL® for Periods III and IV was 3 tablets of 150 mg administered as a single dose (total dose = 450 mg). The study design is summarized in the scheme below:



*Reviewer's comments:*

*The composition of the high fat meal follows the food-effect BA/fed BE guidance and is acceptable.*

Study Medication

**Test Treatment (Cohort 1)**

Drug Product Name: Bupropion HCl

Lot Number: 07040P-02

Manufacturer: (b) (4)

Manufacture Date: 12/07

Dosage Form Description: Extended-Release Tablet  
Dosage Per Unit: 1 x 450 mg  
Cumulative Maximal Dosage: 450 mg

**Reference Treatment (Cohort 2)**

Drug Product Name: Wellbutrin XL®  
Lot Number: P08B016  
Manufacturer: (b) (4) GlaxoSmithKline  
Expiration Date: 07/09  
Dosage Form Description: Extended-Release Tablet  
Dosage Per Unit: 3 x 150 mg  
Cumulative Maximal Dosage: 450 mg

*PK Sampling*

During each study period, 18 blood samples (10 mL each) were collected within 90 minutes prior to administration of study product to the first study participant (0 hour) and after dose administration at study hours 1, 2, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 36, 48, 72, 96, and 120.

*PK Data Analysis*

The standard non-compartment model was used to calculate the following pharmacokinetic parameters for bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion, and PAWC:  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $AUC_{0-t}/AUC_{0-inf}$ ,  $C_{max}$ ,  $T_{max}$ ,  $K_{el}$ ,  $T_{1/2}$ .

Plasma samples from 18 subjects in Cohort 1 were assayed for bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion. Plasma samples from nine (9) subjects in Cohort 2 were assayed for bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion.

*Statistical Data Analysis*

Analyses of variance (ANOVA) were performed on the ln-transformed pharmacokinetic parameters  $AUC_{0-t}$ ,  $AUC_{0-inf}$  and  $C_{max}$ . The ANOVA model included sequence, formulation and period as fixed effects and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term. A 10% level of significance was used to test the sequence effect. Each analysis of variance included calculation of least squares means, the difference between adjusted formulation means and the standard error associated with this difference. The above statistical analyses were done using the appropriate SAS® procedure.

In agreement with the two one-sided test for bioequivalence<sup>1</sup>, 90% confidence intervals for the difference between drug formulation least-squares means (LSM) were calculated for the parameters  $AUC_{0-t}$ ,  $AUC_{0-inf}$  and  $C_{max}$  using ln-transformed data. The confidence intervals were expressed as a percentage relative to the LSM of the reference formulation.

Safety Assessments

Physical examination, vital signs, ECGs, and clinical laboratory tests were performed and evaluated to assess subject safety. All reported adverse events and serious adverse events were collected and evaluated.

Bioanalytical Method

Plasma concentrations of bupropion, hydroxybupropion, threo-hydrobupropion, and erythro-hydrobupropion were measured using a validated HPLC/MS/MS method performed at (b) (4) Bupropion-d9, hydroxybupropion-d6, threo-hydroxybupropion-d9, and erythro-hydroxybupropion-d9 were used as internal standard. The 10-point calibration standard curves were constructed covering 2.5-500 ng/mL range for bupropion, 12.5- 2500 ng/mL range for hydroxybupropion, 8-1600 ng/mL range for threo-hydroxybupropion, and 4-800 ng/mL range for erythro-hydroxybupropion. Each calibration curve was calculated using a linear weighted regression, 1/concentration for bupropion and hydroxybupropion, and 1/concentration<sup>2</sup> for erythro-hydroxybupropion and threo-hydroxybupropion.

Precision and accuracy were evaluated by replicate analyses of human plasma quality control pools prepared at concentrations across the calibration range. The basic information of assay validation for the study is summarized in the table below:

**Table 1.** Assay Validation for Study No. S08-0027

	<b>Bupropion</b>	<b>Hydroxy-bupropion</b>	<b>Threohydro-bupropion</b>	<b>Erythrohydro-bupropion</b>
<b>Method</b>	HPLC/MS/MS	HPLC/MS/MS	HPLC/MS/MS	HPLC/MS/MS
<b>Standard curve</b>				
Range:	2.5 – 500 ng/mL	12.5 – 2500 ng/mL	8 – 1600 ng/mL	4 – 800 ng/mL
Precision:	2.1 - 6.2%	2.4 – 7.3%	1.4 – 5.3%	1.1 – 5.4%
Accuracy:	-6 - 3%	-2.4 – 2.6%	-5.6 – 3.8%	-3.6 – 3.1%
Linearity:	r <sup>2</sup> ≥0.995	r <sup>2</sup> ≥0.996	r <sup>2</sup> ≥0.993	r <sup>2</sup> ≥0.997
<b>LOQ</b>				
LLOQ	2.5 ng/mL	12.5 ng/mL	8 ng/mL	4 ng/mL
<b>QC</b>				
QC1	7.5 ng/mL	37.6 ng/mL	24 ng/mL	12 ng/mL
Precision	5%	8.7%	4%	5%
Accuracy	1.2%	0.8%	2.5%	-0.8%
QC2	35 ng/mL	175 ng/mL	112 ng/mL	56 ng/mL
Precision	6%	5.7%	6.5%	6.7%
Accuracy	0.6%	-1.7%	0	-2.3%
QC3	125 ng/mL	626 ng/mL	400 ng/mL	200 ng/mL
Precision	6.5%	9.2%	5.9%	6%
Accuracy	1.6%	-1.9%	1%	0
QC4	376 ng/mL	1880 ng/mL	1200 ng/mL	600 ng/mL
Precision	3.3%	2.6%	2.6%	2.4%
Accuracy	1.6%	1.6%	-3.3%	-0.3%

(Ref: Module 5.3.1.4.1)

Performance measures of bupropion and its active metabolites are also summarized in the table below:

	<b>Bupropion</b>	<b>Hydroxy-bupropion</b>	<b>Threohydro-bupropion</b>	<b>Erythrohydro-bupropion</b>
Standard curve range	2.5 – 500 ng/mL (weighted 1/x, $r^2 \geq 0.9995$ )	12.5 – 2500 ng/mL (weighted 1/x, $r^2 \geq 0.996$ )	8 – 1600 ng/mL (weighted 1/x <sup>2</sup> , $r^2 \geq 0.993$ )	4 – 800 ng/mL (weighted 1/x <sup>2</sup> , $r^2 \geq 0.997$ )
QC sample concentrations	7.5, 35, 125, and 376 ng/mL	37.6, 175, 626, and 1880 ng/mL	24, 112, 400, and 1200 ng/mL	12, 56, 200, and 600 ng/mL
Precision (%)	Intra-day: 1.9-13.4 Inter-day: 3.2-7.7	Intra-day: 1.6-9.8 Inter-day: 3.2-9.3	Intra-day: 2.3-7.6 Inter-day: 3.5-7.9	Intra-day: 2.4-14.1 Inter-day: 3.8-8.6
Accuracy (%)	Intra-day: 0.4-4.8 Inter-day: 0.3-6.8	Intra-day: -2.4-1.6 Inter-day: -4-0.6	Intra-day: -4.4-2.3 Inter-day: -5.6-2.3	Intra-day: -13-1.5 Inter-day: -3.6-5.3
Internal standard	Bupropion-d9 Lot number: 1031-021A1	hydroxybupropion-d6 Lot number: 1010-028A1	threohydroxybupropion-d9 Lot number: 1010-076A3	erythrohydroxybupropion-d9 Lot number: 2-SWS-94-2
Reference standard	Bupropion Lot number: 1031-220A1 Purity: >98%	Hydroxybupropion Lot number: 1032-180A1 Purity: >98%	Threhydrobupropion Lot number: 1034-119A1 Purity: >98%	Erythrohydrobupropion Lot number: 1010-096A4 Purity: >98%
Specificity	No interference			
Recovery	78% Internal Standard: 83%	74% Internal Standard: 77%	83% Internal Standard: 88%	82% Internal Standard: 86%
Matrix	Human Plasma			
Stability (in human plasma)	Room Temperature (RT): 15 h Freeze-thaw: 5 FT cycles			

*Reviewer's comments:*

*The bioanalytical method employed in this study met the criteria set by the 'Guidance for Industry: Bioanalytical Method Development' and is acceptable.*

**Study Results**

*Subject Demographics*

A total of 20 subjects (Cohort 1) were enrolled in the study, 8 males and 12 females. A total of 18 subjects completed Periods I and II of the study. Two subjects were withdrawn from the study after receiving one dose of the study drug. Subject No. 06, (b)(6), (44 years old; female) was withdrawn from the study due to vomiting 7.75 hours after receiving one dose of BUP-450 in the fasted condition. Subject No. 10, (b)(6), (26 years old; male) dropped out of the study due to transportation issues after receiving one dose of BUP 450 in the fed condition.

After completion of Periods I and II, 10 subjects from Cohort 1 were randomly chosen to participate in Periods III and IV of this study. A total of nine (9) subjects completed Periods III and IV of the study. One subject was withdrawn from the study after receiving one dose of study drug in the fed condition. This subject, No. 09, (b)(6) (20 years old; male) was withdrawn due to missing all five (5) return blood draws.

Subject dispositions for Cohort 1 and Cohort 2 are summarized below:

**Table 10.2 Summary of Subject Disposition – Cohort No. 1**

	Sequence		Total
	Fast-Fed	Fed-Fast	
Subjects Randomized	10	10	20
Subjects Successfully Completed	9	9	18
Subjects Who Withdrew Consent <sup>a</sup>	0	1	1
Subjects Discontinued <sup>b</sup>	1	0	1

Reference: Appendix 16.2.1

<sup>a</sup>: Withdrew consent due to transportation issues

<sup>b</sup>: Discontinued due to AE of vomiting

**Table 10.3 Summary of Subject Disposition – Cohort No. 2**

	Sequence		Total
	Fast-Fed	Fed-Fast	
Subjects Randomized	5	5	10
Subjects Successfully Completed	5	4	9
Subjects Who Withdrew Consent	0	0	0
Subjects Discontinued <sup>a</sup>	0	1	1

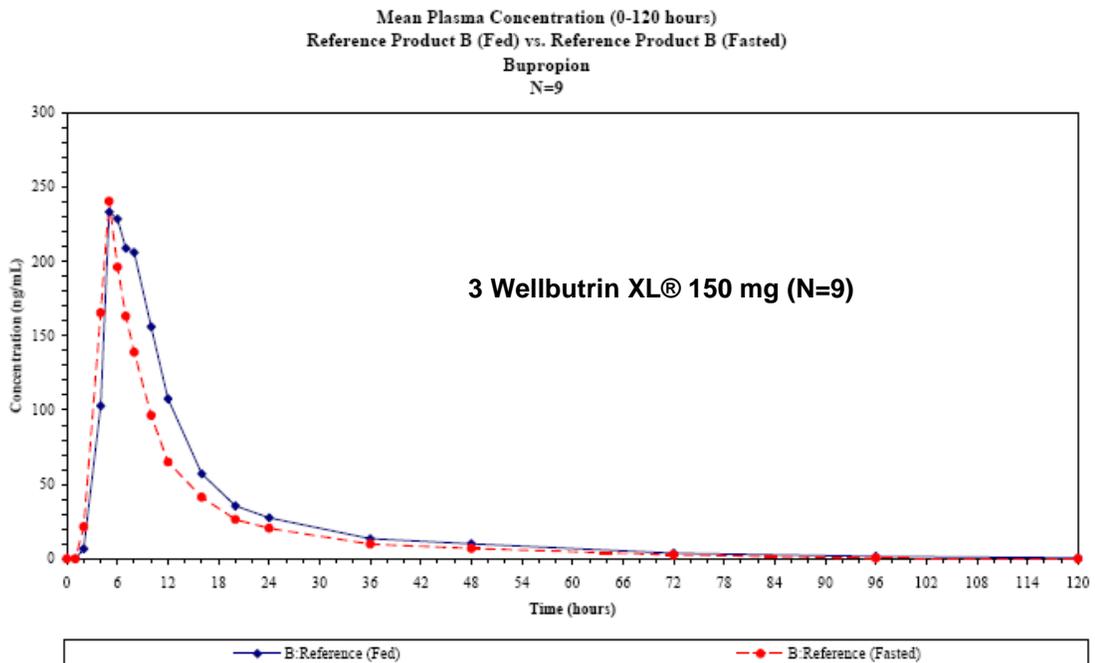
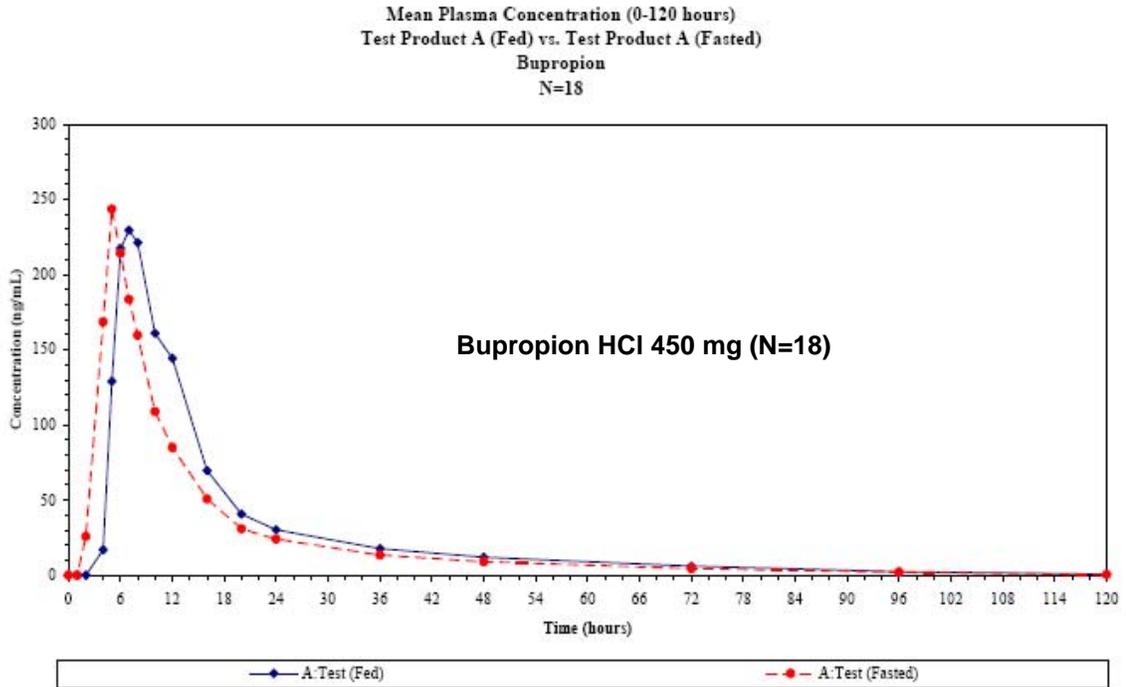
Reference: Appendix 16.2.1

<sup>a</sup>: Discontinued due to missing all 5 return blood draws

PK and Statistical Results

**(A) PK of bupropion:**

- Mean bupropion plasma concentrations following Bupropion HCl 450 mg and 3 Wellbutrin XL® 150 mg tablets under fasted and fed conditions are shown below, respectively:



- Mean PK parameters for bupropion following Bupropion HCl 450 mg (Test Product A) and 3 Wellbutrin XL® 150 mg (Reference Product B) tablets under fasted and fed conditions are summarized below:

**Table 11.5 Summary Statistics by Treatment Arm and Pharmacokinetic Parameter for Bupropion:**

Parameter (units)	Arithmetic Mean (%CV) Median (Range) for T <sub>max</sub>			
	Test Product A Fasted (N=18)	Test Product A Fed (N=18)	Reference Product B Fasted (N=9)	Reference Product B Fed (N=10)
AUC <sub>0-t</sub> (ng·hr/mL)	2591.60 (35.72)	2948.59 (32.54)	2184.61 (14.98)	2800.64 (33.26)
AUC <sub>0-inf</sub> (ng·hr/mL)	2708.42 (35.09)	3093.64 (31.47)	2280.76 (14.05)	2907.81 (32.27)
AUC <sub>0-t</sub> /AUC <sub>0-inf</sub>	0.95 (1.77)	0.95 (3.94)	0.96 (1.94)	0.96 (1.21)
C <sub>max</sub> (ng/mL)	258.11 (23.85)	344.44 (45.50)	256.33 (20.09)	236.60 (52.71)
T <sub>max</sub> (hr)	5 (4-7)	7.5 (5-12)	5 (4-8)	6 (5-10)
Kel (1/hr)	0.0399 (54.70)	0.0390 (59.11)	0.0461 (47.22)	0.0457 (58.65)
T <sub>1/2</sub> (hr)	21.22 (39.15)	21.87 (38.04)	17.84 (39.81)	19.53 (46.16)

Reference Tables 14.2.5-14.2.8

*Reviewer's comments: The variability of C<sub>max</sub> is large (CV ~46%) for bupropion following administration of Bupropion HCl 450 mg (Test Product A) under fed conditions.*

- For Bupropion HCl 450 mg (BUP-450), food significantly increased C<sub>max</sub> and AUC of bupropion by ~25% and ~15%, respectively. The results of statistical analysis for bupropion PK following Bupropion HCl 450 mg tablet (BUP-450) under fasted and fed conditions are summarized below:

PK Variable	Ln-Transformed Data								
	Least Squares Mean		Geometric Mean		% Ratio	90% Confidence Interval (Lower Limit, Upper Limit)	P-values for Product Effects	Power of ANOVA	ANOVA % CV
	Test-Fed	Test-Fast	Test-Fed	Test-Fast					
C <sub>max</sub>	5.749	5.525	313.80	250.91	125.07	(107.51, 145.49)	0.0201	0.6768	26.44
AUC <sub>0-t</sub>	7.943	7.805	2815.85	2453.23	114.78	(104.64, 125.9)	0.0192	0.9767	15.99
AUC <sub>0-inf</sub>	7.995	7.851	2965.66	2568.79	115.45	(105.07, 126.86)	0.0171	0.9723	16.30

PK Variable	Non-Transformed Data						
	Least Squares Mean			% Ratio	90% Confidence Interval (Lower Limit, Upper Limit)	P-values for Product Effects	Power of ANOVA
	Ref-Fed	Ref-Fast					
T <sub>max</sub>	6.25	5.40	115.74	(85.64, 145.84)	0.3548	0.1938	
Kel	0.0468	0.0465	100.51	(90.32, 110.7)	0.9270	0.8882	
T <sub>1/2</sub>	19.34	17.84	108.40	(95.93, 120.87)	0.2424	0.7414	

For Wellbutrin XL, food “significantly” decreased C<sub>max</sub> and increased AUC of bupropion. The results of statistical analysis for bupropion PK following

Wellbutrin XL (3X150 mg) under fasted and fed conditions are summarized below:

Ln-Transformed Data									
PK Variable	Least Squares Mean		Geometric Mean		% Ratio	90% Confidence Interval (Lower Limit, Upper Limit)	P-values for Product Effects	Power of ANOVA	ANOVA % CV
	Ref-Fed	Ref-Fast	Ref-Fed	Ref-Fast					
$C_{max}$	5.430	5.513	228.15	247.77	92.08	(64.6, 131.26)	0.6727	0.1788	41.04
$AUC_{0-t}$	7.908	7.677	2718.01	2157.22	126.00	(99.99, 158.76)	0.1001	0.3526	26.15
$AUC_{0-inf}$	7.947	7.721	2825.71	2255.09	125.30	(100.1, 156.85)	0.0987	0.3697	25.38

Non-Transformed Data							
PK Variable	Least Squares Mean			% Ratio	90% Confidence Interval (Lower Limit, Upper Limit)	P-values for Product Effects	Power of ANOVA
	Ref-Fed	Ref-Fast					
$C_{max}$	251.65	253.78	99.16	(61.11, 137.22)	0.9679	0.1391	
$AUC_{0-t}$	2851.12	2177.26	130.95	(102.24, 159.66)	0.0805	0.2083	
$AUC_{0-inf}$	2957.68	2273.75	130.08	(102.4, 157.76)	0.0785	0.2205	
$T_{max}$	6.25	5.40	115.74	(85.64, 145.84)	0.3548	0.1938	
Ke1	0.0468	0.0465	100.51	(90.32, 110.7)	0.9270	0.8882	
$T_{1/2}$	19.34	17.84	108.40	(95.93, 120.87)	0.2424	0.7414	

*Reviewer's comments:*

*The administration of 450 mg bupropion (BUP-450) with food significantly increased  $C_{max}$  and AUC of bupropion by ~25% and ~15%, respectively. There is a food effect on exposure to bupropion when BUP-450 is given with a high fat meal.*

*In the current study, for reference product (3x Wellbutrin XL® 150 mg), food decreased  $C_{max}$  of bupropion by ~8% and increased AUC of bupropion by ~25%.*

*In NDA21-515 (Wellbutrin XL), food decreased  $C_{max}$  of bupropion by 8% and increased AUC of bupropion by 10%, which did not show statistical difference between fasted and fed conditions.*

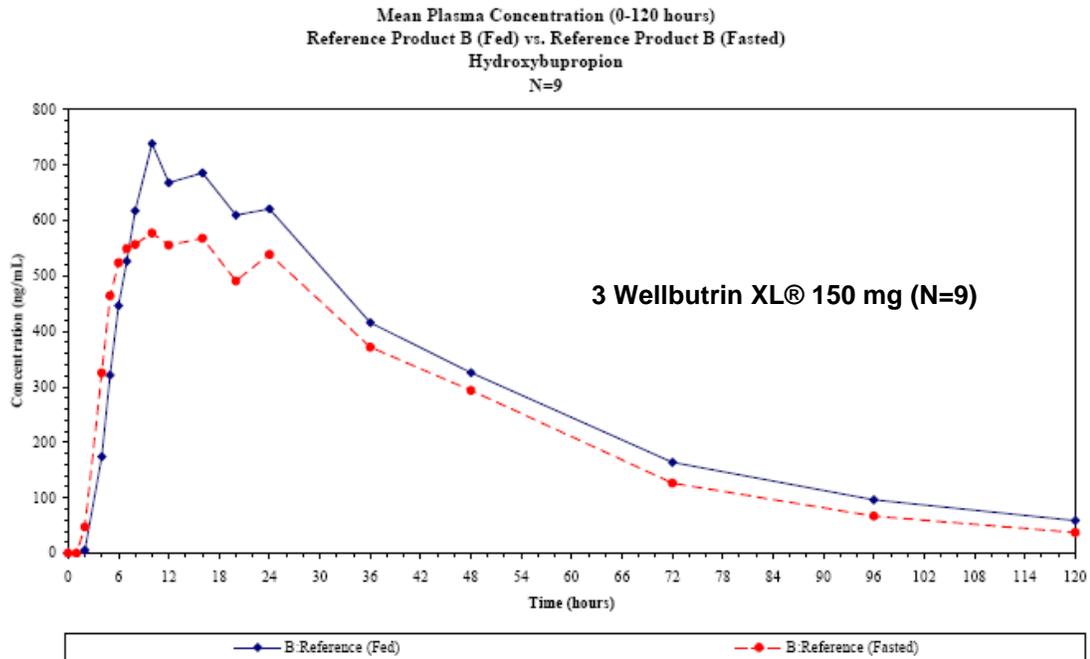
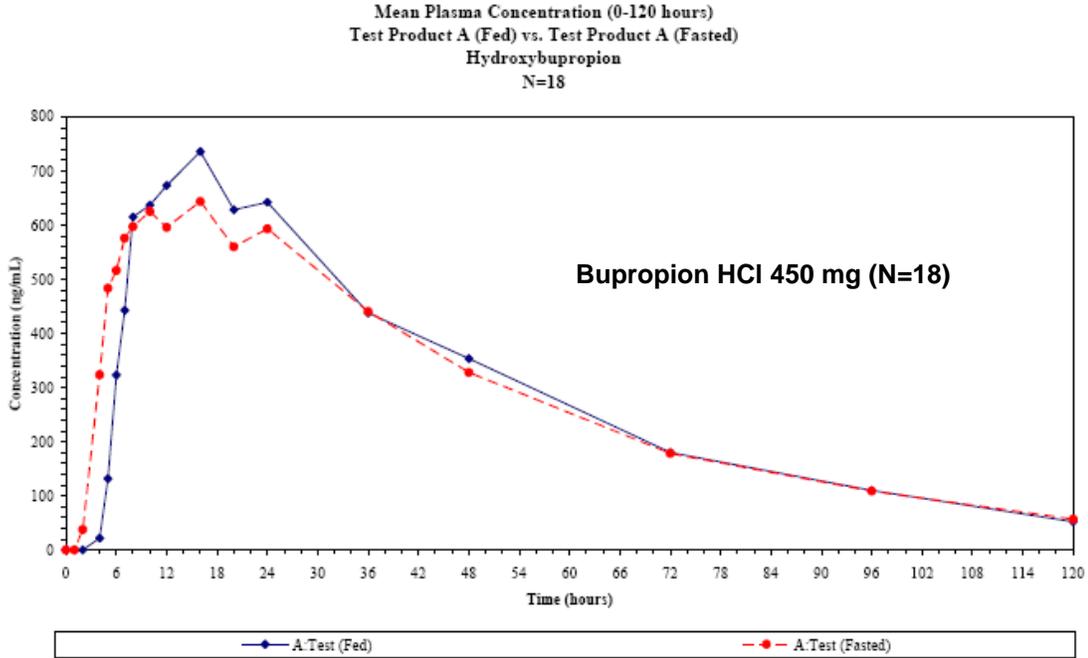
*Individual data for  $C_{max}$  of bupropion under fasted and fed conditions after administration of 450-mg Cary's BUP 450 XL in the study were analyzed by OCP:*

*67% of subjects (12 out of 18 subjects) showed that food increased  $C_{max}$  by >1 fold. In these 12 subjects, 2 subjects showed that food increased  $C_{max}$  by >2 fold (2.19 fold for Subject 11 and 2.75 fold for Subject 17); 4 subjects showed that food increased  $C_{max}$  by >1.5 fold but < 2 fold. Three subjects were > 1.2 fold and < 1.5 fold; remaining 3 subjects were <1.1 fold.*

*Two-fold increase of  $C_{max}$  is equivalent to a dose of "900 mg", 1.5-fold increase of  $C_{max}$  is equivalent to a dose of "675 mg", and 1.2-fold increase of  $C_{max}$  is equivalent to a dose of "540 mg". The detailed information can be found in the Appendix following Section 5.2 (the food effect study review).*

**(B) PK of hydroxy-bupropion:**

- Mean hydroxy-bupropion plasma concentrations following Bupropion HCl 450 mg (BUP-450) and 3 Wellbutrin XL® 150 mg tablets under fasted and fed conditions are shown below, respectively



- Mean PK parameters for hydroxy-bupropion following Bupropion HCl 450 mg (BUP-450) (Test Product A) and 3 Wellbutrin XL® 150 mg

(Reference Product B) tablets under fasted and fed conditions are summarized below:

**Table 11.6 Summary Statistics by Treatment Arm and Pharmacokinetic Parameter for Hydroxybupropion:**

Parameter (units)	Arithmetic Mean (%CV)			
	Median (Range) for T <sub>max</sub>			
	Test Product A Fasted (N=18)	Test Product A Fed (N=18)	Reference Product B Fasted (N=9)	Reference Product B Fed (N=10)
AUC <sub>0-t</sub> (ng·hr/mL)	33987.44 (37.71)	34867.96 (31.61)	29094.95 (46.84)	33868.77 (42.66)
AUC <sub>0-inf</sub> (ng·hr/mL)	37004.27 (39.41)	37377.03 (32.70)	30844.11 (48.74)	36971.76 (50.25)
AUC <sub>0-t</sub> /AUC <sub>0-inf</sub>	0.93 (5.39)	0.94 (5.24)	0.95 (2.88)	0.93 (5.69)
C <sub>max</sub> (ng/mL)	722.61 (29.47)	819.11 (33.57)	667.33 (38.87)	790.70 (41.01)
T <sub>max</sub> (hr)	14 (7-24)	12 (6-16.03)	8.02 (5-24)	11 (10-24)
Kel (1/hr)	0.0267 (20.36)	0.0274 (23.83)	0.0291 (24.08)	0.0262 (24.65)
T <sub>1/2</sub> (hr)	26.95 (20.07)	26.73 (24.80)	25.29 (27.23)	28.45 (33.91)
Reference Tables 14.2.37-14.2.40				

- There is no statistically significant difference between fasted and fed conditions for systemic exposure of hydroxy-bupropion. The results of statistical analysis for hydroxy-bupropion PK following Bupropion HCl 450 mg tablet (BUP-450) under fasted and fed conditions are summarized below:

PK Variable	Ln-Transformed Data								
	Least Squares Mean		Geometric Mean		% Ratio	90% Confidence Interval (Lower Limit, Upper Limit)	P-values for Product Effects	Power of ANOVA	ANOVA % CV
	Test-Fed	Test-Fast	Test-Fed	Test-Fast					
C <sub>max</sub>	6.645	6.535	769.22	688.74	111.69	(101.39, 123.03)	0.0634	0.9653	16.74
AUC <sub>0-t</sub>	10.403	10.360	32954.46	31570.61	104.38	(95.42, 114.19)	0.4167	0.9823	15.53
AUC <sub>0-inf</sub>	10.469	10.438	35217.28	34135.03	103.17	(93.33, 114.05)	0.5941	0.9540	17.35

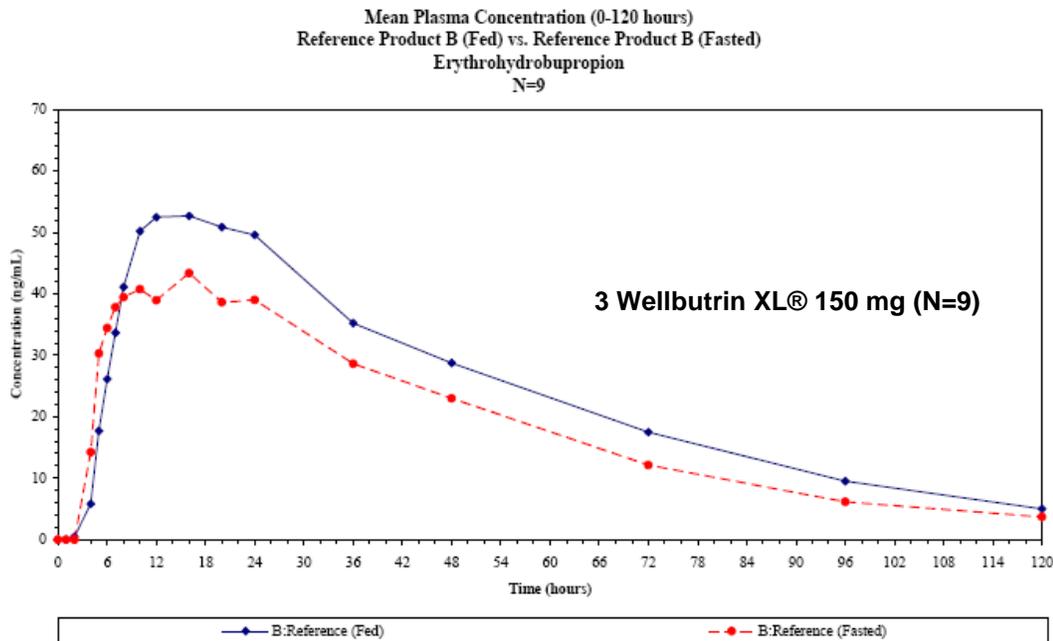
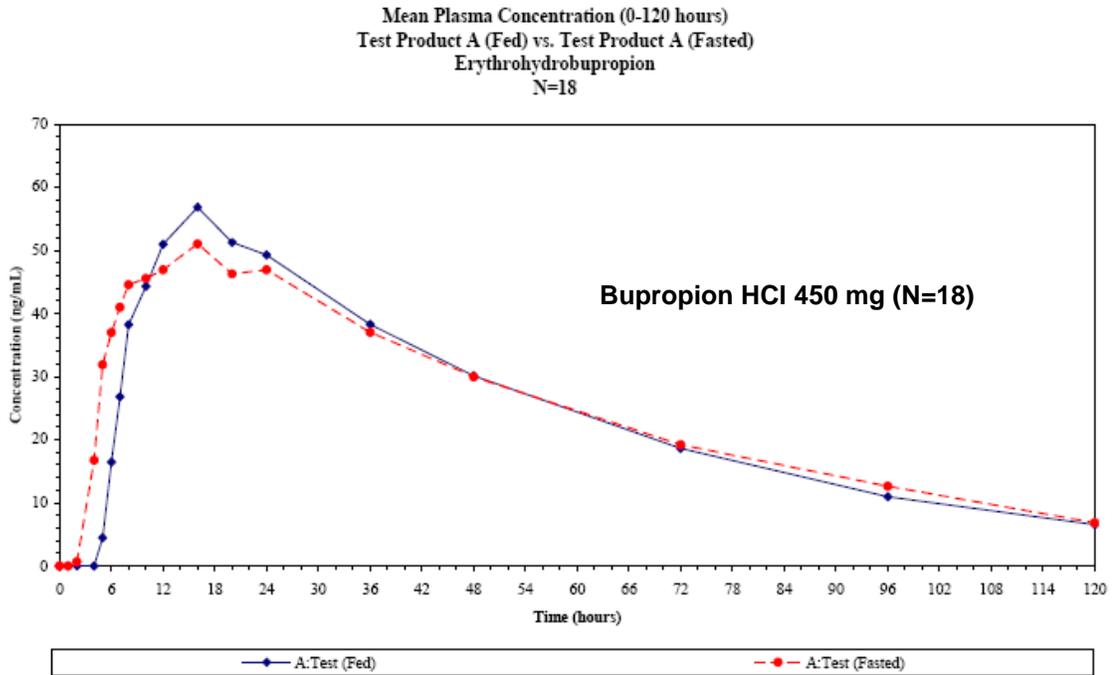
PK Variable	Non-Transformed Data						
	Least Squares Mean			% Ratio	90% Confidence Interval (Lower Limit, Upper Limit)	P-values for Product Effects	Power of ANOVA
	Test-Fed	Test-Fast	Test-Fast				
T <sub>max</sub>		11.78	14.22	82.82	(61.37, 104.27)	0.1812	0.3341
Kel		0.0274	0.0267	102.54	(94.98, 110.09)	0.5661	0.9911
T <sub>1/2</sub>		26.73	26.95	99.19	(92.18, 106.19)	0.8422	0.9966

*Reviewer's comments:*

*The administration of 450 mg bupropion (BUP-450) with food increased C<sub>max</sub> (~12%) and AUC (~3%) of hydroxybupropion.*

**(C) PK of erythrohydrobupropion:**

- Mean erythrohydrobupropion plasma concentrations following Bupropion HCl 450 mg (BUP-450) and 3 Wellbutrin XL® 150 mg tablets under fasted and fed conditions are shown below, respectively



- Mean PK parameters for erythrohydrobupropion following Bupropion HCl 450 mg (BUP-450) (Test Product A) and 3 Wellbutrin XL® 150 mg (Reference Product B) tablets under fasted and fed conditions are summarized below:

**Table 11.8 Summary Statistics by Treatment Arm and Pharmacokinetic Parameter for Erythrohydrobupropion:**

Parameter (units)	Arithmetic Mean (%CV) Median (Range) for T <sub>max</sub>			
	Test Product A Fasted (N=18)	Test Product A Fed (N=18)	Reference Product B Fasted (N=9)	Reference Product B Fed (N=10)
	AUC <sub>0-t</sub> (ng·hr/mL)	2962.31 (43.27)	2995.38 (44.75)	2246.32 (52.97)
AUC <sub>0-inf</sub> (ng·hr/mL)	3547.92 (46.88)	3420.72 (45.07)	2567.42 (49.01)	3143.52 (33.92)
AUC <sub>0-t</sub> /AUC <sub>0-inf</sub>	0.85 (8.69)	0.88 (7.62)	0.85 (11.61)	0.91 (3.34)
C <sub>max</sub> (ng/mL)	52.96 (30.92)	59.87 (36.29)	45.44 (35.92)	56.87 (31.81)
T <sub>max</sub> (hr)	16 (7-36)	16 (7-24)	16 (7-24)	16 (12-24)
Kel (1/hr)	0.0207 (28.22)	0.0230 (32.60)	0.0238 (23.96)	0.0249 (26.07)
T <sub>1/2</sub> (hr)	35.70 (25.00)	32.97 (31.66)	30.48 (21.47)	29.57 (24.79)

Reference Tables 14.2.101-14.2.104

- There is no statistically significant difference between fasted and fed conditions for systemic exposure of erythrohydrobupropion. The results of statistical analysis for erythrohydrobupropion PK following Bupropion HCl 450 mg tablet (BUP-450) under fasted and fed conditions are summarized below:

PK Variable	Ln-Transformed Data								
	Least Squares Mean		Geometric Mean		% Ratio	90% Confidence Interval (Lower Limit, Upper Limit)	P-values for Product Effects	Power of ANOVA	ANOVA % CV
	Test-Fed	Test-Fast	Test-Fed	Test-Fast					
C <sub>max</sub>	4.044	3.923	57.04	50.55	112.83	(102.61, 124.07)	0.0412	0.9704	16.42
AUC <sub>0-t</sub>	7.923	7.897	2761.31	2689.09	102.69	(90.71, 116.24)	0.7138	0.8388	21.54
AUC <sub>0-inf</sub>	8.058	8.065	3157.70	3182.27	99.23	(88.2, 111.63)	0.9100	0.8736	20.45

PK Variable	Non-Transformed Data						
	Least Squares Mean			% Ratio	90% Confidence Interval (Lower Limit, Upper Limit)	P-values for Product Effects	Power of ANOVA
	Test-Fed	Test-Fast	Test-Fast				
T <sub>max</sub>	14.45	14.78	97.76	(82.58, 112.93)	0.7995	0.5801	
Kel	0.0230	0.0207	111.07	(101.52, 120.62)	0.0600	0.9291	
T <sub>1/2</sub>	32.97	35.70	92.34	(83.8, 100.88)	0.1371	0.9694	

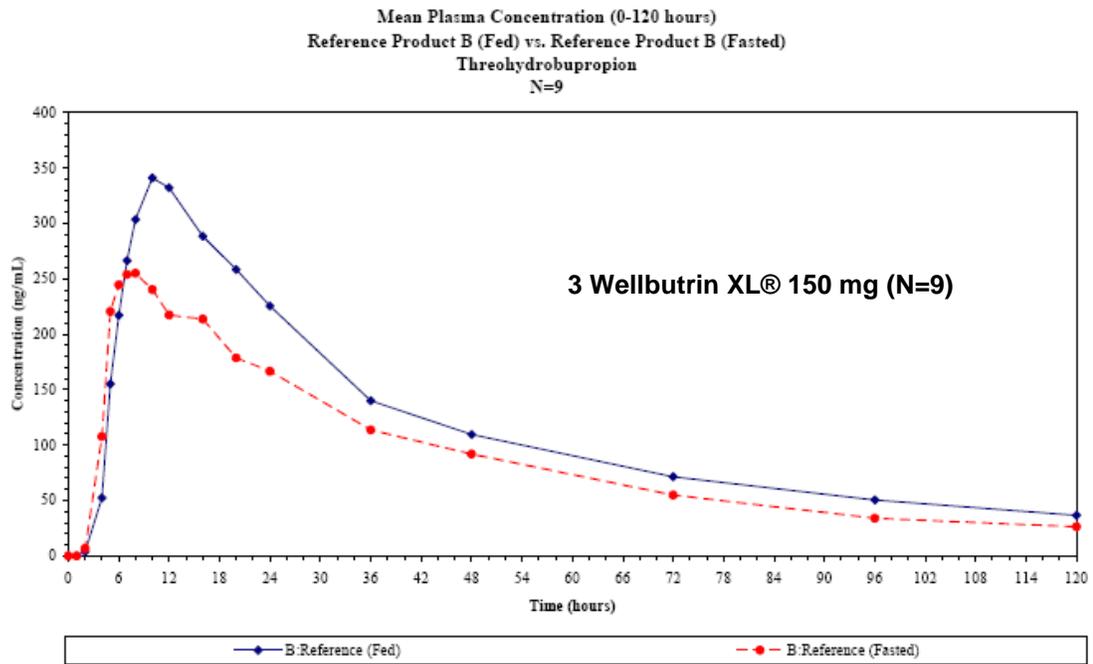
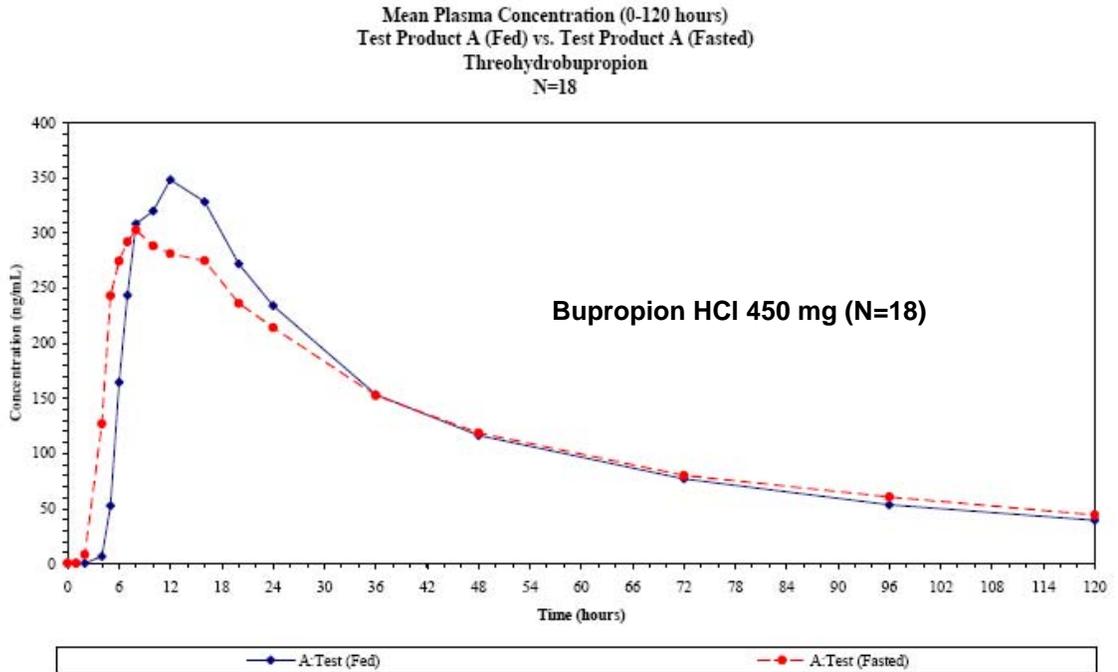
*Reviewer's comments:*

*Five values of AUC<sub>inf</sub> were excluded from the re-analysis due to >20% extrapolation ratio for the calculation. The re-analyzed % Ratio is 93.29 and 90% CI is 83.22-104.59.*

*The administration of 450 mg bupropion (BUP-450) with food increased C<sub>max</sub> (~13%), and decreased AUC (~7%) of erythrohydrobupropion.*

**(D) PK of threohydrobupropion:**

- Mean threohydrobupropion plasma concentrations following Bupropion HCl 450 mg (BUP-450) and 3 Wellbutrin XL® 150 mg tablets under fasted and fed conditions are shown below, respectively:



- Mean PK parameters for threohydrobupropion following Bupropion HCl 450 mg (BUP-450) (Test Product A) and 3 Wellbutrin XL® 150 mg (Reference Product B) tablets under fasted and fed conditions are summarized below:

**Table 11.7 Summary Statistics by Treatment Arm and Pharmacokinetic Parameter for Threohydrobupropion:**

Parameter (units)	Arithmetic Mean (%CV) Median (Range) for T <sub>max</sub>			
	Test Product A Fasted (N=18)	Test Product A Fed (N=18)	Reference Product B Fasted (N=9)	Reference Product B Fed (N=10)
	AUC <sub>0-t</sub> (ng·hr/mL)	14250.54 (41.39)	14602.76 (38.71)	10845.92 (41.64)
AUC <sub>0-inf</sub> (ng·hr/mL)	18316.99 (43.83)	17582.82 (36.04)	13032.23 (44.22)	16766.15 (26.54)
AUC <sub>0-t</sub> / AUC <sub>0-inf</sub>	0.79 (12.95)	0.83 (12.87)	0.85 (8.28)	0.83 (12.60)
C <sub>max</sub> (ng/mL)	317.78 (30.12)	414.83 (30.46)	272.00 (35.57)	351.70 (35.01)
T <sub>max</sub> (hr)	8 (5-16)	10 (6-16.03)	8 (5-24)	10 (8-16)
Kel (1/hr)	0.0148 (35.11)	0.0170 (38.75)	0.0168 (42.91)	0.0160 (36.79)
T <sub>1/2</sub> (hr)	53.91 (42.71)	46.50 (37.34)	47.25 (34.72)	49.05 (37.91)
Reference Tables 14.2.69-14.2.72				

- Food significantly increased C<sub>max</sub> of threohydrobupropion by ~31%. The results of statistical analysis for threohydrobupropion PK following Bupropion HCl 450 mg tablet (BUP-450) under fasted and fed conditions are summarized below:

Ln-Transformed Data									
PK Variable	Least Squares Mean		Geometric Mean		% Ratio	90% Confidence Interval (Lower Limit, Upper Limit)	P-values for Product Effects	Power of ANOVA	ANOVA % CV
	Test-Fed	Test-Fast	Test-Fed	Test-Fast					
C <sub>max</sub>	5.986	5.714	397.85	303.19	131.22	(118.45, 145.36)	0.0003	0.9462	17.72
AUC <sub>0-t</sub>	9.522	9.475	13650.66	13030.17	104.76	(93.86, 116.94)	0.4707	0.9138	19.06
AUC <sub>0-inf</sub>	9.716	9.718	16573.53	16616.12	99.74	(89.64, 110.98)	0.9670	0.9282	18.50

Non-Transformed Data							
PK Variable	Least Squares Mean			% Ratio	90% Confidence Interval (Lower Limit, Upper Limit)	P-values for Product Effects	Power of ANOVA
	Test-Fed	Test-Fast					
T <sub>max</sub>	10.56	10.33	102.17	(79.65, 124.68)	0.8687	0.3083	
Kel	0.0170	0.0148	115.25	(100, 130.51)	0.1001	0.5754	
T <sub>1/2</sub>	46.50	53.91	86.25	(71.1, 101.39)	0.1325	0.5814	

*Reviewer's comments:*

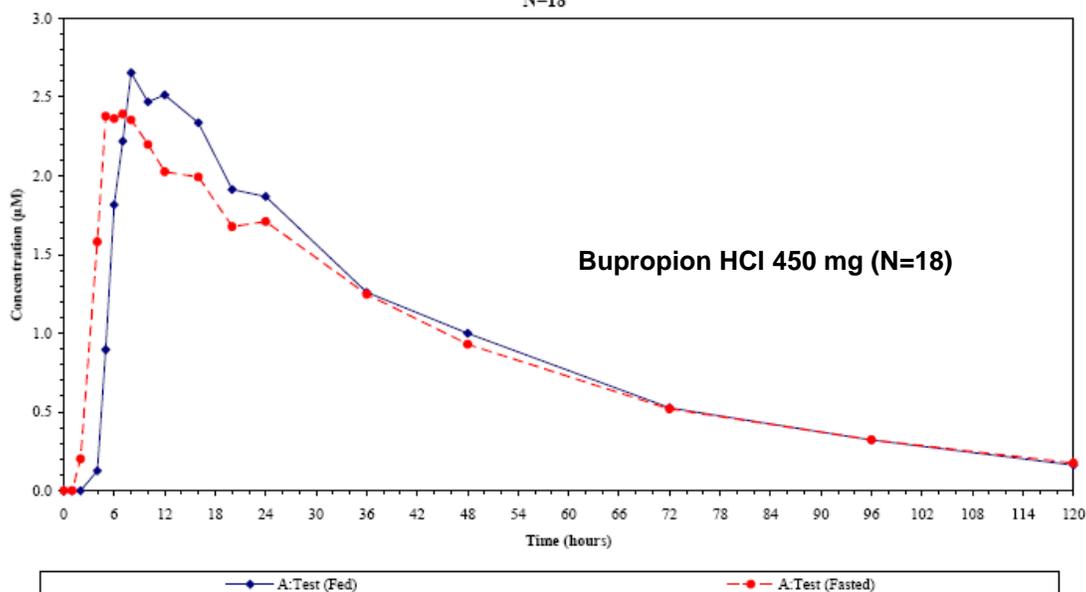
*Sixteen values of AUC<sub>inf</sub> were excluded from the re-analysis due to >20% extrapolation ratio for the calculation. The re-analyzed % Ratio is 99.98 and 90% CI is 86.32-115.79.*

*The administration of 450 mg bupropion (BUP-450) with food significantly increased  $C_{max}$  (~31%) of threohydrobupropion. AUC of threohydrobupropion was similar between fasted and fed conditions.*

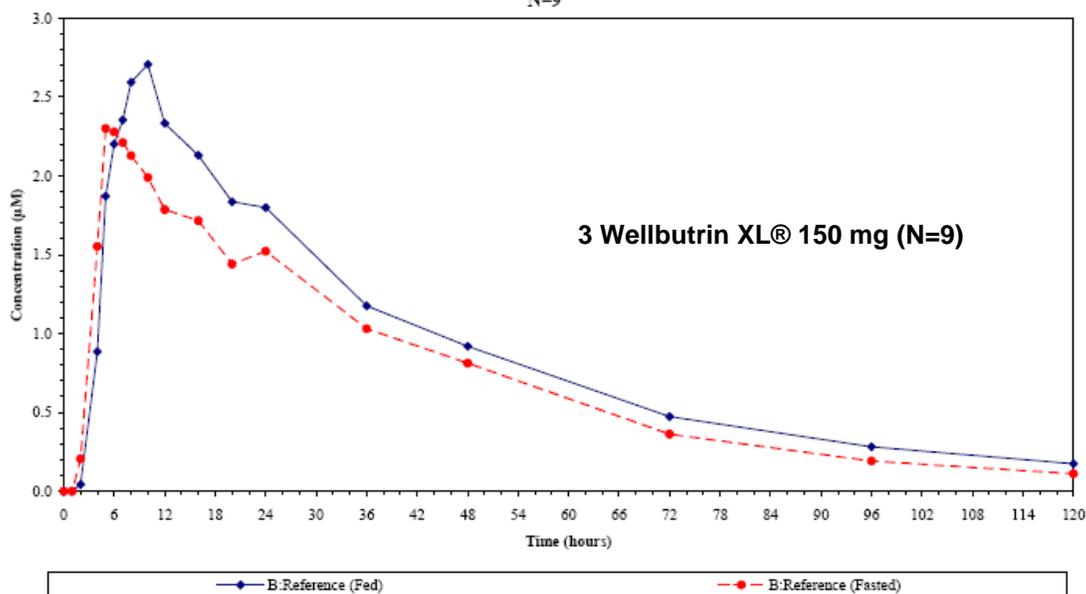
**(E) PK of PAWC:**

- Mean PAWC plasma concentrations following Bupropion HCl 450 mg (BUP-450) and 3 Wellbutrin XL® 150 mg tablets under fasted and fed conditions are shown below, respectively:

Mean Plasma Concentration (0-120 hours)  
 Test Product A (Fed) vs. Test Product A (Fasted)  
 PAWC  
 N=18



Mean Plasma Concentration (0-120 hours)  
 Reference Product B (Fed) vs. Reference Product B (Fasted)  
 PAWC  
 N=9



- Mean PK parameters for PAWC following Bupropion HCl 450 mg (Test Product A) and 3 Wellbutrin XL® 150 mg (Reference Product B) tablets under fasted and fed conditions are summarized below:

**Table 11.9 Summary Statistics by Treatment Arm and Pharmacokinetic Parameter for PAWC:**

Parameter (units)	Arithmetic Mean (%CV) Median (Range) for T <sub>max</sub>			
	Test Product A Fasted (N=18)	Test Product A Fed (N=18)	Reference Product B Fasted (N=9)	Reference Product B Fed (N=10)
	AUC <sub>0-t</sub> (μM·hr)	105.02 (32.84)	108.88 (27.32)	88.48 (37.88)
AUC <sub>0-inf</sub> (μM·hr)	114.88 (34.80)	116.72 (27.82)	93.66 (39.95)	114.02 (39.58)
AUC <sub>0-t</sub> / AUC <sub>0-inf</sub>	0.92 (5.50)	0.93 (5.00)	0.95 (2.98)	0.93 (4.51)
C <sub>max</sub> (μM)	2.60 (21.98)	3.45 (32.53)	2.55 (25.99)	2.85 (32.27)
T <sub>max</sub> (hr)	6 (5-12)	8 (5-16.03)	6 (5-24)	10 (8-12)
Kel (1/hr)	0.0251 (25.63)	0.0262 (24.97)	0.0276 (24.86)	0.0247 (23.87)
T <sub>1/2</sub> (hr)	29.21 (23.65)	27.81 (22.30)	26.57 (25.64)	29.72 (28.07)
Reference Tables 14.2.133-14.2.136				

- Food significantly increased C<sub>max</sub> of PAWC by ~29%. The results of statistical analysis for PAWC PK following Bupropion HCl 450 mg tablet (BUP-450) under fasted and fed conditions are summarized below:

Ln-Transformed Data									
PK Variable	Least Squares Mean		Geometric Mean			90% Confidence Interval (Lower Limit, Upper Limit)	P-values for Product Effects	Power of ANOVA	ANOVA % CV
	Test-Fed	Test-Fast	Test-Fed	Test-Fast	% Ratio				
C <sub>max</sub>	1.189	0.934	3.28	2.55	129.05	(116.23, 143.29)	0.0006	0.9371	18.13
AUC <sub>0-t</sub>	4.652	4.600	104.76	99.50	105.29	(96.71, 114.63)	0.3051	0.9902	14.68
AUC <sub>0-inf</sub>	4.721	4.683	112.27	108.12	103.84	(94.47, 114.13)	0.4967	0.9716	16.35

Non-Transformed Data							
PK Variable	Least Squares Mean			90% Confidence Interval (Lower Limit, Upper Limit)	P-values for Product Effects	Power of ANOVA	
	Test-Fed	Test-Fast	% Ratio				
T <sub>max</sub>	9.28	6.67	139.19	(115.88, 162.5)	0.0097	0.2911	
Kel	0.0262	0.0251	104.72	(97.71, 111.73)	0.2568	0.9966	
T <sub>1/2</sub>	27.81	29.21	95.20	(88.63, 101.78)	0.2211	0.9987	

*Reviewer's comments:*

*The administration of 450 mg bupropion (BUP-450) with food significantly increased C<sub>max</sub> (~29%) of PAWC. AUC of PAWC was increased by ~4% after a high fat meal.*

*In the current study, for reference product (3x Wellbutrin XL® 150 mg), food increased C<sub>max</sub> of PAWC by ~10% and increased AUC of PAWC by ~27% (Ref: Table 14.2.150 in the report). In NDA21-515 (Wellbutrin XL), food did not significantly increase C<sub>max</sub> (2%) and AUC (5%) of PAWC.*

### Safety Results

No death or serious adverse events (SAE) were reported.

Following administration of BUP-450, three subjects (~16%) experienced AEs that were considered possibly drug related: one AE (vomiting; Subject 06, (b) (6) ~5%) under fasted conditions happened at 7.75 hours post-dose, which resulted in discontinuation from the study; two subjects (Subject 05 and Subject 11; ~11%) experienced mild headache at 12-118 hours post dose under fed conditions, which lasted for 8-62 hours.

Following administration of Wellbutrin XL, three subjects (~33%) experienced AEs that were considered possibly or remotely drug related: Subject 08 experienced mild lightheaded, headache, and chills (possibly drug related) at 8.5-12 hours post-dose under fasted conditions; Subject 05 experienced mild headache (possibly drug related) at 11.5 hours post-dose under fasted conditions, also the subject experienced mild headache (possibly drug related) at 11 hours post-dose under fed conditions; Subject 03 experienced mild sinus pressure under fed conditions, which was considered remotely drug related. The AE profile was similar between fasted and fed conditions.

### **Conclusions**

The administration of 450 mg bupropion ER tablets (BUP-450) with food significantly increased  $C_{max}$  and AUC of bupropion by ~25% and ~15%, respectively. Additionally, food significantly increased  $C_{max}$  (~31%) of threohydrobupropion, one of active metabolites of bupropion. Food prolonged the bupropion absorption from 5 hours to 7.5 hours.

- a) Based on the package insert for Wellbutrin XL, bupropion is associated with a dose-related risk for seizure. For example, the IR formulation of bupropion suggested that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day. Thus, the therapeutic index of the drug, bupropion, is narrow above the recommended dose.
- b)  $C_{max}$  of bupropion was increased by 25% after administration of 450-mg BUP 450 XL under fed conditions, which is equivalent to about 112 mg *more* dose ( $450 \times 0.25$ ), i.e., the subjects were dosed more under fed conditions than under fasted conditions: 562-mg BUP 450 XL ( $450 + 112$ ) under fed conditions vs. 450-mg BUP 450 XL under fasted conditions; Additionally, based on the upper limit of 90% CI (107.5-145.5) for the increase of  $C_{max}$ , some subjects have been exposed to even much higher levels of bupropion under fed conditions, which is equivalent to the dose at 653-mg BUP 450 XL ( $450 + 450 \times 0.45$ ).
- c) In the current study, 67% of subjects (12 out of 18 subjects) showed that food increased  $C_{max}$  by >1 fold. In these 12 subjects, 2 subjects showed that food increased  $C_{max}$  by >2 fold (2.19 fold for Subject 11 and 2.75 fold for Subject 17); 4 subjects showed that food increased  $C_{max}$  by >1.5 fold but < 2 fold. Three subjects were > 1.2 fold and < 1.5 fold; remaining 3 subjects were <1.1 fold.

Two-fold increase of  $C_{max}$  is equivalent to a dose of “900 mg”, 1.5-fold increase of  $C_{max}$  is equivalent to a dose of “675 mg”, and 1.2-fold increase of  $C_{max}$  is equivalent to a dose of “540 mg”. The detailed information can be found in the Appendix following Section 5.2 (the food effect study review).

This increase in  $C_{max}$  of BUP 450 XL product is a very serious safety concern as there is a very serious risk of increase in seizures.

BUP 450 XL should only be taken **without** food.

## APPENDIX

Table 1. Individual data of  $C_{max}$  under fasted and fed conditions for Cary's BUP 450 XL.

Subject	$C_{max}$		
	Fasted (ng/mL)	Fed (ng/mL)	Ratio (Fed/Fasted)*
1	279	238	0.85
2	279	480	1.72
3	339	633	1.87
4	246	301	1.22
5	328	271	0.83
7	313	249	0.80
8	192	176	0.92
9	215	207	0.96
11	198	433	2.19
12	216	290	1.34
13	248	312	1.26
14	321	491	1.53
15	144	156	1.08
16	260	444	1.71
17	253	696	2.75
18	377	390	1.03
19	258	260	1.01
20	180	173	0.96
N	18	18	18
Min	-	-	0.80
Max	-	-	2.75
Median	-	-	1.15

\* The red highlight indicates  $C_{max}$  increase > 1 fold.

Table 2. Individual data of  $C_{max}$  under fasted and fed conditions for GSK's Wellbutrin XL.

Subject	$C_{max}$		
	Fasted (ng/mL)	Fed (ng/mL)	Ratio (Fed/Fasted)*
3	148	291	1.97
4	240	177	0.74
5	291	175	0.60
7	300	231	0.77
8	281	116	0.41
9	-	151	-
15	202	558	2.76
17	264	216	0.82
18	282	182	0.65
19	299	269	0.90
N	9	10	9
Min	-	-	0.41
Max	-	-	2.76
Median	-	-	0.77

\* The red highlight indicates  $C_{max}$  increase > 1 fold.

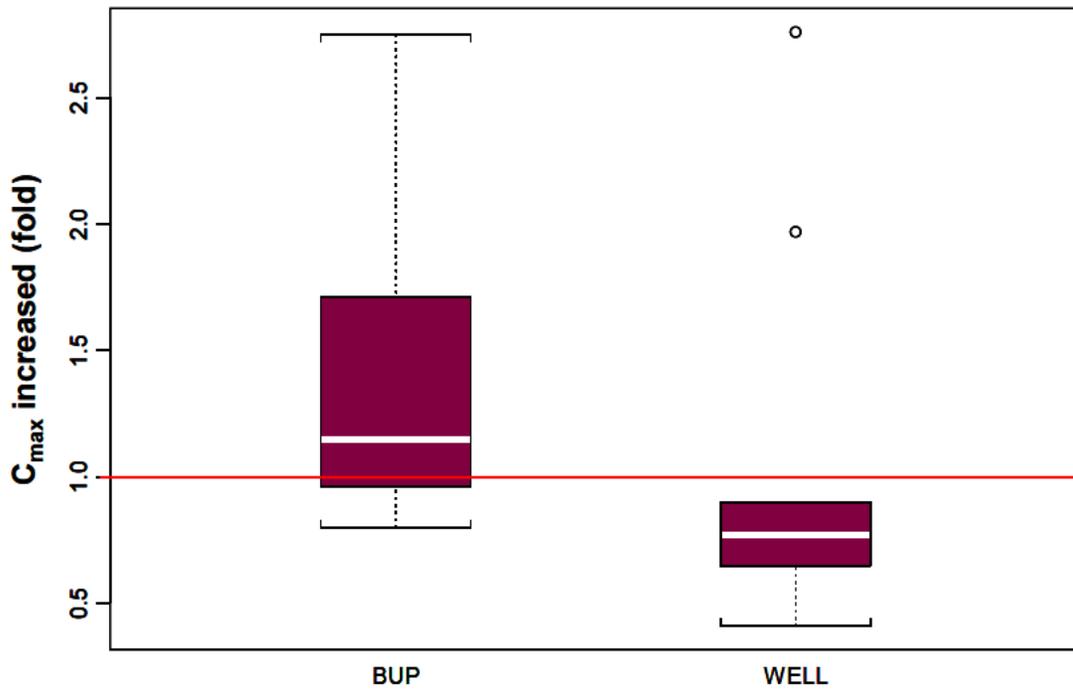


Figure 1. Boxplots for change in  $C_{max}$  by food for both Cary's BUP 450 XL (BUP) and GSK's Wellbutrin XL (WELL).

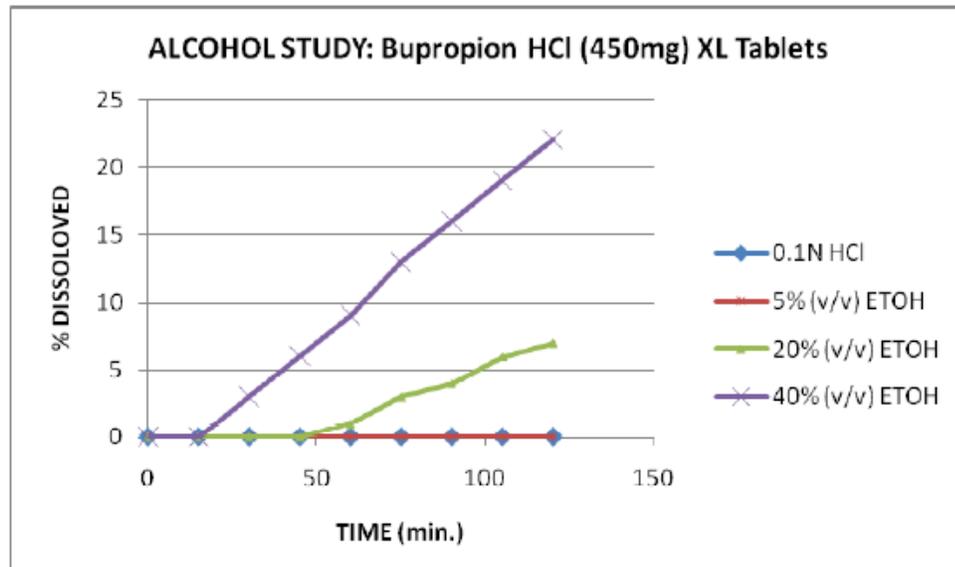
### 5.3. Effect of Alcohol on the Dissolution of Bupropion HCl from BUP-450 Tablets (dose dumping study with alcohol)

Dissolution profiles were generated on 12 dosage units using USP Apparatus 1 (basket) at 75 rpm in 900 ml of dissolution medium as specified below. Data were collected every 15 minutes for a total of two hours.

- Test 1: 0.1 N hydrochloric acid;
- Test 2: 5% (v/v) of test medium replaced with Alcohol USP;
- Test 3: 20% (v/v) of test medium replaced with Alcohol USP;
- Test 4: 40% (v/v) of test medium replaced with Alcohol USP;

For up to 2 hours, 5% and 20% (v/v) ethanol had no effect on BUP-450 tablet, compared to “no ethanol” (0%). The presence of 40% (v/v) of alcohol (worst case scenario) caused a 22% increase (16-25%) in bupropion HCl from BUP-450 tablets at 2 hours. The effect of alcohol on the dissolution of bupropion HCl from BUP-450 tablets is summarized in the graph and table below:

**Graph 1:** Effect of alcohol on the dissolution of Bupropion HCl from BUP-450 tablets

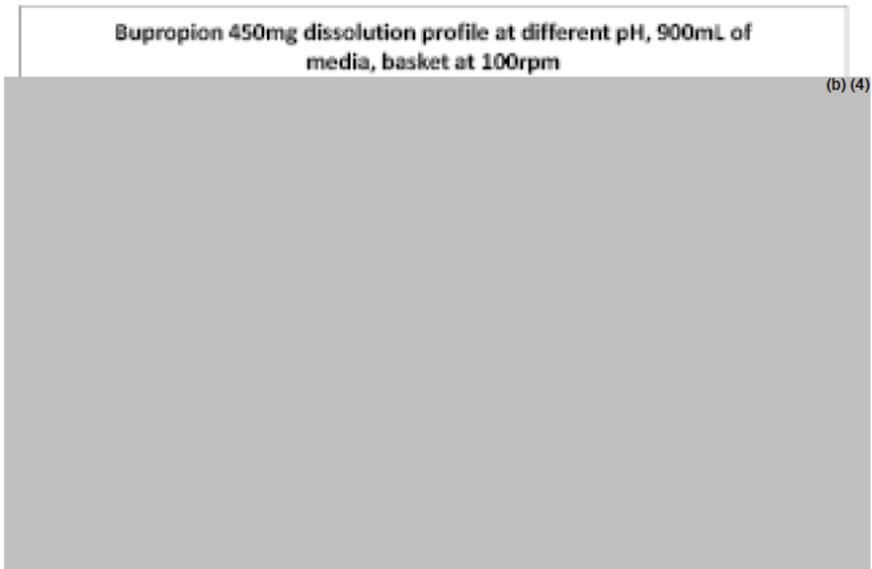


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**Table 1: Summary Table**

TIME (min.)	% DISSOLVED			
	0.1N HCl	5% (v/v) ETOH	20% (v/v) ETOH	40% (v/v) ETOH
0	0	0	0	0
15	0	0	0	0
30	0	0	0	3
45	0	0	0	6
60	0	0	1	9
75	0	0	3	13
90	0	0	4	16
105	0	0	6	19
120	0	0	7	22

*(Ref: Module 3.2.R.6. Effect of pH and Alcohol on the Dissolution of Bupropion HCl from BUP-450 Tablets)*

Additionally, the effect of pH on the dissolution of bupropion HCl from BUP-450 tablets and Wellbutrin 150 mg XL tablets (reference) are shown in the graphs below, respectively:



*Reviewer's comments:*

*The above study design and results are acceptable. However, the presence of 40% of alcohol caused a 22% increase in dissolved bupropion HCl from BUP-450 tablets (the maximum dissolved was 25%). Therefore, a cautionary note should be placed in the labeling.*

## 6. OCPB filing form

Office of Clinical Pharmacology and Biopharmaceutics				
<i>NEW DRUG APPLICATION FILING AND REVIEW FORM</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA Number	22-497	Brand Name	BUP-450 XL	
OCPB Division (I, II, III)	OCP1	Generic Name	Bupropion HCL	
Medical Division	Psychiatry Product	Drug Class	Antidepressant	
OCPB Reviewer	Bei Yu, PhD	Indication(s)	Major Depressive Disorder	
OCPB Team Leader	Raman Baweja, PhD	Dosage Form	Extended-release tablets	
		Dosing Regimen	QD	
Date of Submission	03/31/2009	Route of Administration	Oral	
Estimated Due Date of OCPB Review	11/20/2009	Sponsor	Cary Pharmaceuticals, Inc.	
PDUFA Due Date	02/06/2010	Priority Classification	Standard 10 months	
Division Due Date	1/06/2010			
<u>Clin. Pharm. and Biopharm. Information</u>				
	"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:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X	1	1	
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>	X	1	1	
<b>Dissolution:</b>	X	1	1	
<b>(IVVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				

III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		3	3	
<i>Filability and QBR comments</i>				
	"X" if yes	Comments		
Application fileable ?	X	Reasons if the application is <u>not</u> 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"> <li>1. Is the (1X) 450 mg strength tablet bioequivalent to (3X) 150 mg approved Wellbutrin XL reference product?</li> <li>2. To assess the effect of food on the 450 mg tablet formulation.</li> </ol>		
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

**7. Attachment 1**

**MEMORANDUM for the Inspection.**

MEMORANDUM

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

DATE: November 10, 2009  
TO: Thomas Laughren, M.D.  
Director, Division of Psychiatry Products (DPP)  
Office of New Drugs (HFD-130)  
FROM: Sripal R. Mada, Ph.D.  
Division of Scientific Investigations (HFD-48)  
THROUGH: C.T. Viswanathan, Ph.D. *Mart K. Yan 11/10/09*  
Associate Director (Bioequivalence)  
Division of Scientific Investigations (HFD-48)  
SUBJECT: Review of EIR Covering NDA 22-497, Bupropion HCl 450 mg ER tablets from Cary Pharmaceuticals, Inc.

At the request of Division of Psychiatry Products (DPP), the Division of Scientific Investigations (DSI) audited both clinical and analytical portions of the following bioequivalence (BE) study:

**Study # 3631:** "A Two-Way Crossover, Open-Label, Single-Dose, Fasting, Bioequivalence Study of Bupropion HCl 450 mg ER tablets versus Wellbutrin XL<sup>®</sup> 150 mg Tablets in Normal, Healthy, Nonsmoking Male and Female Subjects"

Study #3631 was conducted by (b)(4)  
at two research facilities in (b)(4) The first (b)(4)  
facility is located at (b)(4)  
(b)(4) and the second facility is located at (b)(4)

Following the inspection (October 26-30, 2009), Form FDA-483 was issued (**Attachment 1**). The Form FDA-483 observations and DSI's evaluations are provided below.

(b) (4)

**1. Failure to retain the study reserve samples (test product: Bupropion HCl 450 mg ER tablets; reference product: Wellbutrin XL 150 mg tablets) used in bioequivalence Study # 3631 as required by the regulations. The reserve samples were sent back to the study co-sponsor (IntelGenx Corp., Quebec, Canada).**

(b) (4) fails to meet the regulatory requirements for retention of products used in bioavailability or bioequivalence study (21 CFR 320.38 and 320.63). Per the request of co-sponsor of this NDA, (b) (4) shipped back all the reserve samples (see documents collected during the inspection in **Attachments 2, 3 and 4**).

As the test and reference products were not retained at the clinical study site, the authenticity of the products used in Study #3631 cannot be confirmed.

**2. Failure to perform sufficient assessments of Incurred Sample Reproducibility (ISR). Only 2.78% (39/1405) of bupropion and its metabolite samples were reanalyzed for ISR.**

As cited in the above 483 observation, the SOP for ISR at the time when the study was conducted was not adequate. However, (b) (4) has now revised their SOP (effective January 2, 2009) to address the sample size issue by requiring 10% (instead of <3%) of study samples to be re-assayed. Moreover, a review of the ISR data obtained by (b) (4) previously from 39 subject samples shows that the original and repeat data are similar, suggesting significant ISR problem is unlikely.

**3. Pipettes are calibrated only once every three months. There is no other procedure employed to check the accuracy of the pipettes during the entire three-month period, which would include the study period.**

Per the current SOP, the performance of pipettes will not be checked at anytime other than the calibration performed once in every 3 months. During the inspection close out meeting, (b) (4) acknowledged this observation and agreed to revise the current SOP to address this issue.

4. Raw data sheets and the analytical study reports were not always documented correctly and/or accurately. For example:

- A. Corrections on raw data entry sheets were not signed and dated in several occasions.
- B. Failure to provide the reason for corrections/strike-outs in the data entry sheets.
- C. Hemolyzed samples were not mentioned or discussed in the analytical study reports, even though sample processing and study update records recorded a large number of hemolyzed study samples.

(b) (4) acknowledged their mistakes in raw data sheets and their failure to report the number of hemolyzed samples in the analytical report submitted to the FDA. DSI confirmed during the inspection that (b) (4) had conducted validation experiment using hemolyzed samples. The results showed that hemolyzed samples did not affect the precision and accuracy of the analytical method.

**Conclusion:**

The inspection at (b) (4) found that the regulatory requirements concerning retention of study products used in bioavailability or bioequivalence study were not followed (see 483 item 1). Consequently, the authenticity of the test and reference products tested in Study 3631 cannot be assured. The other findings (i.e., 483 items 2, 3 and 4) are not likely to affect the study outcomes.

Please note that DSI has not yet received the written response to the Form FDA-483 from (b) (4). DSI will update DPP if our review of the response upon receipt resulted in a change of our recommendation.

After you have reviewed this transmittal memo, please append it to the original NDA submission.



---

Sripal R. Mada, Ph.D.

**Final Classification:**

**Clinical and Analytical**

**VAI -** [REDACTED] (b) (4)

**FEI:** [REDACTED] (b) (4)

cc:  
DSI/GLPBB/Mada/Kaufman/Rivera-Lopez/CF  
ODE1/DPP/Ansah/Laughren  
OCP/DCP1/Baweja/Yu  
Draft: SRM 11/04/2009  
Edit: MKY 11/05,09/2009  
DSI: 5976; O:\Bioequiv\EIRCover\22497bio.bup.doc  
FACTS: 1061165

Email:  
CDER DSI PM TRACK  
HFR-CE450/Kondas - Karen.Kondas@fda.hhs.gov

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22497	ORIG-1	CARY PHARMACEUTICA LS INC	BUP-450 (BUPROPION HCL)450MG ER ORAL TAB

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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.**  
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/s/  
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SRIPAL R MADA  
11/10/2009

Dr. Yau (Acting for Dr. Viswanathan) signed the paper copy on 11/10/2009. Paper copies available on request. The scanned paper document has the original signature.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22497	ORIG-1	CARY PHARMACEUTICA LS INC	BUP-450 (BUPROPION HCL)450MG ER ORAL TAB

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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.**

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/s/  
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BEI YU  
01/25/2010

RAMAN K BAWEJA  
01/25/2010  
Concur.