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Steady State Plasma Levels of Bupropion After Administration of 3x150 Mg Extended Release Reference Tablets and Switching to 1x450 Mg Extended Release 450ER Tablets

Review Article

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Abstract

In order to provide patients who take 450 mg/day bupropion hydrochloride for the treatment of severe depressive disorder with a safe and convenient alternative to currently existing dose regimens, a high-dose bupropion ER tablet formulation containing 450 mg of bupropion hydrochloride was developed. The results of the single dose pharmacokinetic study demonstrated bioequivalence of the 450 mg ER tablet with three tablets of the 150 mg strength taken at once, thus confirming that the 450 mg tablet is safe and effective. In addition, the simulation of steady state bupropion plasma levels after administration of 3x150 mg bupropion ER fasting and subsequent switch to 1x450 mg bupropion ER fed confirm that even under "worst case conditions" patients who switch from 3x150 mg to 1x450 mg bupropion ER won't experience an elevated average C_{max} and hence are not exposed to an increased risk of seizures.

Keywords: Bupropion; Pharmacokinetics; ER Formulation; Steady State; Simulations.

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Introduction

Bupropion extended release tablets are administered for the treatment of major depressive disorders. Initially, patients suffering from depression are commonly treated with lower doses and the daily dose is increased until the desired therapeutic effect is observed. Bupropion hydrochloride was initially developed as an immediate release tablet that was administered three-times per day. It was later developed into a twice a day tablet (Wellbutrin SR®) followed by a once-daily tablet (Wellbutrin XL®) (3-4). Patients receiving the once-per-day bupropion product may require high daily doses; Bupropion HCl is approved for a maximum daily dose of 450 mg. However, because the commercial product is only available as 150 and 300 mg tablets, patients requiring 450 mg have to take multiples of the available lower strength tablets.

Bupropion hydrochloride 450 mg extended-release tablets (450ER), was developed to allow patients to take one tablet as opposed to multiple tablets, hence eliminating the risk of an accidental dosing errors. In a single dose, three-period, three-treatment, cross-over study, it was demonstrated that 450ER (1 x 450 mg tablet) was bioequivalent to REF (3 x 150 mg tablets) when dosed in the fasting state. However, when 450ER tablets were administered with a standard high fat/high calorie meal and compared to the fasting treatment, C_{max} was bioequivalent but AUC increased slightly (25%) and didn't meet the 80 – 125% bioequivalence (BE) confidence interval criteria (CI).

However, this increase of AUC after administration with food is routinely observed in bupropion extended-release products. REF shows a fed/fasting ratio of 110% (CI: 104-116%) for AUC while C_{max} was lower (point estimate: 92 %). Similarly, Aplenzin® (Bupropion hydrobromide extended-release tablets containing the same dose of bupropion as 450ER tablets), show a ratio fed/fasting of 107.48% (CI: 98.20-117.64%) for C_{max} and a ratio fed/fasting of 119.47% (CI: 113.23-126.06%) for AUC_{τ} (5). Both products are labeled indicating that they may be taken with no regard to food or meal timing.

It is known from the history of bupropion HCl (1-2) that high C_{max} values may be linked to higher seizure risk. A reduction in the frequency of reported seizures occurred after the marketing transition from Bupropion immediate release to Bupropion twice a day and Bupropion extended release (3). Thus, it was hypothesized that an increase in bupropion exposure with 450ER could result in an increase in the frequency of seizures. This concern was directed at those patients who would be switched from the current commercial bupropion 3x150mg to 450ER. PK modeling and simulation provide the context needed to compare these two oral formulations. Steady-state simulations may provide insight into the steady-state PK of bupropion in patients receiving REF tablets (3x150 mg) and who may be switched to the 450ER tablets (taken with food). One goal was to predict potential increases in steady-state C_{max} or AUC values which might indicate that patients would experience a higher risk of developing seizures.

Materials and Methods

Clinical studies

Two single dose clinical studies form the basis of these simulations. The first study (Study 1) was a three-way cross over study in healthy volunteers comparing Forfivo XLTM 450mg (Bupropion hydrochloride

extended-release tablets, 450ER, Edgemont Pharmaceutical LLC, manufactured by Pillar5 Pharma Inc. in Ontario Canada) under fasting and fed condition to Wellbutrin XL® 3 x 150 mg (REF, Glaxo Smith Kline Inc., Manufactured by DSM Pharmaceutical Inc. North Carolina, USA) under fasting condition only. This study was conducted on 36 healthy subjects. The second study (Study 2) was a four-way cross over comparing these same products both under fasting and fed conditions. This study was conducted on 20 healthy subjects, except the fed portion of REF which was conducted on 10 subjects. The protocols for both studies were reviewed and approved by investigational review boards. Bioanalyses for both studies were conducted using a validated LC/MS/MS procedure.

Steady State Simulations

Steady-state simulations were conducted to better understand the steady-state PK of bupropion in patients receiving REF (3x150 mg) and who may be switched to the 450ER tablets (taken with food). The goal was to predict potential increases in C_{max} or AUC_{τ} values which might indicate that patients would experience a higher risk of developing seizures.

Single dose of REF data generated in the four-way crossover showed a delayed T_{max} and a lower C_{max}. This lower exposure would support a safer product since the assumption is that seizures are associated with elevated C_{max}. In keeping with this hypothesis, the published seizure rate for bupropion sustained-release formulations decreased to 0.1% at doses of up to 300 mg/day (4).

Steady-state plasma concentration versus time profiles were simulated with the Nonparametric Superposition (NPS) feature within WinNonlin® Pro (Pharsight Corporation, St. Louis, MO) using individual single dose profiles obtained from the study 2. Steady-state plasma concentration-time profiles were simulated for each individual subject.

In order to assess the effect of switching patients from REF 3x150mg to 450ER, steady-state plasma concentration versus time profiles (after 8 daily doses) were simulated for each individual subject. These simulations included additional points beyond the last 8th dose in order to provide the concentrations 288 hrs. Single dose profiles for 450ER were simulated using NPS to allow manual superposition of these single dose profiles (Day 9) with the steady-state profiles (Days 8 to 9). Pharmacokinetic parameters were derived for each subject's simulated profile using noncompartmental modeling in WinNonlin Pro.

Treatment Assumptions

For the switch assessment (switching from REF 3x150mg to 450ER on Day 9), it was assumed that REF steady-state was achieved by the 8th daily dose. A visual assessment of Panel A in Figure 1A shows that steady-state was achieved by Days 3 or 4 validating the assumption of steady-state achievement by Day 8.

Biostatistical Evaluation

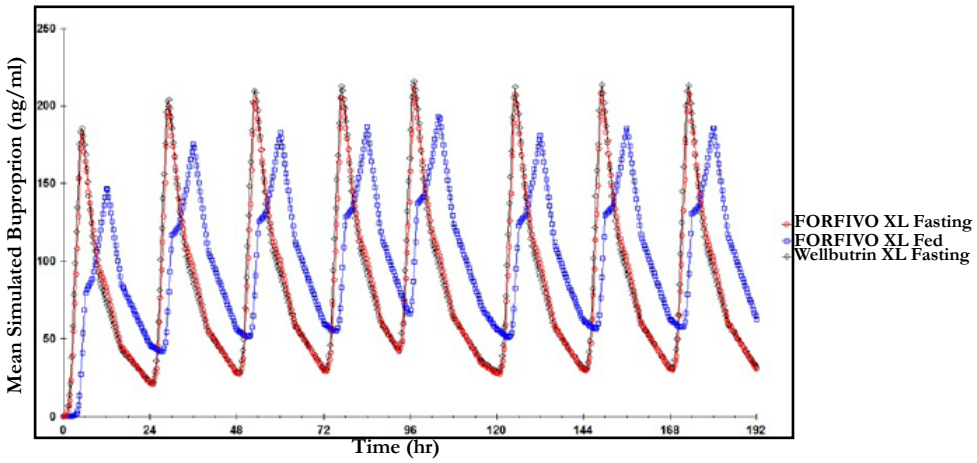
To assess the equivalence of treatments, particularly after switching from REF 3x150 mg fasting to 450ER fed, 90% confidence intervals of the geometric means of the individual ratios of the simulated C_{max} and AUC_{τ} were calculated using the BE Wizard in WinNonlin Pro.

Results and Discussion

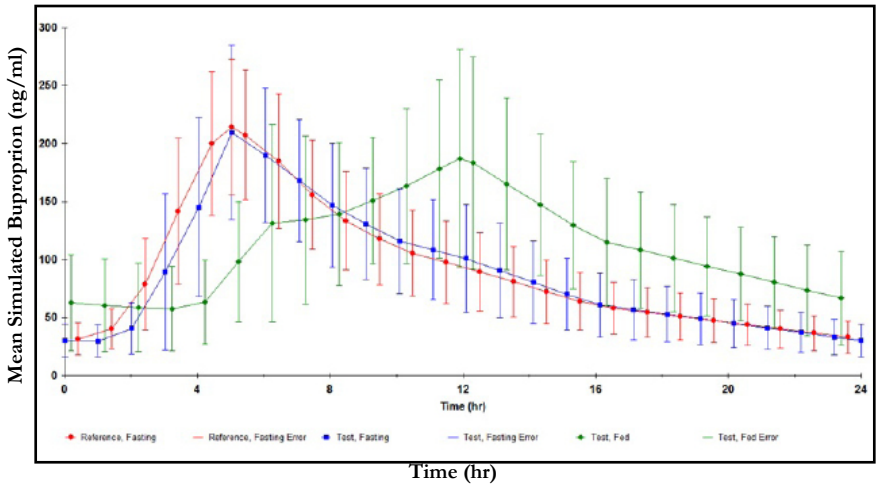
Figure 1A illustrates the mean concentration-time profiles for 450ER

Figure 1: Average simulated plasma bupropion concentrations after eight consecutive doses of each treatment (A) Average simulated steady-state plasma bupropion concentrations (B) and Simulated mean (SD) steady state plasma bupropion concentrations after administration of REF (fasting) for 8 Days with switch to 450ER (fed) on day 9 (C)

A



B



C

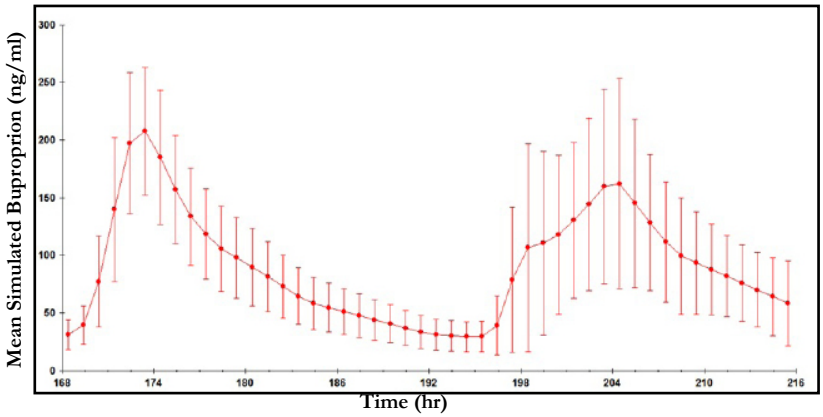


Table 1: Summary Statistics for Simulated Steady-State Bupropion PK Parameters and Ln transformed steady-state simulated bupropion data, Ratio (% Ref) and 90% confidence intervals for AUC_{last} and C_{max}

	450ER Fasting			450ER Fed			REF Fasting		
	C_{max} (ng/mL)	T_{max} (hr)	AUC_{τ} (hr*ng/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{τ} (hr*ng/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{τ} (hr*ng/mL)
N	35	35	35	35	35	35	35	35	35
Mean	231	5.64	2140	249	10.99	2660	240	4.78	2170
SD	66.5	2.04	659	80.6	4.23	703	58.9	0.81	566
Min	103	3.03	862	102	0.00	1380	160	3.03	1230
Median	234	5.04	2290	257	11.90	2620	237	4.84	2140
Max	339	12.1	3290	441	24.00	4010	389	6.05	3330
CV%	28.8	36.1	30.8	32.3	38.5	26.4	24.5	17.0	26.1
95% CI Lower	208	4.94	1910	222	9.536	2420	220	4.50	1980
95% CI Upper	254	6.341	2360	277	12.441	2900	261	5.062	2370

	Dependent	Ref	Test	Ratio (% Ref)	CI 90 Lower	CI 90 Upper
450ER Fasting vs. REF Fasting	$Ln(AUC_{\tau})$ (hr*ng/mL)	7.6486	7.6144	96.63	**89.98**	**103.78**
	$Ln(C_{max})$ (ng/mL)	5.4538	5.3980	94.58	**86.00**	**104.01**
450ER Fed vs. REF Fasting	$Ln(AUC_{\tau})$ (hr*ng/mL)	7.6486	7.8505	122.37	**113.94**	**131.41**
	$Ln(C_{max})$ (ng/mL)	5.4538	5.4656	101.19	**92.02**	**111.28**

(fasting), 450ER (fed) and REF (fed). The two fasting treatments in this figure were nearly superimposable. This figure confirms that bupropion steady-state is achieved before Day 8. Because the extrapolated portions of the concentration-time curves are critical to the superposition approach, the fits were assessed by comparing the half lives derived from the nonparametric simulations with those determined from the noncompartmental analyses of the single dose data. The graphics provided in Figure 2 demonstrate excellent agreement between these half lives and confirm that the superposition approach provides reasonable estimates of steady-state concentrations.

The mean (SD) graphs of the simulated steady-state concentration time profiles for each of the three treatments are provided as Figure 1B. This figure illustrates that REF provides tighter control of plasma concentrations with lower peak to trough fluctuations. Summary statistics for the simulated steady-state C_{max}, T_{max} and AUC values are provided in Table 1. Additionally Table 1 provides the corresponding 90% confidence intervals of the ln-transformed individual ratios of C_{max} and AUC_{τ} for 450ER (fed and fasting) relative to REF (fasting).

The point estimates and confidence intervals from the steady-state simulations were similar to those reported in the single dose study where 450ER (fasting) was equivalent to REF (fasting). The Test/Ref point estimates for steady state AUC and C_{max} were 96.63% and 94.58%, respectively. The Test/Ref point estimates from the single dose BE study were 94.94% and 96.51%, respectively and confidence intervals fell within 80.00% to 125.00%. For the 450ER (fed) to REF (fasting) comparison, steady-state C_{max} values were equivalent, but AUC was high, similar to the single dose study. The Test Fed/Ref point estimates for steady state AUC and C_{max} were 122.37% and 101.19%, respectively; the point estimates from the single dose BE study were 124.89% and 101.41%, respectively. The confidence intervals for simulated steady-state AUC and C_{max} were 113.94% to 131.41% and 92.02% to 111.28%, respectively. The similarity in the statistics serves to validate these simulations.

Figure 2: Correlation of half lives derived using noncompartmental analysis of single dose data (Study 1), and nonparametric simulations to derive predicted steady-state concentrations. Top, middle and bottom panels illustrate correlations for 450ER fasting, 450ER fed and REF fasting, respectively.

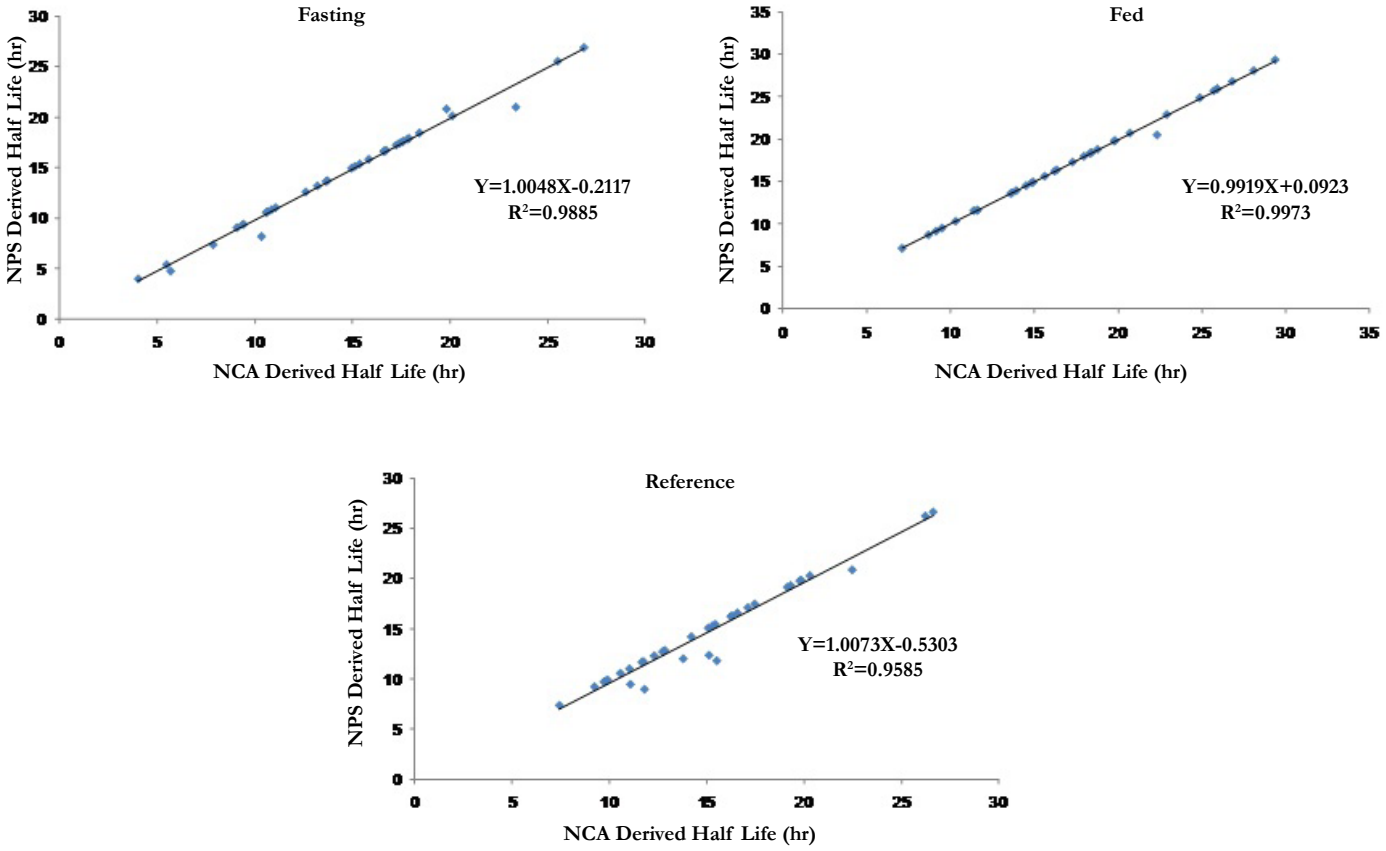


Table 2: Summary Statistics for Simulated Bupropion PK Parameters for REF after 8 Days of dosing and for 450ER after dosing on Day 9, and Ln transformed data. Ratio (% Ref) and 90% confidence intervals for AUC_{last} and C_{max}

	Day 8 = REF Fasting			Day 9 = 450ER Fed		
	C_{max} (ng/mL)	T_{max} (hr)	AUC_{last} (hr*ng/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{last} (hr*ng/mL)
N	35	35	35	35	35	35
Mean	240	4.8	2160	237	11.9	2200
SD	59.0	0.8	556	82.2	4.8	606
Min	160	3.0	1220	78.0	6.1	940
Median	238	5.0	2140	241	12.1	2130
Max	394	6.0	3320	435	24.1	3190
CV%	24.5	17.0	25.8	34.7	40.0	27.6
95% CI Lower Mean	220	4.5	1970	209	10.3	1990
95% CI Upper Mean	261	5.1	2350	265	13.6	2400

AUC_{last} = AUC_{tau}

Dependent	Ref	Test	Ratio (% Ref)	CI 90 Lower	CI 90 Upper
Ln(AUC_{last}) (hr*ng/mL)	7.6444	7.6544	101.01	**90.36**	**112.90**
Ln(C_{max}) (ng/mL)	5.4534	5.3981	94.62	**82.86**	**108.05**

Figure 3: Mean plasma concentrations of 450ER after administration of 450 mg as REF 3 x 150 mg tablets to healthy volunteers under fed and fasted conditions

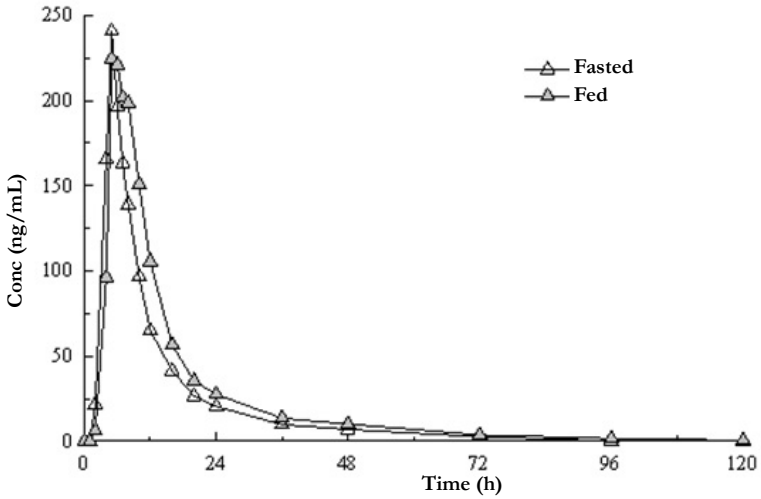


Table 3: Summary of statistical analysis (Study 2), REF (fed) vs REF (fasted), Bupropion, N=9

Ln-Transformed data									
PK Variable	**Least Squares Mean**		**Geometric mean**			**90% Confidence interval**	**P-values for product effects**	**Power of ANOVA**	**ANOVA % CV**
	Ref-Fed	**Ref-Fast**	**Ref-Fed**	**Ref-Fast**	**% Ratio**	**Lower and upper limit**			
C_{max}	5.43	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**			**90% Confidence interval**	**P-values for product effects**	**Power of ANOVA**
	Ref-Fed	**Ref-Fast**	**% Ratio**	**P-values for product effects**		
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, 157.76	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	5.4	115.74	85.64, 145.84	0.3548	0.1938
Kel	0.0468	0.0465	100.51	90.2, 110.7	0.9270	0.8882
$T_{1/2}$	19.34	17.84	108.40	95.93, 120.87	0.2424	0.7414

The point estimates and confidence intervals from this simulation, as listed in Table 2, predict that both C_{max} and AUC were bioequivalent. That is, on the initial day when a patient is switched from REF (3 x 150 mg, while fasting) to 450ER (450 mg with food), the predicted C_{max} and AUC values will be bioequivalent. The Test/Ref point estimates for AUC and C_{max} were 101.01% and 94.62%, respectively; the confidence intervals for AUC and C_{max} were 90.36% to 112.90% and 82.86% to 108.05%, respectively.

Conclusion

The results show that the 90% confidence intervals for ln-transformed AUC_{tau} and C_{max} values on Day 9 (after switching to 450ER) relative to day 8 (steady-state REF before switching) are within the 80 – 125 % bioequivalence acceptance range. This predicts that switching from a steady-state dosing regimen of 3x150 mg REF tablets to 450ER taken with food will not result in significantly increased AUC or C_{max} levels. These simulations support the equivalence of 450ER and REF and that a switch from REF in patients who take the product in the fasting state to 450ER if taken with food (the worst case scenario) does not significantly increase bupropion exposure and therefore, does not expose patients to elevated risk of seizures. When patients switch from REF to 450ER fasting, the two products would also be bioequivalent as demonstrated by the single-dose study.

Although the professional labeling for REF states that food did not affect the C_{max} or AUC of bupropion, data generated in the single dose study demonstrated that there is a small food effect that is similar in these two products (REF and 450ER). Observed C_{max} and AUC values are provided in Table 3. Figure 3 illustrates the mean bupropion concentrations obtained after administration of REF when fasting or after a standard FDA meal. The Test/Ref (Fed/Fasting) point estimates for REF bupropion AUC and C_{max} were 125.30% and 92.08%, respectively. In the most recent 450ER study (Study 1), the Fed/Fasting bupropion point estimates for AUC and C_{max} were 124.89% and

101.41%, respectively. Thus, the extent of absorption for both 450ER and REF increases by 25% when the products are dosed with food, relative to the fasting state. Given the safety experience with REF, this increase in exposure is not clinically relevant.

References

[1]. Anthony w. Peck, Warren C. Stern, Catherine Watkinson, Incidence of seizures during treatment with tricyclic antidepressant drugs and bupropion. J. Clin. Psychiatry. 1983; 44:5(Sec 2):197-201

[2]. James W. Jefferson, James F. Pradko, Keith T. Muir, Bupropion for major depressive disorder: pharmacokinetic and formulation considerations. Clinical Therapeutics, 2005; 27(11):1685-1695

[3]. Maurezio Fava, John Rush, Michael E Thase et al. 15 years of experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. 2005; J. Clin Psychiatry, 7(3):106-113

[4]. Dunner DL, Zisook S, Billow AA et al. A prospective safety surveillance study for bupropion sustained-release in the treatment of depression. J Clin Psychiatry. 1998;59(7):366-73

[5]. Aplenzin® prescribing information, http://products.sanofi.us/aplenzin/aplenzin.pdf