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APPLICATION NUMBER: NDA 20-711

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NOV 6 1996

NDA 20-711

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Bupropion Hydrochloride Sustained Release Tablets for Smoking Cessation

Tradename:	Wellbutrin SR	GlaxoWellcome
Strength:	20mg,50mg,100mg	Five Moore Drive
		PO Box 13398
Submitted:	May 1996.	Research Triangle Park
Submission Type:	New indication	
Reviewer:	Peter Lockwood MS	North Carolina 27709

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1. BACKGROUND:

Wellbutrin (Bupropion hydrochloride) was initially developed as an antidepressant of the aminoketone class. Its mechanism of action is not known but in vitro, bupropion blocks the neuronal re-uptake of dopamine, norepinephrine and serotonin. Bupropion has three active metabolites; 306U73 (hydroxybupropion), and the aminoalcohol isomers 494U73 (threohydrobupropion) and 17U67 (erythrohydrobupropion). Further biotransformation of these metabolites results in the formation of *meta*-chlorobenzoic acid which is then conjugated with glycine to produce *meta*-chlorohippuric acid as the major urinary metabolite.

An immediate release (IR) formulation (75 and 100mg strengths) was approved in December 1985 for the treatment of depression at doses of 300-450mg per day given in divided doses not to exceed 150mg/dose. Seizures were reported in 0.4% of the individuals taking doses of 450mg per day. A sustained release (SR) formulation of the drug was approved in October 1996, based on its demonstrated bioequivalence with the immediate release formulation.

Inspection of the material reviewed by "Neuropharmalogical Drug Products; ODE 1" revealed that the pharmacokinetics of this drug and aspects associated with an SR formulation have been suitably investigated. An overview is contained in Appendix 1.

The interest in studying bupropion as an aid to smoking cessation was based on the observation that depressed patients stopped smoking while being treated with this compound. This NDA seeks approval of Bupropion hydrochloride sustained release tablets as an aid to smoking cessation. There is no information about use in children/teens but there is guidance for geriatric use. The recommend dose and duration are 150mg p.o. b.i.d. for 7-12 weeks.

2. SYNOPSIS OF NDA 20-711:

Three placebo controlled clinical studies were submitted. Two of these studies used the immediate release formulation of Bupropion which the sponsor claims was effective as an aid to smoking cessation. Based on the demonstrated bioequivalence of the immediate release and sustained release formulations, the sponsor argues that the sustained release tablets would also be effective. A third study used the sustained-release formulation and defined the dose response relationship, establishing 300mg as the recommended daily dose given as 150mg b.i.d. This was based on an hypothesis testing approach comparing treatment groups with placebo.

Pharmacokinetic and bioavailability information that has been previously submitted to NDA 18-644 and 20-358 for the treatment of depression is incorporated in this application by reference. Perusal of the Biopharmaceutics Review files indicate studies necessary to delineate the pharmacokinetics of Wellbutrin have been conducted and reviewed.

Three pharmacokinetic studies were included in this submission which were not included in NDA's 18-644 and 20-358. They are as follows;

1) a study comparing the PK of Bupropion and its metabolites in smokers with non-smokers following a single 150mg dose Wellbutrin SR (study 407);

2) A logistic regression analysis of a dose ranging study (Study 403) using NONMEM to determine the dose- and concentration-response relationship;

3) an in vitro metabolism study of Bupropion by human liver microsomes;

An additional biopharmaceutics study was conducted which compared the in vitro dissolution release rates of intact and divided Wellbutrin SR tablets and the effect of varying pH on dissolution rates. This data demonstrated that the divided tablets had a faster *in vitro* dissolution rate than the intact tablets, but a slower *in vitro* dissolution compared with the immediate release formulation. The data further suggested that *in vivo* dissolution may be independent of physiological pH.

The regression analysis using NONMEM indicated that the mean 17U67 concentration and the number of cigarettes smoked per day at baseline emerged as a statistically significant predictors of smoking cessation. When dose was forced into the model in place of the mean 17U67 concentration, the results were not statistically significantly different suggesting **that dose was just as effective at predicting outcome as was the metabolite concentration.**

Reported CNS adverse events are anxiety, constipation, depression, concentration disturbance, dizziness, dream abnormality, dry mouth, headache, insomnia, irritability and nausea. Using a backward elimination process of a multivariate model dry mouth was positively correlated with 494U73 concentration and negatively correlated with weight. Insomnia was positively correlated with the mean 17U67 concentration. Anxiety (a symptom of withdrawal) was

negatively correlated with bupropion concentration. Females were more likely to experience headache than males, but this was not related to drug exposure.

There was no difference in the pharmacokinetics of bupropion when administered to smokers or non-smokers.

3. REVIEWERS COMMENTS

The use of logistic regression in this application was encouraging. However there was no account of whether patients dropped out or whether a placebo effect was apparent. If patients dropped out, this means the analysis is biased to patients who were sensitive to the treatments, thus over estimating the probability of the outcome. In the absence of consideration of these factors in the modeling process the estimated odds ratio's may be confounded. It is not clear from the submission whether the metabolite concentrations used were the individual patient means or the population mean and this will affect the estimate of the probability of the outcome. Further analysis of the data or at least some consultation with the analyst would be useful, but in any case whether the outcomes determined are real or not, will not affect the approvability of this product.

A further comment regarding the analysis relates to the use of a one compartment model for bupropion, when a two compartment model is more appropriate. The consequence is that the estimate of the volume of distribution will be inaccurate while the clearance estimate should reflect reality. In any event, even if these parameters are erroneous they should not affect the steady state plasma concentration prediction which was used as a covariate in the logistic regression.

Non compartmental pharmacokinetic parameters ($AUC_{0-\infty}$, $t_{1/2}$, C_{max}, T_{max}) for bupropion (smoker group), determined in Study 407, were estimated using MKModel (ver 5.05 May 1995) by the reviewer. These estimates were consistent with those provided by the sponsor.

4. ACTION or COMMENTS TO BE SENT TO SPONSOR

The package insert could be better organised and does not include important pharmacokinetic information. An ammended package insert has been drafted and this should be forwarded to the sponsor to use as "suggested text" for a redrafted version.

5. RECOMMENDATION:

This submission satisfies the Office of Pharmaceutical Sciences (ODE II) biopharmaceutics requirements.

6. TABLE OF CONTENTS

7. SIGN OFF:

Reviewed by: P. A. Lockwood

Peter Lockwood, MS; Friday, October 18, 1996
Pharmacokineticist

Draft; Initialed by; DFC 11/6/96
Dale Conner PharmD, Friday, October 18, 1996

Distribution:
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8. STUDY DETAILS

8.1 STUDY 403

A PK/PD analysis of a dose response study (Study 403) was conducted to evaluate the dose-response and concentration-response relationships for both the efficacy and safety of Wellbutrin (WB).

8.1.1 Study Details

Description; parallel, randomized, double blind, placebo-controlled trial conducted at three centers.

Patients; male and female > 18 years who were chronic smokers

Dose; group 1; WB SR 100mg/day (50 mg b.i.d.)
group 2; WB SR 150mg/day (150mg q.d.)
group 3; WB SR 300mg/day (150 mg b.i.d)
group 4: placebo

Primary Efficacy Measure; abstinence (0 cigarettes) from smoking during weeks 4-7 (4 week period) of the treatment phase. This was confirmed by exhaled carbon monoxide levels (CO) (< 10ppm)

PK measurements: samples were drawn at weeks 3 & 6. Parent and metabolite concentrations were measured. The number of patients available for analysis are listed in Table 1. Not all the PK data collected was used. When missing information or errors were detected in the dosing or concentration data for a particular patient with another valid concentration measurement, the sample in question was deleted from the analysis, but the patient was retained in the data set.

When missing information or errors in the concentration or dosing data would have resulted in the patient being deleted from the analysis, these patients were not included in the pharmacokinetic analysis but were retained in the pharmacodynamic anlysis with bupropion clearance set to the population mean. The number of patients used for the PK analysis is displayed in Table 2.

Table 1 Patient and No of samples collected:

	pat no	2 pk samples	1 pk sample	total samples
WB		82%	18%	708
plac				
total pats				

Table 2: No of patients and samples used in PK analysis after exclusion of dubious data.

	pat no	no of samples used in analysis
WB		652

Data Analysis; Individual Cl was determined by fitting data to a one compartment model with first order absorption using NONMEM. These estimates were used to predict steady state bupropion concentrations in each patient.

Table 3: Population pharmacokinetic parameter estimates for bupropion.

parameter	estimate	inter-individual variability (%)
Clearance (L/hr)	210	30
Volume	227	85

Logistic regression was performed using NONMEM . Three logistic models were evaluated for efficacy. They were;

1) included intercept only (comparable to baseline probability before accounting for co-variates);
2) included intercept plus dose effect
3) included intercept plus dose plus clearance

A series of patient covariates were tested for inclusion in the intercept only model in a univariate manner. A summary of the statistically significant co-variates is contained in Appendix 3. Each covariate associated with statistical significance was incorporated into a multi-variate model. A backward elimination procedure was then applied to each full model to determine the final model for efficacy and safety responses.

8.1.2 Conclusions

There was a strong dose-response relationship for Wellbutrin SR and smoking cessation. Patients receiving 300 mg/day were 2.8 times more likely to achieve smoking cessation compared to placebo, whereas patients receiving 100 mg/day were 1.4 times as likely to achieve smoking cessation compared to placebo.

In the multi-variable analysis of efficacy, the mean 17U67 concentration emerged as a statistically significant predictor of smoking cessation, but when dose was forced into the model in place of the mean 17U67 concentration, the results were not statistically different, suggesting that dose was just as effective at predicting outcome as was the metabolite concentration.

The number of cigarettes smoked per day at baseline emerged as a statistically significant predictor of efficacy. As the number of cigarettes smoked per day at baseline increased, the likelihood of quitting decreased.

In the multi-variable analyses of safety; anxiety, dry mouth and insomnia were associated with bupropion Cpss, mean 494U73 and 17U67 concentrations, respectively. For anxiety, the higher the bupropion Cpss, the lower the risk of anxiety. For dry mouth and insomnia, there was a positive association where increasing metabolite concentrations were associated with a high incidence of these events.

The risk of headache was approximately two times greater in female smokers than in male smokers in this population, but was not associated with Wellbutrin SR dose. None of the other adverse events studied were associated with gender. Neither age nor race significantly influenced the risk of any adverse event studied. However, these covariates represent very small sample sizes in this population and these results should be interpreted cautiously.

8.2 A STUDY OF THE IN VITRO METABOLISM OF BUPROPION BY HUMAN LIVER MICROSOMES AND cDNA EXPRESSED HUMAN CYTOCHROME P450'S

The objective of the study was to investigate in vitro metabolism of bupropion using phenotyped human liver microsomes and cDNA expressed human cytochrome P450's in the presence and absence of selective isozyme inhibitors to identify which P450's are involved in the biotransformation of bupropion.

8.2.1 Study Details

8.2.1.1 Description;

Bupropion and its metabolites were synthesized at Glaxo

In vitro experiments were conducted with 8 individual phenotyped human liver microsomes and a pool of microsomes from several donors. Microsomes were also prepared from human-B-lymphoblastoid cell line (AHH-1 TK+/-) which contained the DNA for specifically expressing the following enzymes.
CYP 1A1 (40pmol P450/mg protein)
CYP 1A2 (100pmol P450/mg protein)
CYP 2A6 ((83pmol P450/mg protein)
CYP 2B6 (120pmol P450/mg protein)
CYP 2C9 (16pmol P450/mg protein)
CYP 2D6-val (44pmol P450/mg protein)
CYP 2E1 (150pmol P450/mg protein)
CYP 3A4 (50pmol P450/mg protein)
NADPH-P450 reductase was co-expressed in microsomes prepared from cell lines expressing cDNA for CYP 2C9, 2D6, 2E1, and 3A4.

Bupropion was incubated with microsomes at clinical concentrations (approx. 2-25ng/ml for the microsomes containing cDNA expressed P450 and 2-120ng in the presence and absence of inhibitors. The reaction was terminated by addition of ice-chilled acetonitrile. Michaelis Menten kinetic parameters (Km and V_{max}) were determined for the substrates 306U73 and 494U73. The supernatant from the microsome incubation mixture was analyzed by for bupropion and metabolites.

The inhibitors were as follows:

Table 4: Inhibitors of P450 isozymes

Furafylline (20μm),	CYP1A2
Coumarin (200μm),	high-affinity selective CYP2A6
Orphenadrine (500μm),	CYP2B6
Sulphaphenazole (20 μm),	CYP2C9
Qunidine (10 μm),	CYP2D6
Troleandomycin (50 μm)	CYP3A4
Menandione (500 μm)	Carbonyl reductase
1-aminobenzotriazole	(general P450 inhibitor)

8.2.1.2 Results

The in vitro finding supported the in vivo findings i.e 306U73 and 494U73 are the major circulating metabolites in human plasma. 306U73 was formed by each isozyme. 494U73 was not detected suggesting P450's may not be involved in its formation. The highest rate of formation of 306U73 was observed from incubation with CYP2B6. Detectable levels were observed following incubation with the CYP1A2, 2A6, 2C9, 2E1 and 3A4 but these were all significantly lower (50-90fold lower) than the levels formed following incubation with 2B6.

In the human microsomal preparations, incubations in the presence of 1-aminobenzotriazole resulted in approximately 90% inhibition of the formation of 306U73. The percent reduction in formation of this metabolite was as follows;

Table 5; % reduction in metabolite formation.

INHIBITOR	ISOZYME	306U73 REDUCTION (%)
Furafylline (20μm),	CYP1A2	39 ± 8%
Coumarin (200μm),	high-affinity selective CYP2A6	24 ± 6%
Orphenadrine (500μm),	CYP2B6	72% (63-80)
Sulphaphenazole (20 μm),	CYP2C9	22 ± 11%
Qunidine (10 μm),	CYP2D6	27 ± 9.2%
Troleandomycin (50 μm)	CYP3A4	30 ± 9.4%
Menandione (500 μm)	Carbonyl reductase	
1-aminobenzotriazole	(general P450 inhibitor)	89 ± 6.3%

In human liver microsomes, 1-aminobenztriazole did not inhibit the formation of 494U73 from bupropion. Similarly other P450 isozyme-specific chemical inhibitors did not have any significant result on the formation of this metabolite.

Bupropion contains a ketone group which is reduced to an alcohol during metabolism by a carbonyl reductase. This enzyme is inhibited by menadione. Menadione (0.5mM) caused substantial inhibition (85%) of the formation of 494U73 suggesting an involvement of carbonyl reductase.

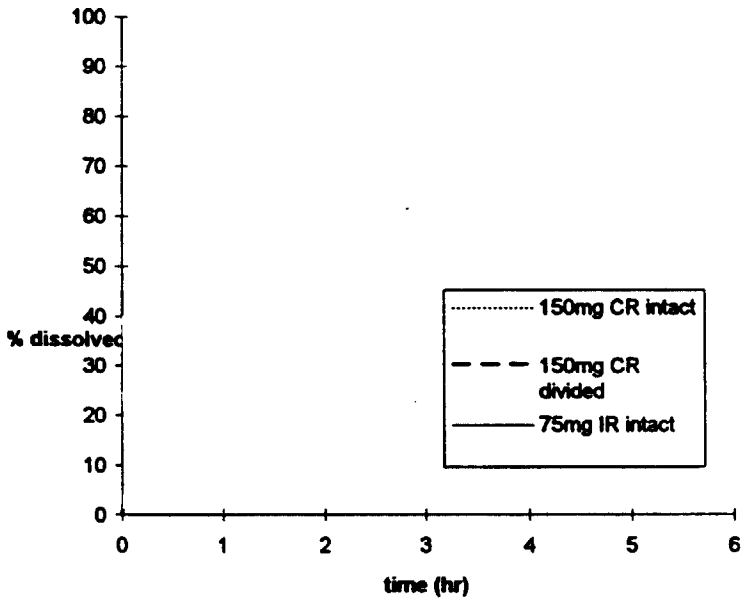
8.3 IN VITRO DISSOLUTION STUDY

This study was performed in response to FDA concerns about the robustness of the formulation with regard to divided Wellbutrin SR tablets. In addition, pH effect on the dissolution of Wellbutrin SR tablets was also tested. The dissolution conditions for comparing

the intact and divided tablets were USP paddle, 900mL distilled water, 50 RPM, water at 37 degree C. The results are displayed in Figure 1.

This figure demonstrates that the that dissolution rate of the divided tablet was faster than the intact tablet (150mg Wellbutrin SR, barch 5M2780) , and substantially slower than the 75mg

Figure 1; Dissolution results of Wellbutrin CR and IR



IR product (batch 3O6001).

Dissolution testing of Wellbutrin SR tablets (50mg, 100mg, & 150mg) was carried out in distilled water, 0.1N Hcl, pH 4.5 phosphate buffer and pH 7.5 phosphate buffer to study the pH effect. For all three doses the in vitro release rate was similar in all media.

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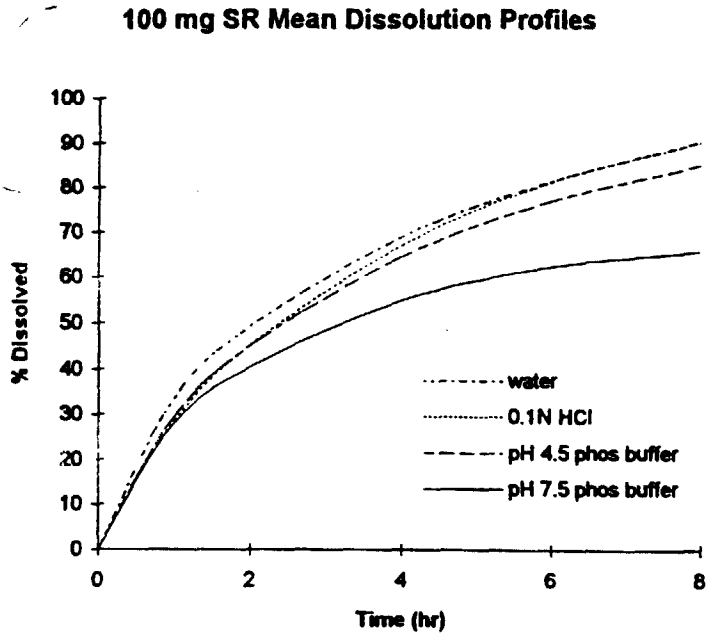
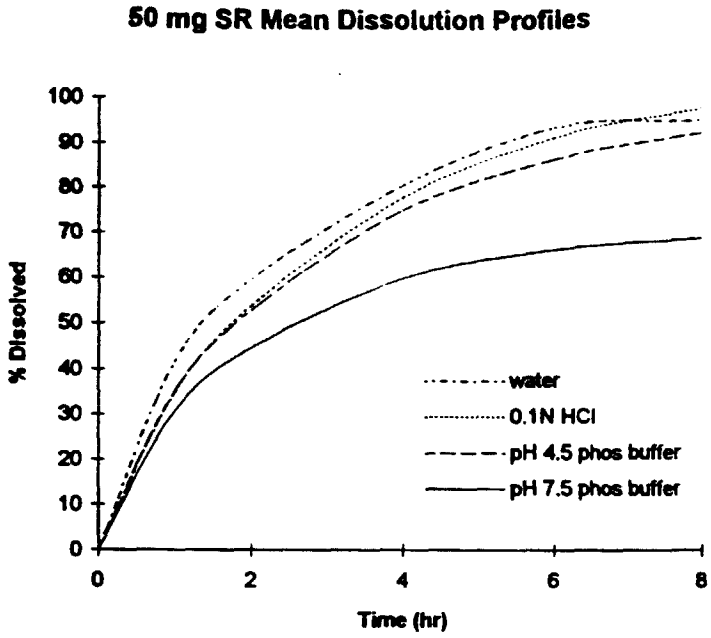
Figure 3





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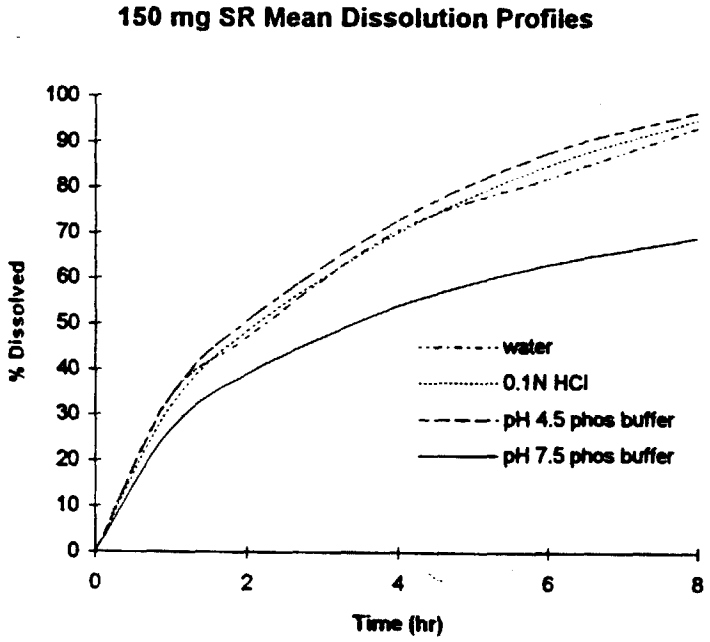

Figure 2, Figure 3 and Figure 4, demonstrate similar dissolution rates in water, 0.1N HCl and phosphate buffer pH 4.5. The lower dissolution rate displayed in phosphate buffer pH 7.5 was considered by the sponsor to be a consequence of the degradation of bupropion HCl upon standing in high pH buffer. Collectively this data suggests that the dissolution rate of Wellbutrin SR is independent of physiological pH.

8.4 A STUDY COMPARING THE PHARMACOKINETICS OF WELLBUTRIN SR IN HEALTHY SMOKERS VERSUS NON-SMOKERS (STUDY 407)

The objective of the study was to compare the pharmacokinetics of bupropion and its metabolites (306U73, 494U73 and 17U67) between healthy smokers and non-smokers.

8.4.1 Study Details

8.4.1.1 Description;

Single dose; 36 subjects enrolled and 34 completed, (17 smokers (9 male & 9 female) and 17 non-smokers); 19 blood samples collected over a 72 hour period in each volunteer.

8.4.1.2 Dose and Batch Details

Dose - 150mg
Batch No: 4P2748
Batch size: tablets

8.4.1.3 Sample Analysis;

Samples were analyzed for bupropion, 306U73 and the aminoalcohol isomers 494U73 and 17U67. The concentrations were determined by a liquid-liquid extraction procedure adapted to Chem Eluts. Following extraction the samples were analyzed by liquid chromatography tandem mass spectrometry.

Where possible plasma samples from the same subject were run in the same analytical batch. Each batch contained 10 standards ng/ml) in duplicate and 4 duplicate QC standards same (0.4, 4, 40, 150ng/ml) placed at the beginning and end of a run. Based on data collected during the analysis of subject samples, accuracy and precision for standards and QC samples was always less than 10% at any concentration.
Concentrations of 494U73 and 17U67 were presented as a composite total because they have the same mass spectrometric response (i.e co-eluted)

8.4.1.4 Data Analysis;

Pharmacokinetic (PK) parameters AUC_{0-72}, $AUC_{0-\infty}$, C_{max}, T_{max}, CL/F and $t_{1/2}$ were estimated from the data. ANOVA was performed on pertinent log transformed PK parameters to evaluate differences between smokers and non-smokers. The results are displayed in Table 6. There were no significant differences in any of the pharmacokinetic parameters for bupropion or its metabolites between smokers and non-smokers.

Table 6; Summary of ANOVA and confidence intervals for Ln-transformed pharmacokinetic parameters

Parameter	Units	Geometric Mean		90% Confidence Intervals		ANOVA	
		non-smokers	smokers	lower limit	upper limit	p-value	power
BUPROPION							
AUC_{0-72}	(hr*ng/ml)	1108	1095	0.86	1.13	0.886	91
$AUC_{0-\infty}$	(hr*ng/ml)	1144	1124	0.86	1.13	0.828	90
C_{max}	(ng/ml)	141	138	0.85	1.13	0.775	89
$t_{1/2}$	(hr)	19	18	0.83	1.06	0.347	--
CL/F	(L/hr)	131	133	0.89	1.17	0.828	--
306U73							
AUC_{0-72}	(hr*ng/ml)	12347	13560	0.86	1.40	0.518	28
$AUC_{0-\infty}$	(hr*ng/ml)	13833	15523	0.87	1.45	0.454	26
C_{max}	(ng/ml)	398	406	0.81	1.28	0.876	32
$t_{1/2}$	(hr)	21	22	0.87	1.18	0.842	--
49U73 + 17U67							
AUC_{0-72}	(hr*ng/ml)	3667	4290	1.01	1.35	0.075	66
$AUC_{0-\infty}$	(hr*ng/ml)	5452	6350	0.97	1.40	0.169	52
C_{max}	(ng/ml)	131	144	0.93	1.28	0.335	68
$t_{1/2}$	(hr)	46	45	0.81	1.18	0.859	--

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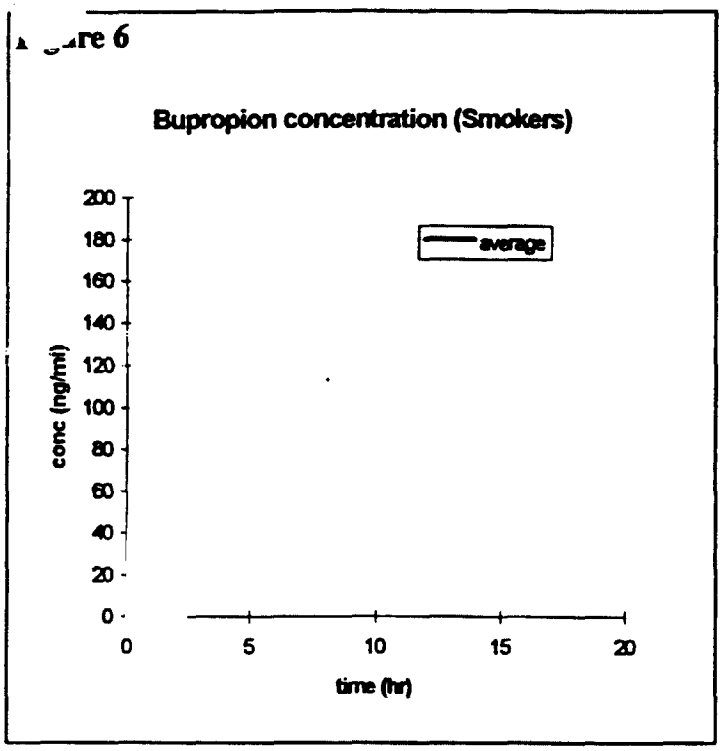
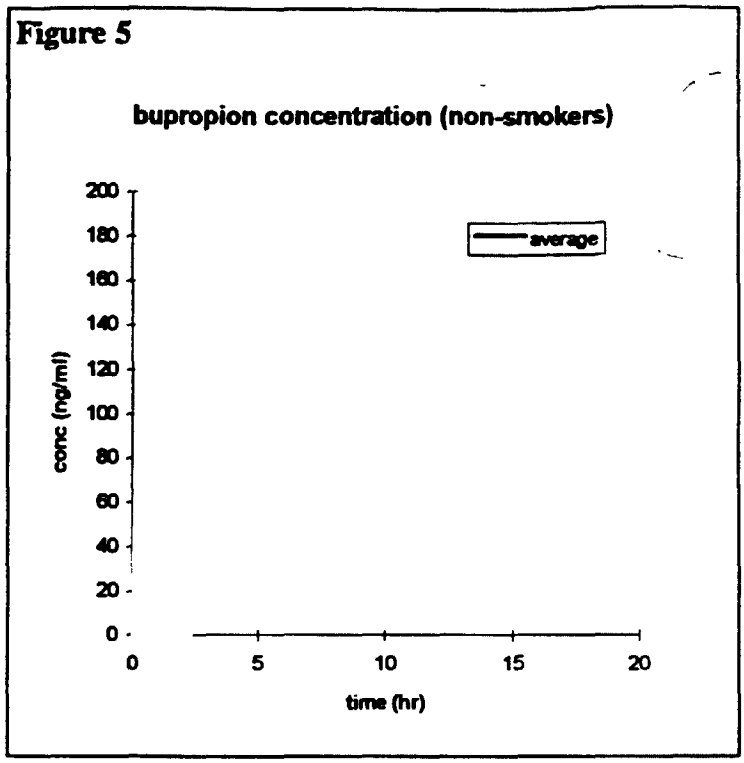

Bupropion concentration (Smokers)
conc (ng/ml)
200
180
160
140
120
100
80
60
40
20
0
0
5
10
15
20
time (hr)
average

Figure 5


bupropion concentration (non-smokers)
conc (ng/ml)
200
180
160
140
120
100
80
60
40
20
0
0
5
10
15
20
time (hr)
average

9. APPENDIX 1: OVERVIEW OF PHARMACOKINETICS OF BUPROPION IR AND SR (Previous Submissions)

9.1 Different dosage forms (IR & SR) are bioequivalent (Study 204)

C_{max} and AUC for the different dosage forms were equivalent when a single dosage regimen of 2x50mg SR, and 1x100mg IR were compared.

9.2 *Different dosage strengths (SR) are bioequivalent (Study 207)*

Single doses of 6x50mg SR, 3x100mg SR or 2x150mg SR were considered bioequivalent treatments with respect to AUC and C_{max}.

9.3 Comparison of rate and extent of absorption parameters for IR and SR dosage forms (Study 96, Study 206)

A multiple dose bioequivalence study demonstrated the highest strength SR tablet (150mg/b.i.d.) was equivalent to 100mg IR given every 6, 6, and 12 hours. AUC and Cmin were inside the 80%-125% confidence intervals while C_{max} was just outside (78%-98%). The fluctuation index was 15% lower for the SR compared with the IR formulation.

9.4 Linear kinetics at steady state (Study 96)

Over the dosing range of 300-450mg IR formulation/day, the kinetics of bupropion, 494U73 and 17U67 are linear. Steady state plasma levels of the parent and metabolite were reached within eight days.

9.5 Food effect on SR dosage forms (Study 202)

Taking the SR dosage form with food had the following outcomes: AUC ↑16%, C_{max} ↑11%; 494U73 : AUC ↑11%.

9.6 In-vitro/in-vivo correlation (Study 201)

An in-vitro/in-vivo correlation was demonstrated for dissolution of the SR product in 0.1N HCl

9.7 ADME (Study 407)

Following oral administration of 200mg C14-bupropion HCl aqueous solution, 81% was recovered in the urine and 10% in the feces over 48 hours. 0.5% of the dose was recovered unchanged in the urine. Bupropion is approximately 84% bound to albumin at concentrations up to 200ug/ml.

25 pages (16-40)
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Draft Labeling