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CARBATROL (Carbamazepine SR) Pharmavene Inc.

200 and 300 mg capsules Rockville, MD 20850

NDA 20-712

Reviewer: Iftekhar Mahmood, Ph.D.

Submission Date: April 3, August 2, October 11 and November 20, 1996

Indication: Antiepileptic

INTRODUCTION

Carbamazepine (CBZ) is an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration. Carbamazepine is a white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236. The pharmacokinetics of CBZ (immediate release) and CBZE is summarized below:

Peak plasma levels of carbamazepine are variable and may range from 0.5-25 μg/mL, with peak plasma levels reaching between 4 to 8 hours (peak plasma levels may occur as late as 24 to 26 hours). Usual adult therapeutic levels are between 4 and 12 μg/mL. The apparent volume of distribution is 1.4 ± 0.4 l/kg. Carbamazepine is 75% bound to plasma proteins. Carbamazepine is metabolized in the liver. After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged carbamazepine. Since carbamazepine induces its own metabolism, the half-life is also variable. Initial half-life values following a single dose range from 18-55 hours and 5-26 hours on repeated dosing. The apparent oral clearance following a single dose ranged from 13-25 mL/min and 30-600 mL/min following multiple dosing.

One of the major metabolites of CBZ is CBZ-10-11-epoxide (CBZE). CBZE has an anticonvulsant activity comparable with that of the parent compound in animal models of

epilepsy. Following a single 100 mg oral dose of CBZE enteric-coated tablet, the T_{max} and C_{max} of CBZE were 6.7 ± 3 hours (range = 3-12 hrs) and 1.1 ± 0.3 µg/mL (range = 0.71-1.52 µg/mL), respectively. The volume of distribution (V/F) was 1.1 ± 0.2 l/kg (range = 0.79-1.27 l/kg). CBZ-10-11-epoxide is 50% bound to plasma proteins. The plasma half-life for CBZ epoxide was 7.4 ± 1.8 hours (range = 4.8-10.7 hrs), whereas clearance was 119 ± 21 mL/min (range = 96-157 ml/min). The half-life of CBZE is shorter following administration of CBZE than the half-life of CBZE following administration of CBZ.

Pharmavene, Inc. has developed a multi-unit sustained-release formulation of carbamazepine (CARBATROL, CBZ-SR) designed to enable twice daily administration in patients with epilepsy. The multi-unit is composed of a three pellet formulation of carbamazepine, with each pellet being combined in specific ratios within one capsule. The three types of pellets consist of immediate-release, sustained-release, and enteric-release pellets , with each capsule containing many pellets of each type. In this 505 (b) (2) application, Pharmavene is seeking approval to market both 200 mg and 300 mg capsules based upon bioequivalency studies. The reference product is approved immediate release Tegretol tablet (NDA 16-608), which the Sponsor is using to provide evidence for the efficacy and safety of CBZ. However, Pharmavene has undertaken 3 clinical trials (one controlled efficacy trial, n = 100 patients) and 2 uncontrolled safety trial (n= 150 patients) to support the use of CARBATROL.

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The total number of pharmacokinetic studies submitted in this NDA were 11, of which 6 were reviewed. The 5 studies (not reviewed) were non-pivotal or exploratory pharmacokinetic studies undertaken early in the program to develop each pellet formulation.

SUMMARY

Bioequivalence:

The pivotal study in this NDA involves the comparison of Pharmavene sustained release product (CBZ-SR, bio or alpha batch) with Tegretol IR (study #1, Protocol PI 101.103). Twenty four patients with epilepsy (9 of the patients were on a fixed dose of phenytoin, phenobarbital, clorazepate, primidone or valproic acid) received a daily dose of 800 (n =9), 1200 (n =9) or 1600 (n =6) mg CBZ-SR or Tegretol IR for 14 days. Tegretol IR was given every 6 hours and CBZ-SR was given every 12 hours. On day 14, subjects were given a high fat meal (FDA recommended) 30 minutes before the administration of both dosage forms (this was the only high fat meal given to the patients during the whole study period, otherwise patients remained on controlled regular diet). The 90% confidence interval was applied on log transformed data on the AUC, C_{max}, C_{min}, $C_{average}$ and Fluctuation Index (FI) without dose normalization of these parameters (details can be found in study #1). Mean values for AUC, C_{max}, C_{min}, and C_{ave} for CBZ, CBZE and CBZ **plus** CBZE following administration of CBZ-SR and Tegretol were within the recommended 0.80-1.25 limits of bioequivalence. The Fluctuation Index (FI) for CBZ-SR appeared to be slightly higher (0.33 vs 0.28) as compared to Tegretol. However, this difference was not statistically significant (P = 0.066). The FI for CBZE and CBZ+CBZE was also not statistically different between CBZ-SR and Tegretol (P = 0.965, 0.164, respectively).

In the ClinPharm/Biopharm Briefing, it was agreed that 90% C.I. should only be applied on the parent compound because of the low exposure to the epoxide metabolite (even if one considers it to be equally safe and effective as the parent). However, the metabolite should be monitored and the evaluation for the metabolite would be descriptive in nature. For the 800 mg dose group (n=9), the sponsor was able to show that the CBZ-SR is bioequivalent to the CBZ-IR for all three primary parameters: AUC, C_{max} and C_{min} and for all three dosing interval comparisons (0-12hr, 12-24hr and 0-24hr). The epoxide PK

parameters were found to be statistically not significant between the two treatments (SR vs IR) for all the three dose groups ($p>0.05$). The sponsor really does not need to establish BE for all dose levels when the total daily dose and the dosing interval are consistent for the CBZ-SR and the CBZ-IR dosage form. The 800 mg daily dose is within the therapeutic dosing regimen for this drug. Therefore, this study demonstrates that Pharmavene's carbamazepine sustained-release formulation given every 12 hours is bioequivalent to Tegretol given every 6 hours (Study #1). Even in the 1200 mg dose group (n=9) except $C_{min0\text{-}12\ hr}$, all other parameters for all the three dosing interval comparison could be considered to meet the 90% C.I. analysis. Obviously, for the 1600 mg dose group (n=6), the small sample size results in failure of more PK parameters to meet the acceptable 90% C.I. range. In other BE studies in this NDA, sample size of 12 subjects were adequate to meet the 90% C.I. criteria for different formulations of CBZ-SR (details can be found in study #1).

The batch of pellets used for the pivotal bioavailability study described above (Study #1) was manufactured in 1993. Because of low batch yields, the manufacturing process was changed in 1994 and 1995. A pharmacokinetic link was established between batches manufactured in 1993 and 1995. A bioequivalence study (Study #4) was undertaken to compare the product intended for marketing (gamma batch) and the Biobatch (alpha batch) used in 1993. The results of this study demonstrated that the 200 mg CBZ-SR capsule intended for marketing is bioequivalent to the 200 mg CBZ-SR Biobatch.

In terms of dosage forms, the Biobatch was a 200 mg capsule (Study #1), which contained approximately 280 mg of pellets. Pharmavene is also seeking approval for a 300 mg capsule. The 300 mg capsule is simply a larger capsule shell which contains approximately 420 mg of pellets. The only difference between the formulas is the color of the capsule shells, which contain different dyes in order to differentiate one strength from the other. A bioequivalence study was undertaken to compare the two strengths of beta batches (Study #5). The bioequivalence was tested by giving 2x300 mg capsules or 3x200

mg capsules to 12 subjects. The results of this study indicated that these two strengths of CBZ-SR capsules are bioequivalent.

A bioequivalence study was conducted to evaluate whether or not alpha and beta batches are bioequivalent. Twelve male volunteers received 2x200 mg CBZ-SR capsule of either alpha (1993) or beta (1994) batches in a crossover design. This study demonstrated comparable bioavailability and pharmacokinetic profiles for CBZ-SR manufactured from the 1993 and 1994 batches of drug. The plasma levels of carbamazepine were bioequivalent as determined from AUC and C_{max}. The metabolite, carbamazepine-10,11-epoxide, was bioequivalent in terms of AUC but C_{max} failed to meet the bioequivalence criteria by a very narrow margin (1.07-1.26). The study demonstrates that the batches of 1993 and 1994 of the sustained-release, multi-unit form of carbamazepine can be considered to be bioequivalent for both CBZ and CBZE (Study #6).

Dose Proportionality:

Mean values of C_{max} and AUC of CBZ and CBZE (β-batch) increased with dose, demonstrating dose proportionality over the single dose range of 200 to 800 mg (Study # 3). The elimination half-life ranged from 35 to 40 hours for CBZ and 27-34 hours for CBZE over the dose range of 200 to 800 mg CBZ-SR.

Multiple Dosing:

A twenty-four patient study was conducted to assess the bioavailability of a Pharmavene multiparticulate sustained-release dosage form of CBZ-SR administered every twelve hours compared with Tegretol IR administered every six hours (Study #1). Each patient received a daily dose of either 800, 1200 or 1600 mg of Tegretol or the Pharmavene Carbamazepine Sustained-Release Capsules. The results of this study are as follows:

Carbamazepine:

The mean (AUC_{0-12} hr) following CBZ-SR was 113 ± 27 µg.hr/mL compared with 120 ± 26 µg.hr/mL for the Tegretol IR treatment. The C_{max} for 0-12 hour interval for CBZ-SR was 11.0 ± 2.5 µg/mL and for the Tegretol IR treatment was 11.5 ± 2.3 µg/mL. The T_{max} for CBZ-SR was 5.9 ± 1.8 hours and for the Tegretol IR treatment was 6.4 ± 3.7 hours. The C_{min} for 0-12 hour interval for CBZ-SR was 8.0 ± 2.1 µg/mL and for the Tegretol IR treatment was 8.8 ± 2.0 µg/mL. The C_{avg} for 0-12 hour interval for CBZ-SR was 9.4 ± 2.3 µg/mL and for the Tegretol IR treatment were 10.0 ± 2.1 µg/mL. The mean fluctuation index (FI) for 0-12 hour interval for CBZ-SR was 0.33 ± 0.10 and for the Tegretol IR treatment was 0.28 ± 0.08.

The relative bioavailability of CBZ-SR formulation (in terms of the AUC) compared with Tegretol was 98.8%, 90.3%, and 93.4% for the 800 mg, 1200 mg, and 1600 mg doses, respectively.

Carbamazepine epoxide:

The mean (AUC_{0-12} hr) following CBZ-SR was 22 ± 9 µg.hr/mL compared with 24 ± 8 µg.hr/mL for the Tegretol IR treatment. The relative exposure of carbamazepine epoxide following treatment with CBZ-SR compared with the Tegretol IR tablets was 91.5%. The mean C_{max} and C_{min} observed for CBZ-SR were 2.1 ± 0.9 µg/mL and 1.5 ± 0.6 µg/mL, respectively, compared with the corresponding values for the Tegretol IR treatment of 2.4 ± 0.9 µg/mL and 1.6 ± 0.5 µg/ml, respectively. The C_{avg} for 0-12 hour interval for CBZ-SR was 1.8 ± 0.8 µg/mL and for the Tegretol IR treatment was 2.0 ± 0.7 µg/mL. The fluctuation Index observed following CBZ-SR was 0.34 ± 0.09 compared to the Tegretol fluctuation Index of 0.37 ± 0.22.

Food Effect:

Following a high fat meal (the FDA recommended), both AUC and C_{max} of CBZ increased by 12% and 34% respectively as compared to fasting state after oral administration of a single dose of 2 x 200 mg CBZ-SR capsule. The AUC and C_{max} of CBZE increased by 12% and 50% (0.2 µg/mL to 0.3 µg/mL) in fed state than the fasting state and this increase in AUC and C_{max} was statistically significant ($p < 0.01$). T_{max} of CBZ was reduced by 10 hours when given with food compared to fasting state. The elimination half-life remains unchanged between fed and fasting state. It appears that the rate of absorption of carbamazepine increases in the presence of a high-fat meal relative to a fasting state (Study #2). However, the multiple dose study conducted in the fed state showed that the steady-state C_{max} values were within the therapeutic concentration range. Also a comparison of PK values between the 0-12 hr interval (high fat meal) and 12-24 hr interval (regular meal) did not show any effect of different meals (Study #1).

The pharmacokinetic profiles of sustained-release carbamazepine was similar when given by sprinkling over applesauce to fasted state. The AUC, C_{max}, T_{max} and $t_{1/2}$ of CBZ and CBZE were not statistically different ($p < 0.01$) between fasted and sprinkled groups (Study # 2).

Gender:

No difference ($p > 0.2$) in the mean AUC and C_{max} of carbamazepine and carbamazepine-epoxide was found between males (n =11) and females (n = 13) (Study #1).

Dissolution:

The Sponsor's proposed Dissolution Method and Specifications for Carbatrol-SR Capsules are as follows:

Dosage Form:	Sustained Release Capsule
Strengths:	200 mg and 300 mg

Dissolution Specification for Carbamazepine Sustained-Release Capsules are as follows:

Time (hr)	% Dissolved
1	
4	
6	
12	

The following dissolution Specification for both strengths of Carbamazepine Sustained-Release Capsules (200 and 300 mg) is proposed by OCPB.

Time (hr)	% Dissolved
1	
4	
6	
12	

NLT= Not less than

Dosage Form:

Pharmavene, Inc. has developed a multi-unit extended-release capsule formulation of carbamazepine (CARBATROL; CBZ-SR; carbamazepine sustained-release, gamma batch) designed to enable twice daily administration in patients with epilepsy. The multi-unit is composed of three types of pellet, with each pellet type being combined in a specific ratio within one capsule. The three types of pellets consist of immediate-release, sustained-release, and enteric-release pellets, with each capsule containing many pellets of each type. The ratios of the immediate-release, sustained-release, and enteric-release pellets are identical for each dosage strength as shown below:

Dosage Strength	% of pellets within each CBZ Extended-Release capsule		
	Immediate-release	Sustained-release	Enteric-release
200 mg capsule			
300 mg capsule			

Analytical Methods:

The samples assayed in the pharmacokinetic studies included the

In-Vitro/In-Vivo Correlation:

An analysis was undertaken to establish the relationship between the 12 hour in-vitro dissolution release profile of the drug and the 72 hour in-vivo fraction absorbed profile of the drug from Carbamazepine Sustained-Released Capsules. The in-vitro data were generated by a dissolution procedure. The in-vivo data were obtained from several single dose pharmacokinetic studies, which were conducted to evaluate the bioavailability of the Carbamazepine Sustained-Released Capsules.

The mean plasma level data from the pharmacokinetic studies were

Comments to the Office of Clinical Pharmacology and Biopharmaceutics

In this NDA, the Sponsor has measured CBZ and its active metabolite CBZE following CBZ-SR administration. The bioequivalence was assessed not only for CBZ and CBZE individually but also for CBZ plus CBZE. Following a single oral dose of CBZ-SR (200-800 mg) the AUC and C_{max} of CBZE were less than 10% of CBZ. Following multiple dosing of CBZ-SR (800-1600 mg daily for 14 days), the AUC and C_{max} of CBZE were less than 20% of CBZ. Following multiple dosing of Tegretol IR (800-1600 mg daily for 14 days), the AUC and C_{max} of CBZE were comparable to that obtained for CBZ-SR (21% of CBZ). Assuming that CBZE is equally potent anticonvulsant as CBZ (though remains to be confirmed in humans), the contribution of CBZE to the overall anticonvulsant activity of CBZ is fairly small. Therefore, the application of bioequivalence criteria on CBZE or CBZ plus CBZE may not be of any significance and in the opinion of this reviewer should be avoided not only for this sustained release formulation of CBZ but any future CBZ product. However, CBZE concentrations should be monitored and the evaluation of the metabolite would be descriptive in nature.

Comments to the Clinical Reviewer

In the pivotal bioeqivalence study, Tegretol given every 6 hours (q. i. d.) was bioequivalent to the sustained release Carbatrol given every 12 hours (b. i. d.). Based on this study, the proposed dosing regimen of Carbatrol under 'Dosage and Administration' may need to be evaluated.

IVIVC Comments (To be sent to the Sponsor)

1. The in vitro-in vivo correlation (IVIVC) provided by the sponsor is not complete and needs to be investigated further as suggested in the IVIVC-ER Guidance proposed by the Agency. A validated IVIVC may serve as a surrogate for in vivo bioequivalency testing for changes in formulation, equipment, process, manufacturing site and batch size, and may also aid in revising dissolution specifications. Specifically, the following elements need to be considered:

(a) Data obtained from separate studies, where all formulations being used to develop the IVIVC may have been studied in independent studies, may be utilized if normalized properly.

(b) It appears that in vitro drug dissolution is much [illegible]han in vivo drug absorption, and time scaling may be necessary for the in vivo fraction absorbed data (e.g., T/2). Alternatively, the in vitro dissolution testing conditions may be optimized by using different USP apparatus, and preferably at their recommended rotation speeds

(c) Unless in vitro dissolution of carbamazepine from the SR capsules is shown to be independent of dissolution test conditions (e.g. pH and agitation), results from a single formulation (i.e., one release rate) is not sufficient. In such a case, formulations with at least 2 different release rates (e.g., slow, medium and/or fast) will be necessary in the development of an IVIVC.

Labeling Comments

1. The Sponsor is requested to make the following changes on the submitted labeling. Under the **Clinical Pharmacology** section, paragraph 3 should be replaced with the following (it should be noted that the text in normal font represents new labeling information for Carbatrol, whereas the text in bold indicates original Tegretol labeling information):

Pharmacokinetics:

Carbamazepine:

Following a single 200 mg oral sustained-release dose of carbamazepine, peak plasma concentration was 1.9 ± 0.3 µg/mL and the time to reach the peak was 19 ± 7 hours. Following chronic administration (800 mg every 12 hours), the peak levels were 11.0 ± 2.5 µg/mL and the time to reach the peak was 5.9 ± 1.8 hours. The pharmacokinetics of sustained-release carbamazepine is linear over the single dose range of 200-800 mg. Following a b.i.d. dosing regimen, carbamazepine sustained-release capsules provide steady state plasma levels comparable to immediate-release Tegretol tablets given q.i.d., when administered at the same total mg daily dose.

Carbamazepine is 75% bound to plasma proteins. Carbamazepine is primarily metabolized in the liver. After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged carbamazepine. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10-11-epoxide.

Since carbamazepine induces its own metabolism, the half-life is also variable. Following a single sustained-release dose of carbamazepine, the average half-life range from

35-40 hours and 12-17 hours on repeated dosing. The apparent oral clearance following a single dose was 25 ± 5 mL/min and following multiple dosing was 80 ± 30 mL/min.

Carbamazepine-10-11-epoxide:

Carbamazepine-10-11-epoxide is considered to be an active metabolite of carbamazepine. Following a single 200 mg oral sustained-release dose of carbamazepine, the peak plasma concentration of carbamazepine-10-11-epoxide was 0.11 ± 0.012 µg/mL and the time to reach the peak was 36 ± 6 hours. Following chronic administration of a sustained release dose of carbamazepine (800 mg every 12 hours), the peak levels of carbamazepine-10-11-epoxide were 2.2 ± 0.9 µg/mL and the time to reach the peak was 14 ± 8 hours. The plasma half-life of carbamazepine-10-11-epoxide was 34 ± 9 hours. Following a single oral dose of sustained-release carbamazepine (200-800 mg) the AUC and C_{max} of carbamazepine-10-11-epoxide were less than 10% of carbamazepine. Following multiple dosing of sustained-release carbamazepine (800-1600 mg daily for 14 days), the AUC and C_{max} of carbamazepine-10-11-epoxide were less than 20% of carbamazepine. Carbamazepine-10-11-epoxide is 50% bound to plasma proteins.

Food Effect:

A high fat meal diet increased the rate of absorption (mean T_{max} was reduced by 10 hours and C_{max} increased from 3.2 to 4.3 µg/mL) but not the extent (AUC) of absorption. The elimination half-life remains unchanged between fed and fasting state. The multiple dose study conducted in the fed state showed that the steady-state C_{max} values were within the therapeutic concentration range. The pharmacokinetic profile of sustained-release carbamazepine was similar when given by sprinkling the capsule contents over applesauce compared to the intact capsule administered in the fasted state.

Special Population:

Hepatic Dysfunction:

The effect of hepatic impairment on the pharmacokinetics of carbamazepine is not known.

Renal Dysfunction:

The effect of renal impairment on the pharmacokinetics of carbamazepine is not known.

Gender:

No difference in the mean AUC and C_{max} of carbamazepine and carbamazepine-epoxide was found between males and females.

Age:

Carbamazepine is more rapidly metabolized to carbamazepine-10-11-epoxide in young children than adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age.

Race:

No information is available on the effect of race on the pharmacokinetics of carbamazepine.

2. The information provided in Drug-Interactions under 'PRECAUTIONS' should be replaced with the following.

Drug Interaction:

<u>Agents that may affect carbamazepine plasma levels:</u>

CYP 3A4 inhibitors inhibit carbamazepine metabolism and can thus increase plasma carbamazepine levels. Drugs that have been shown, or would be expected, to increase plasma carbamazepine levels include: cimetidine, danazol, diltiazem, macrolides, erythromycin, troleandomycin, clarithromycin, fluoxetine, terfenadine, isoniazid, niacinamide,

nicotinamide, propoxyphene, ketoconazole, itraconazole, verapamil, valproate.

CYP 3A4 inducers can increase the rate of carbamazepine metabolism and can thus decrease plasma carbamazepine levels. Drugs that have been shown, or would be expected, to decrease plasma carbamazepine levels include: cisplatin, doxorubicin HCl, felbamate, rifampin, phenobarbital, phenytoin, primidone, theophylline.

Effect of carbamazepine on plasma levels of concomitant agents:

Tegretol increases levels of clomipramine HCl, phenytoin and primidone

Tegretol induces hepatic CYP activity. Tegretol causes, or would be expected to cause decreased levels of acetaminophen, alprazolam, clonazepam, clozapine, dicumarol, doxycycline, ethosuximide, haloperidol, methsuximide, oral contraceptives, phensuximide, phenytoin, theophylline, valproate, warfarin. The doses of these drugs may therefore have to be increased when carbamazepine is added to the therapeutic regimen. Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects. Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

Nursing Mothers:

Tegretol and its epoxide metabolite are transferred to breast milk and during lactation the concentrations of Tegretol and its epoxide metabolite is approximately 50% of the maternal plasma concentration. Because of the

potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

3. Under **'Dosage and Administration'** the statement "Medication should be taken with meals" should be replaced by "Carbatrol could be taken with or without meals".

Recommendation:

From a pharmacokinetic point of view this NDA is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. The Sponsor is requested to incorporate all the labeling changes.

Please forward Labeling Comments and the IVIVC Comments to the Sponsor.

Iftekhar Mahmood, Ph.D. Imahmood 12/23/96

RD/FT initialed by Mohammad Hossain, Ph.D. MHossain 12/23/96

Division of Pharmaceutical Evaluation I

Office of Clinical Pharmacology and Biopharmaceutics

Draft prepared before Clinpharm/Biopharm Briefing: October 23, 1996.

Clinpharm/Biopharm Briefing on November 12, 1996.

Note: Dr. Mohammad Hossain assisted in the review and provided comments involving IVIVC analysis.

CC: NDA 20-712, HFD-120, HFD-860 (Mahmood, Hossain, Malinowski), HFD-340 (Viswanathan), and HFD 870: Chron, Drug, Reviewer and FOI (HFD-19) files (Clarence Bott, PKLN, RM 13B-31).

Study #1

Title: Multi-Dose Evaluation of Pharmacokinetics and Safety of a Multi-Unit Dose of Carbamazepine (Protocol PI 101.103).

Objective:

The objective of this study was to compare the pharmacokinetics, bioavailability, and bioequivalence profile of the multi-unit, sustained-release formulation of carbamazepine (CARBATROL; CBZ-SR) to the marketed formulation of carbamazepine (Tegretol).

Study Design:

The study was a two-way, two sequence, double-blind, randomized, cross-over study, in which 24 patients with epilepsy received CBZ-SR or Tegretol. Among the 24 patients, there were 11 men and 13 women. Seventeen subjects were Caucasian, six were African American and one subject was Hispanic. The subjects' ages ranged from 21-54 years (mean 36.1 years). The daily dose administered to each patient was either 800, 1200, or 1600 mg of CBZ-SR or Tegretol. Patients received either Tegretol every 6 hours with placebo or CBZ-SR every 12 hours (morning and evening) alternating with placebo every 12 hours (midday and midnight) for 14 days. The respective dosing regimens for Tegretol and CBZ-SR are shown below:

Tegretol Dosing Regimen

Dose assigned	6 a.m.	12 noon	6 p.m.	12 midnight
800 mg daily	2 Tegretol 2 placebo	2 Tegretol 2 placebo	2 Tegretol 2 placebo	2 Tegretol 2 placebo
1200 mg daily	3 Tegretol 1 placebo	3 Tegretol 1 placebo	3 Tegretol 1 placebo	3 Tegretol 1 placebo
1600 mg daily	4 Tegretol	4 Tegretol	4 Tegretol	4 Tegretol

CBZ-SR Dosing Regimen

Dose assigned	6 a.m.	12 noon	6 p.m.	12 midnight
800 mg daily	2 CBZ-SR 2 placebo	4 placebo	2 CBZ-SR 2 placebo	4 placebo
1200 mg daily	3 CBZ-SR 1 placebo	4 placebo	3 CBZ-SR 1 placebo	4 placebo
1600 mg daily	4 CBZ-SR	4 placebo	4 CBZ-SR	4 placebo

On day 14 of each treatment period, blood samples were collected 5 minutes before drug administration and hourly for 24 hours after administration. The blood samples were immediately centrifuged, and the separated plasma then stored at -20°C. Carbamazepine and carbamazepine 10,11-epoxide plasma levels were determined by

The limit of detection of CBZ and CBZE was 2-20 μg/mL and 0.25-5.0 μg/mL, respectively.

Drug Administration:

The formulations of CBZ-SR or Tegretol were as follows:

Carbamazepine sustained-release:	200 mg capsules	Lot number 930002
Tegretol tablet in capsule	200 mg capsule	Lot number 930006
	200 mg capsule	Lot number 930020
	100 mg capsule	Lot number 930017
Placebo capsules	capsule	Lot number 930019

Results:

Plasma concentrations of carbamazepine and carbamazepine-10,11-epoxide after 14 days administration of CBZ-SR or Tegretol were very similar. The pharmacokinetic parameters, AUC, C_{max}, C_{min}, and C_{avg} for the time periods, 0-24 hr, 0-12 hr, and 12-24 hr were estimated for both CBZ-SR and Tegretol. Fluctuation Index (FI) was calculated

from (C_{max} -C_{min})/C_{avg} and measured for three periods, 0-24 hr, 0-12 hr, and 12-24 hr, respectively. Mean values for AUC, C_{max}, C_{min}, C_{avg} and FI for plasma concentrations of CBZ, CBZE and CBZ plus CBZE following administration of CBZ-SR and Tegretol are shown in Tables 1-3.

Bioequivalence between CBZ-SR and Tegretol was demonstrated using log transformed values of AUC, C_{max}, C_{min}, and C_{avg} on CBZ, CBZE and **CBZ plus CBZE**. Since carbamazepine and carbamazepine10,11-epoxide are equipotent anticonvulsive agents, plasma concentrations of carbamazepine and carbamazepine-10,11-epoxide at each time point were summed. Then using the plasma concentrations of carbamazepine and carbamazepine-10,11-epoxide AUC, C_{max}, C_{min}, and C_{avg} were estimated and overall bioequivalence of CBZ-SR and Tegretol were evaluated.

The mean values for AUC, C_{max}, C_{min}, and C_{avg} were very similar after administration of CBZ-SR or Tegretol, and were all within the recommended 0.80-1.25 limits of bioequivalence when analyzed on a logarithmic scale. However, it should be noted that FI failed to meet the bioequivalence criteria for both CBZ and CBZE (Tables 1-3).

Since carbamazepine and carbamazepine10,11-epoxide bound to plasma proteins, plasma concentrations of **CBZ plus CBZE** for the unbound drug and metabolite were calculated using literature values (CBZ = 75% bound, CBZE = 50% bound). The pharmacokinetic parameters of AUC, C_{max}, C_{min}, and C_{avg} were all bioequivalent when compared after administering CBZ-SR and Tegretol (Table 4).

Although only 11 males and 13 females were involved in the study an attempt was made to compare pharmacokinetic parameters by gender. Analysis of pharmacokinetic parameters using summed carbamazepine and carbamazepine-epoxide data (total plasma **CBZ *plus* CBZE**) demonstrated there were no statistical differences ($p>0.2$) between the pharmacokinetic values obtained from males and females (Table 5). Additional analysis of pharmacokinetic parameters using summed carbamazepine and carbamazepine-epoxide data

obtained after calculating the unbound plasma concentration of drug (unbound plasma **CBZ *plus* CBZE**) also demonstrated there were no statistical differences ($p>0.3$) between the pharmacokinetic values obtained from males and females (Table 5).

When bioequivalence criteria were calculated for males in the study (n=11), the AUC, C_{max}, C_{min}, and C_{avg} estimated from both total and unbound plasma concentrations of **CBZ plus CBZE** were found to be bioequivalent (Table 6-7).

For the 13 females in the study, daily administration of CBZ-SR and Tegretol was found to be bioequivalent for AUC, C_{max}, and C_{avg}, estimated from both total and unbound plasma concentrations of **CBZ plus CBZE,** but C_{min} was slightly outside the bioequivalent parameters (Tables 8-11). However, one patient (#15) reported taking laxatives throughout the CBZ-SR phase of the study, but not during the Tegretol phase of the study. Since this patient did not take laxative throughout the Tegretol phase of the cross-over study, it seems reasonable to assume the results obtained from this patient could skew the outcome when only small numbers of patients were involved. Indeed, repeating the pharmacokinetic analysis in females, but excluding data from patient #15, demonstrated bioequivalence between most of the pharmacokinetic parameters measured, except C_{min} for the time period of 12-24 hours. However, it should be noted that statistical power to detect a bioequivalent relation between drug products was reduced in this gender group analysis.

Conclusions:

This study demonstrates that Pharmavene's carbamazepine sustained-release capsule given every 12 hours is bioequivalent to Tegretol immediate release tablets given every 6 hours.

Figure 1.1 Mean Plasma Concentrations of Carbamazepine Following 14 Days Administration of CBZ-SR and Tegretol.

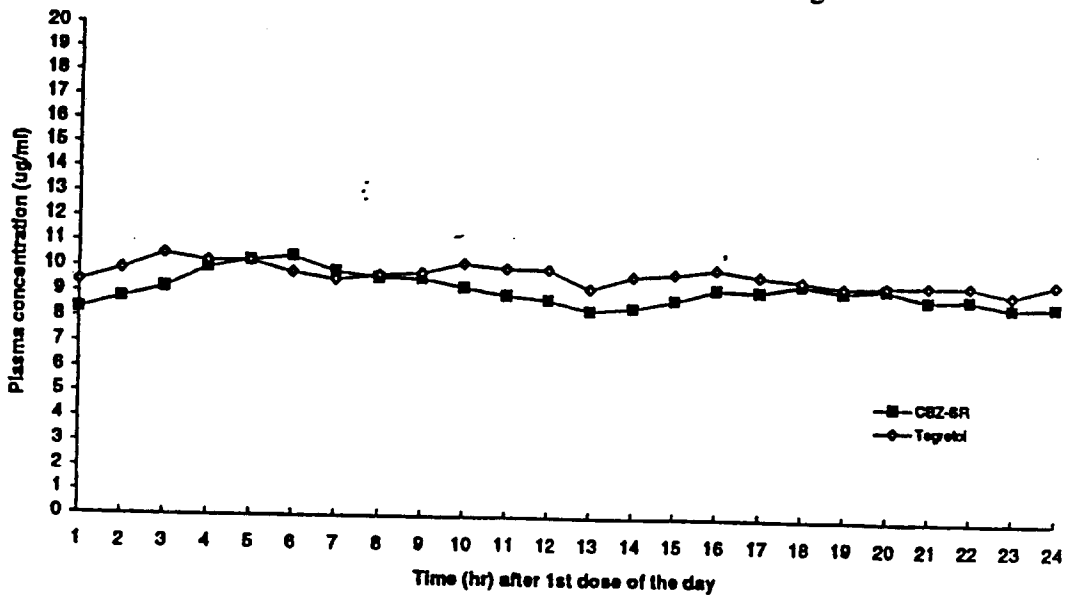

Figure 2.1 Mean Plasma Concentrations of Carbamazepine-10,11-Epoxide Following 14 Days Administration of CBZ-SR and Tegretol.

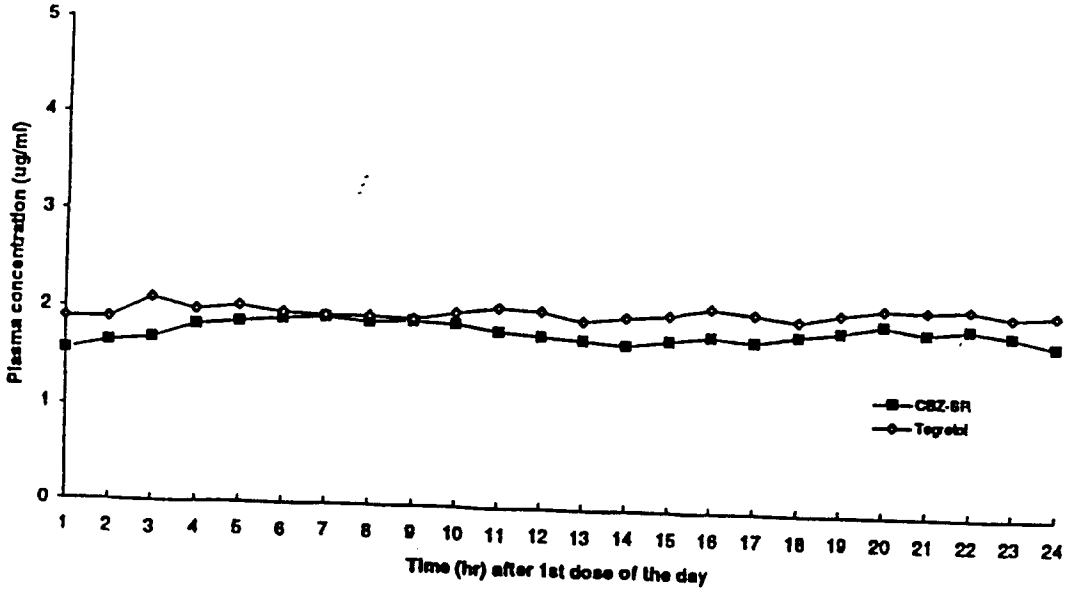

Table 5.1.1 Bioequivalence Analysis Summary I: CBZ
-- ANOVA model with log-transformation

PK Parameters	CBZ-SR (mean)	Tegretol (mean)	Mean % of CBZ-SR to Tegretol	Ratio Estimate (CBZ-SR to Tegretol)	90% CI (ANOVA model)
AUC (0-24 hr)	221.771	235.758	94.3	0.93	(0.89 - 0.98)*
AUC (0-12 hr)	113.258	119.679	95.4	0.94	(0.89 - 1.00)*
AUC (12-24 hr)	108.533	116.088	93.4	0.92	(0.87 - 0.98)*
C max (0-24 hr)	11.238	11.744	96.9	0.96	(0.91 - 1.01)*
C max (0-12 hr)	10.950	11.523	96.0	0.95	(0.89 - 1.01)*
C max (12-24 hr)	10.350	11.014	94.7	0.93	(0.88 - 0.99)*
C min (0-24 hr)	7.500	8.279	90.3	0.89	(0.83 - 0.95)*
C min (0-12 hr)	7.961	8.769	92.1	0.90	(0.83 - 0.98)*
C min (12-24 hr)	7.759	8.563	90.3	0.89	(0.83 - 0.95)*
C avg (0-24 hr)	9.241	9.824	94.3	0.93	(0.89 - 0.98)*
C avg (0-12 hr)	9.438	9.974	95.4	0.94	(0.89 - 1.00)*
C avg (12-24 hr)	9.046	9.675	93.4	0.92	(0.87 - 0.98)*
FI (0-24 hr)	0.428	0.353	129.7	1.20	(1.07 - 1.35)
FI (0-12 hr)	0.326	0.283	121.2	1.15	(1.02 - 1.29)
FI (12-24 hr)	0.297	0.253	139.5	1.18	(0.96 - 1.45)

* : The 90% CI fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on log scale

Table 5.1.2 Bioequivalence Analysis Summary II: CBZ-epoxide
-- ANOVA model with log-transformation

PK Parameters	CBZ-SR (mean)	Tegretol (mean)	Mean % of CBZ-SR to Tegretol	Ratio Estimate (CBZ-SR to Tegretol)	90% CI (ANOVA model)
AUC (0-24 hr)	43.625	48.417	91.5	0.89	(0.82 - 0.97)*
AUC (0-12 hr)	21.658	23.721	92.2	0.89	(0.82 - 0.98)*
AUC (12-24 hr)	21.988	24.692	91.3	0.89	(0.82 - 0.97)*
C max (0-24 hr)	2.236	2.540	90.8	0.88	(0.80 - 0.96)*
C max (0-12 hr)	2.105	2.353	91.2	0.88	(0.79 - 0.97)
C max (12-24 hr)	2.116	2.410	91.0	0.88	(0.80 - 0.97)*
C min (0-24 hr)	1.374	1.559	92.2	0.87	(0.77 - 0.98)
C min (0-12 hr)	1.477	1.605	95.1	0.90	(0.80 - 1.01)*
C min (12-24 hr)	1.499	1.766	89.0	0.85	(0.77 - 0.95)
C avg (0-24 hr)	1.818	2.018	91.5	0.89	(0.82 - 0.97)*
C avg (0-12 hr)	1.805	1.978	92.1	0.89	(0.81 - 0.98)*
C avg (12-24 hr)	1.833	2.058	91.4	0.89	(0.82 - 0.97)*
FI (0-24 hr)	0.473	0.488	122.9	1.05	(0.86 - 1.28)
FI (0-12 hr)	0.344	0.370	111.1	1.00	(0.86 - 1.18)*
FI (12-24 hr)	0.338	0.329	125.4	1.07	(0.87 - 1.32)
AUC epoxide-to-CBZ ratio (0-24 hr)	0.205	0.211	96.7	0.96	(0.91 - 1.01)*
AUC epoxide-to-CBZ ratio (0-12 hr)	0.198	0.205	95.9	0.95	(0.90 - 1.00)*
AUC epoxide-to-CBZ ratio (12-24 hr)	0.213	0.218	98.0	0.97	(0.91 - 1.03)*

* : The 90% CI fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on log scale

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Table 1.1 < PI 101.103 > Bioequivalence Analysis for CBZ plus CBZ-epoxide calculated in ug/mL: Total (all patients)

-- ANOVA model with log-transformation

PK Parameters	CBZ-SR (mean)	Tegretol (mean)	Mean % of CBZ-SR to Tegretol	Ratio Estimate (CBZ-SR to Tegretol)	90% CI (ANOVA model)
AUC (0-24 hr)	265.400	284.179	93.8	0.93	(0.88 - 0.98)*
AUC (0-12 hr)	134.900	143.400	95.0	0.94	(0.88 - 1.00)*
AUC (12-24 hr)	130.500	140.787	93.0	0.92	(0.87 - 0.97)*
C max (0-24 hr)	13.342	14.162	95.6	0.94	(0.89 - 1.00)*
C max (0-12 hr)	13.009	13.801	95.4	0.94	(0.88 - 1.00)*
C max (12-24 hr)	12.411	13.351	93.9	0.93	(0.87 - 0.98)*
C min (0-24 hr)	8.950	9.938	90.4	0.89	(0.83 - 0.95)*
C min (0-12 hr)	9.516	10.439	92.6	0.90	(0.83 - 0.98)*
C min (12-24 hr)	9.313	10.416	89.9	0.88	(0.83 - 0.94)*
C avg (0-24 hr)	11.060	11.841	93.9	0.93	(0.88 - 0.98)*
C avg (0-12 hr)	11.242	11.951	94.9	0.94	(0.88 - 1.00)*
C avg (12-24 hr)	10.876	11.733	93.0	0.92	(0.87 - 0.97)*

* : The 90% CI fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on log scale
Measurement unit: AUC in ug.hr/mL; C max in ug/mL; C min in ug/mL; C avg in ug/mL

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Table 1.2 < PI 101.103 > Bioequivalence Analysis for CBZ plus CBZ-epoxide calculated in ug/mL: Unbound (all patients)

-- ANOVA model with log-transformation

PK Parameters	CBZ-SR (mean)	Tegretol (mean)	Mean % of CBZ-SR to Tegretol	Ratio Estimate (CBZ-SR to Tegretol)	90% CI (ANOVA model)
AUC (0-24 hr)	77.292	83.200	93.5	0.92	(0.87 - 0.98)*
AUC (0-12 hr)	39.158	41.800	94.6	0.93	(0.87 - 1.00)*
AUC (12-24 hr)	38.129	41.396	92.6	0.92	(0.87 - 0.97)*
C max (0-24 hr)	3.871	4.165	94.5	0.93	(0.88 - 0.99)*
C max (0-12 hr)	3.772	4.036	94.7	0.93	(0.87 - 1.00)*
C max (12-24 hr)	3.621	3.934	93.2	0.92	(0.86 - 0.98)*
C min (0-24 hr)	2.593	2.888	90.5	0.89	(0.82 - 0.95)*
C min (0-12 hr)	2.756	3.019	92.9	0.91	(0.83 - 0.98)*
C min (12-24 hr)	2.714	3.063	89.6	0.88	(0.82 - 0.94)*
C avg (0-24 hr)	3.220	3.468	93.5	0.92	(0.87 - 0.98)*
C avg (0-12 hr)	3.264	3.484	94.6	0.93	(0.87 - 1.00)*
C avg (12-24 hr)	3.178	3.450	92.7	0.92	(0.87 - 0.97)*

* : The 90% CI fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on log scale
Measurement unit: AUC in ug.hr/mL; C max in ug/mL; C min in ug/mL; C avg in ug/mL
25% CBZ and 50% CBZ-epoxide was considered unbound or free in calculation

Table 5.6.1 Gender Differences in Carbatrol-to-Tegretol Ratio of PK Parameters for CBZ plus CBZE Total and Unbound Components

(11 male vs. 13 female patients)

Component	PK parameter	Period	Gender	Ratio of Carbatrol to Tegretol Mean	S.D.	t value	p value
Total	AUC	0-24 hrs	male	0.959	0.084	0.7110	0.4861
			female	0.921	0.167		
		0-12 hrs	male	0.966	0.120	0.4741	0.6401
			female	0.936	0.182		
		12-24 hrs	male	0.954	0.089	0.7992	0.4327
			female	0.909	0.167		
	C max	0-24 hrs	male	0.972	0.135	0.4660	0.6458
			female	0.944	0.163		
		0-12 hrs	male	0.978	0.150	0.6097	0.5483
			female	0.935	0.189		
		12-24 hrs	male	0.937	0.101	-0.0540	0.9575
			female	0.941	0.194		
	C min	0-24 hrs	male	0.927	0.153	0.5820	0.5665
			female	0.884	0.202		
		0-12 hrs	male	0.936	0.135	0.2100	0.8356
			female	0.918	0.241		
		12-24 hrs	male	0.940	0.139	1.1082	0.2798
			female	0.864	0.186		
	C avg	0-24 hrs	male	0.959	0.083	0.7112	0.4860
			female	0.921	0.167		
		0-12 hrs	male	0.966	0.120	0.4741	0.6401
			female	0.936	0.182		
		12-24 hrs	male	0.954	0.089	0.7999	0.4323
			female	0.909	0.166		
Unbound	AUC	0-24 hrs	male	0.959	0.093	0.7444	0.4645
			female	0.916	0.172		
		0-12 hrs	male	0.966	0.132	0.5359	0.5974
			female	0.930	0.186		
		12-24 hrs	male	0.954	0.090	0.8706	0.3934
			female	0.904	0.170		
	C max	0-24 hrs	male	0.969	0.148	0.6327	0.5334
			female	0.927	0.169		
		0-12 hrs	male	0.978	0.160	0.7417	0.4661
			female	0.923	0.196		
		12-24 hrs	male	0.934	0.111	0.0373	0.9706
			female	0.932	0.193		
	C min	0-24 hrs	male	0.935	0.164	0.7127	0.4835
			female	0.880	0.206		
		0-12 hrs	male	0.942	0.149	0.3070	0.7617
			female	0.916	0.240		
		12-24 hrs	male	0.942	0.141	1.2066	0.2404
			female	0.857	0.193		
	C avg	0-24 hrs	male	0.959	0.093	0.7425	0.4656
			female	0.916	0.172		
		0-12 hrs	male	0.966	0.131	0.5359	0.5974
			female	0.930	0.186		
		12-24 hrs	male	0.954	0.090	0.8724	0.3924
			female	0.904	0.170		

Note: for unequal variance (F<.05), approximate t value with Satterthwaite's df was used for p value calculation.

Printed by Mohammad Hossain

Electronic Mail Message

Date: 27-Nov-1996 02:32pm
From: Mohammad Hossain
HOSSAINM
Dept: HFD-860 WOC2 2073
Tel No: 301-594-0488 FAX 301-480-3212

TO: See Below
Subject: Carbamazepine SR - Post ClinPharm/Biopharm Briefing Update

E L E C T R O N I C M A I L M E S S A G E

Date: 27-Nov-1996 01:32pm EST
From: Iftekhar Mahmood
MAHMOODI
Dept: HFD-860 WOC2 4054
Tel No: 301-594-5509 FAX 301-594-0499

TO: Mohammad Hossain (HOSSAINM)

Subject: CBZ

Response to the issues raised on Clinpharm/Biopharm day on Carbatrol:

1. **Bioequivalence:**

The pivotal study in this NDA (20-712) involves the comparison of Pharmavene sustained release product (CBZ-SR) with Tegretol IR (Protocol PI 101.103). Twenty four patients with epilepsy (9 of the patients were on a fixed dose of phenytoin, phenobarbital, clorazepate, primidone or valproic acid) received a daily dose of 800 (n =9), 1200 (n =9) or 1600 (n =6) mg CBZ-SR or Tegretol IR for 14 days. Tegretol IR was given every 6 hours and CBZ-SR was given every 12 hours. On day 14, subjects were given a high fat meal (FDA recommended) 30 minutes before the administration of both dosage forms (this was the only high fat meal given to the patients during the whole study period, otherwise patients remained on controlled regular diet). The 90% confidence interval was applied on log transformed data on the AUC, Cmax, Cmin, Caverage and Fluctuation Index (FI) without dose normalization of these parameters.

It was asked whether or not 90% CI was applied by normalizing the dose? Later, this issue was discussed with the Sponsor, Dr. Schuirman and Dr. Venitz. The data indicate (attached Tables) that there is negligible change in the AUC, Cmax and Cmin of CBZ over the dose range of 800 to 1600 mg for both dosage forms. However, the AUC, Cmax and Cmin of CBZE increases with increasing dose.

Patients enrolled in this study were already on different fixed dosing regimens of CBZ which was earlier known to provide plasma

concentrations within the clinical therapeutic concentration range (i.e., 4-12 ug/mL) for each of the patient. Literature reports suggest that plasma concentrations of CBZ increase disproportionally with increasing CBZ dose following multiple dosing, and that CBZ levels generally are in the therapeutic window despite the wide range of prescribed doses. In our discussion with Dr. Venitz this finding did not appear to be surprising to him.

It appears that two factors may be responsible for the similar values of AUC, Cmax and Cmin of CBZ over the dose range. Either the induction of enzymes by CBZ is dose dependent (higher the dose more enzyme induction) and/or the aborption of CBZ is saturable at higher doses (this saturation of absorption at higher doses of CBZ may be solubility rate limited). The CBZE concentration indicates that probably it is the induction of enzymes which is responsible for maintaining a similar plasma concentration at different doses.

Dr. Schuirman pointed out that since the values of AUC, Cmax and Cmin of CBZ does not change with dose, there is no advantage of dividing the patients in different groups or normalizing their PK values according to their dose. Furthermore, dividing the patients according to the dose reduces the power of the test to detect any difference between the two formulations as shown in the 90% CI analysis in Table 1. Therefore, pooling the data from all dose groups is not invalid for the calculation of 90% CI.

Therefore, the conclusion from Study 101.103 that Carbatrol is bioequivalent to Tegretol is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

2. **Food Effect:**

In the labelling, the following was suggested to the Sponsor: Under 'Dosage and Administration' the statement "Medication should be taken with meals" should be replaced by **"Carbatrol could be taken with or without meals"**.

This decision was made based upon the multiple dose fed state study where steady-state Cmax values were within the therapeutic concentration range. Also, it should be noted that comparison of PK values between the 0-12 hr interval (high fat meal) and 12-24 hr interval (regular meal) did not show any effect of different meals.

Distribution:

TO: Lawrence Lesko (LESKOL)
TO: Henry Malinowski (MALINOWSKI)
TO: Nicholas Fleischer (FLEISCHERN)
TO: Mei-Ling Chen (CHENME)
TO: William Gillespie (GILLESPIEW)
TO: Mehul Mehta (MEHTA)
TO: Paul Hepp (HEPP)
TO: Shiew-Mei Huang (HUANGS)

CC: Iftekhar Mahmood (MAHMOODI)
CC: Mohammad Hossain (HOSSAINM)

Table 1 - CBZ

Parameters	800 MG (N=9)		1200 MG (N=9)		1600 MG (N=6)	
	SR bid	IR qid	SR bid	IR qid	SR bid	IR qid
AUC0-12	109.3	111.5	115.9	131.4	113.7	114.4
90% C.I.	0.89-1.07		0.79-1.04		0.85-1.12	
AUC12-24	106.98	106.93	111.07	124.04	107.07	117.88
90% C.I.	0.91-1.07		0.85-0.99		0.72-1.07	
AUC0-24	216.24	218.39	227.97	255.46	220.77	232.27
90% C.I.	0.92-1.05		0.82-1.01		0.79-1.08	
CMAX0-12	10.31	10.57	11.50	12.63	11.09	11.29
90% C.I.	0.87-1.08		0.81-1.06		0.83-1.13	
CMAX12-24	10.11	10.18	10.44	11.76	10.58	11.14
90% C.I.	0.92-1.11		0.86-0.96		0.71-1.17	
CMAX0-24	10.71	10.91	11.68	12.63	11.37	11.66
90%C.I.	0.92-1.08		0.84-1.04		0.83-1.13	
CMIN0-12	8.06	8.32	8.02	9.64	7.72	8.14
90%C.I.	0.86-1.09		0.72-1.01		0.75-1.14	
CMIN12-24	7.87	8.09	7.88	8.95	7.42	8.7
90% C.I.	0.86-1.03		0.84-1.01		0.65-1.0	
CMIN0-24	7.66	7.95	7.60	8.83	7.11	7.95
90% C.I.	0.83-1.02		0.79-1.02		0.69-1.04	

Table 2 - CBZE

Parameters	800 MG (N=9)		1200 MG (N=9)		1600 MG (N=6)	
	SR bid	IR qid	SR bid	IR qid	SR bid	IR qid
AUC0-12	15.74	17.86	20.29	24.43	32.58	31.45
90% C.I.	0.75-1.06		0.72-1.02		0.86-1.24	
AUC12-24	16.63	18.61	20.54	24.96	32.18	33.42
90% C.I.	0.81-1.03		0.75-1.0		0.74-1.23	
AUC0-24	32.37	36.47	40.81	49.4	64.73	64.87
90% C.I.	0.79-1.04		0.74-1.03		0.81-1.22	
CMAX0-12	1.50	1.83	2.0	2.36	3.16	3.12
90% C.I.	0.69-1.05		0.73-1.02		0.85-1.23	
CMAX12-24	1.6	1.98	2.0	2.32	3.08	3.2
90% C.I.	0.72-1.08		0.78-1.01		0.72-1.08	
CMAX0-24	1.62	2.1	2.15	2.41	3.3	3.4
90% C.I.	0.69-1.04		0.79-1.04		0.77-1.22	
CMIN0-12	1.11	1.27	1.41	1.75	2.13	1.88
90%C.I.	0.74-1.06		0.71-0.98		0.76-1.68	
CMIN12-24	1.18	1.31	1.35	1.8	2.2	2.4
90% C.I.	0.78-1.03		0.66-1.0		0.69-1.22	
CMIN0-24	1.06	1.23	1.30	1.71	1.95	1.82
90% C.I.	0.72-1.01		0.65-0.97		0.74-1.61	

Table 3 - CBZE

Parameters	800 MG (N=9)		1200 MG (N=9)		1600 MG (N=6)	
	SR bid	IR qid	SR bid	IR qid	SR bid	IR qid
AUC0-12	15.74	17.86	20.29	24.43	32.58	31.45
P-value	0.26		0.40		0.74	
AUC12-24	16.63	18.61	20.54	24.96	32.18	33.42
P-value	0.23		0.12		0.72	
AUC0-24	32.37	36.47	40.81	49.4	64.73	64.87
P-value	0.24		0.13		0.49	
CMAX0-12	1.50	1.83	2.0	2.36	3.16	3.12
P-value	0.21		0.17		0.83	
CMAX12-24	1.6	1.98	2.0	2.32	3.08	3.2
P-value	0.30		0.15		0.71	
CMAX0-24	1.62	2.1	2.15	2.41	3.3	3.4
P-value	0.19		0.26		0.80	
CMIN0-12	1.11	1.27	1.41	1.75	2.13	1.88
P-value	0.28		0.09		0.54	
CMIN12-24	1.18	1.31	1.35	1.8	2.2	2.4
P-value	0.19		0.12		0.56	
CMIN0-24	1.06	1.23	1.30	1.71	1.95	1.82
P-value	0.14		0.08		0.66	

Statistically not significant at the 0.05 level (all P-values>0.05).

Study #2

Title: A Food Effect Bioavailability Study of CARBATROL (Protocol PI 101.108).

Objective:

The objective of this study was to determine and evaluate the plasma levels of carbamazepine after administering CBZ-SR while fasting, with food (high-fat breakfast), and when sprinkled over a semi-solid food.

Study Design:

The study was an open-label, single dose, randomized, balanced, cross-over design with three treatment arms, in which 12 normal male volunteers received a single dose of CBZ-SR with or without food. Eleven subjects were Caucasian, and one was an African American. The subjects' ages ranged from 21-48 years (mean 33.8 years). The "high-fat breakfast" consisted of two eggs fried in butter, two strips of bacon, six ounces of hash brown potatoes, two slices of toast with two parts of butter, and eight ounces of whole milk. The washout period between each study was at least 14 days.

Blood samples were collected at the following times: 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 29, 34, 48, 72, 96, 168, and 216 hours after CBZ administration. The blood samples were immediately centrifuged, and the separated plasma was stored at -20°C. Carbamazepine (CBZ) and carbamazepine-10,11-epoxide (CBZE) plasma concentrations were determined by The limit of detection for carbamazepine and carbamazepine-10,11-epoxide was 0.02 - 10 µg/mL and 0.01 - 1.0 µg/mL, respectively.

Drug Administration:

Each subject received 400 mg (2 x 200 mg capsules) of the same carbamazepine formulation (Lot No. 940002A) for each treatment.

Treatment A: 2 x 200 mg capsules administered with food (high-fat diet).

Treatment B: 2 x 200 mg capsules administered without food.

Treatment C: 2 x 200 mg capsules opened and sprinkled over applesauce.

Results:

The following Table summarizes the effect of food on the pharmacokinetics of carbamazepine.

Parameters	Species	Fed	Fasting	Sprinkled
$AUC_{(0\text{-inf})}$	CBZ	267 ± 52*	239 ± 41	254 ± 51
(µg*hr/mL)	CBZE	19 ± 4*	17 ± 4	17 ± 3
C_{max}	CBZ	4.3 ± 0.6*	3.2 ± 0.4	3.3 ± 0.3
(µg/mL)	CBZE	0.3 ± 0.05*	0.2 ± 0.05	0.2 ± 0.04
T_{max} (hrs)	CBZ	13.7 ± 6.3*	23.7 ± 8.7	17.3 ± 7.2
	CBZE	34.5 ± 9.8	39.8 ± 8.6	38.6 ± 9.3
$T_{1/2}$ (hrs)	CBZ	36.9 ± 8.6	36.3 ± 6.5	36.8 ± 8.3
	CBZE	27.9 ± 4.2	31.3 ± 6.5	30.8 ± 5.4

* statistically different ($p<0.01$) to values obtained in fasting state.

The results of this study indicate that AUC and C_{max} are statistically different in fed state than the fasting state of CBZ and CBZE. T_{max} of CBZ was reduced by 10 hours when given with food compared to fasting state. The elimination half-life remains unchanged between fed and fasting state.

Conclusions:

The results of this study show that the rate and extent of absorption of CBZ-SR increases in the presence of a high-fat meal relative to a fasting state. Furthermore, the absorption from the CBZ-SR product when given by sprinkling over applesauce, has a pharmacokinetic profile similar to fasted state.

Bioequivalence Assessment of CBZ and CBZE for Sprinkle vs Fasting

Table S1.

Pharmacokinetic Parameters *(CBZ)*	Ratio Estimate	90% Confidence Interval of Ratio (ANOVA)
	(Food to Fasting) Table 1.1	
$AUC_{0\text{-}inf}$	1.12	1.06-1.18*
$AUC_{0\text{-}t}$	1.11	1.06-1.17*
C_{max}	1.35	1.27-1.43
	(Sprinkle to Fasting) Table 1.2	
$AUC_{0\text{-}inf}$	1.06	1.00-1.12*
$AUC_{0\text{-}t}$	1.06	1.00-1.11*
C_{max}	1.04	0.98-1.11*
	(Sprinkle to Food) Table 1.3	
$AUC_{0\text{-}inf}$	0.95	0.90-1.00*
$AUC_{0\text{-}t}$	0.95	0.90-1.00*
C_{max}	0.77	0.73-0.82

Table S2.

Pharmacokinetic Parameters *(CBZE)*	Ratio Estimate	90% Confidence Interval of Ratio (ANOVA)
	(Food to Fasting) Table 2.1	
$AUC_{0\text{-}inf}$	1.16	1.08-1.25*
$AUC_{0\text{-}t}$	1.17	1.07-1.27
C_{max}	1.29	1.19-1.39
	(Sprinkle to Fasting) Table 2.2	
$AUC_{0\text{-}inf}$	1.06	0.99-1.14*
$AUC_{0\text{-}t}$	1.05	0.96-1.14*
C_{max}	1.05	0.98-1.14*
	(Sprinkle to Food) Table 2.3	
$AUC_{0\text{-}inf}$	0.92	0.85-0.98*
$AUC_{0\text{-}t}$	0.89	0.82-0.97*
C_{max}	0.82	0.76-0.89

Figure 1.4 CBZ Average Plasma Concentration-Time Plots for Dosing Conditions

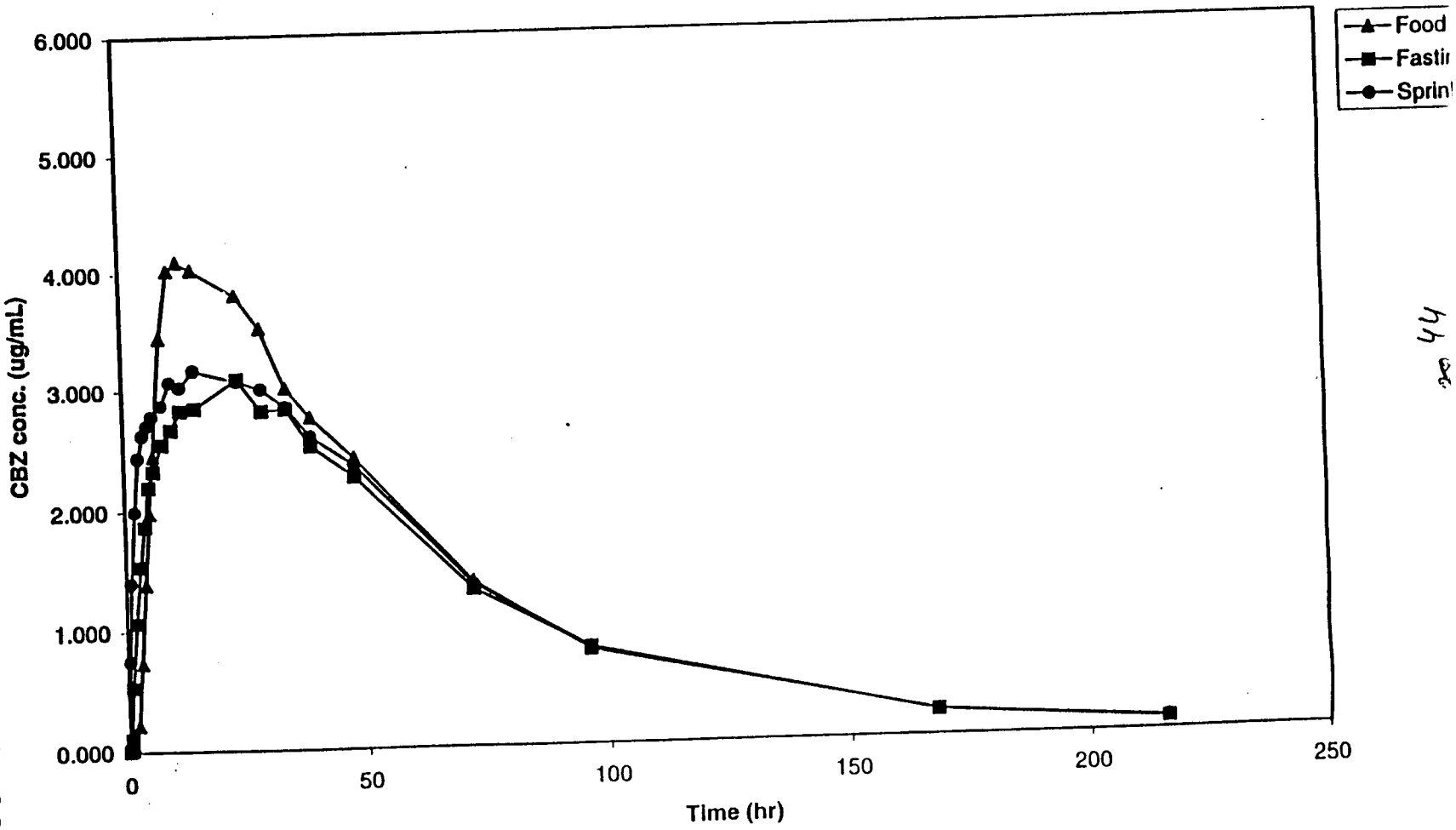
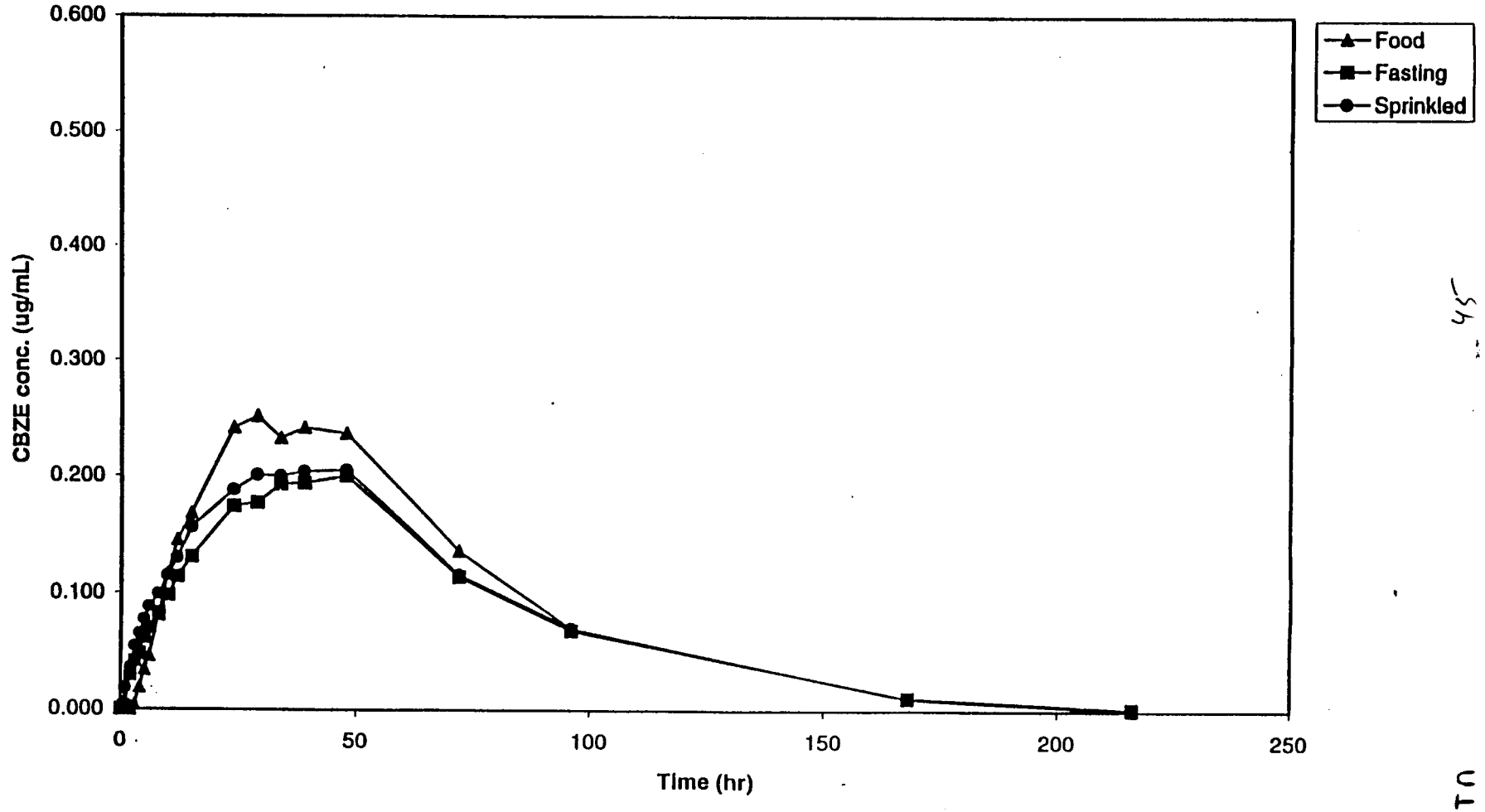


Figure 2.4 CBZE Average Plasma Concentration-Time Plots for Dosing Conditions



Study #3

Title: A Dose Proportionality Study of CARBATROL (Protocol PI 101.109).

Study Objective:

The objective of this study was to evaluate dose proportionality of CBZ-SR following a single oral administration of six different doses (200 -800 mg) of CBZ-SR.

Study Design:

The protocol was designed as an outpatient, open-label, randomized, fasting, six-way crossover study. Twelve healthy male subjects entered the study. Eleven subjects were Caucasian, and one was a Native American. The subjects' ages ranged from 19-49 years (mean 32.8 years). The volunteers received single oral doses of 200, 300, 400, 500, 600, and 800 mg CBZ-SR. The washout period between each dose was 14 days. Blood samples were collected at the following time points on the day of each drug administration: 0 (pre-dose), and, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 29, 34, 39, 48, 72, 96, 168, and 216 hours post-dose. The blood samples were immediately centrifuged, and the separated plasma stored at approximately -20^{0}C. The concentrations of carbamazepine and carbamazepine-10,11-epoxide were determined using

The limit of detection for carbamazepine and carbamazepine-10,11-epoxide was 0.02 - 10 µg/mL and 0.01 - 1.0 µg/mL, respectively.

Drug Administration:

The drug was administered as 200 mg capsules (Lot No. 940002A) and/or 300 mg capsules (Lot No. 940004A) in the following combinations:

Dose	Capsule Combination
200 mg	1 x 200 mg
300 mg	1 x 300 mg
400 mg	2 x 200 mg
500 mg	1 x 200 mg plus 1 x 300 mg
600 mg	2 x 300 mg
800 mg	1 x 200 mg plus 2 x 300 mg

Results:

Pharmacokinetics of Carbamazepine:

The arithmetic mean of $AUC_{0\text{-inf}}$ and C_{max} increased sequentially with increasing doses of CBZ-SR (Table1 & Figures 1 and 2). In contrast to AUC and C_{max}, the mean T_{max} for each dose administered did not increase sequentially with increasing doses of CBZ-SR. The lowest mean Tmax value was 19.2 ± 6.4 hours at the 200 mg dose, and the highest was 24.7 ± 10.3 hours at the 500 mg dose. The differences in T_{max} among these doses were not statistically significant (p=0.27). The plasma half-life of carbamazepine decreased slightly with increasing doses of CBZ-SR. The longest half-life occurred at the 200 mg dose (39.5 ± 5.3 hours) and this value decreased sequentially with increasing doses such that the half-life at the 800 mg dose was 35.5 ± 8.6 hours.

TABLE 1

Dose Administered (CBZ-SR)	$AUC_{0\text{-inf}}$ µg*hr/mL	C_{max} µg/mL	T_{max} hrs	$T_{1/2}$ hrs
200 mg	140.3 ± 31.4	1.9 ± 0.3	19.2 ± 6.8	39.5 ± 5.3
300 mg	190.9 ± 43.1	2.6 ± 0.4	22.1 ± 9.6	37.5 ± 6.7
400 mg	243.7 ± 39.9	3.3 ± 0.4	24.1 ± 8.3	36.3 ± 5.6
500 mg	283.3 ± 45.9	3.9 ± 0.5	24.7 ± 10.3	36.6 ± 6.6
600 mg	331.4 ± 54.7	4.6 ± 0.7	23.3 ± 8.6	37.0 ± 8.9
800 mg	413.5 ± 68.2	5.6 ± 0.8	24.4 ± 7.3	35.5 ± 8.6

Mean ± sd

Pharmacokinetics of carbamazepine-10,11-epoxide:

The arithmetic mean of $AUC_{0\text{-inf}}$ and C_{max} increased sequentially with increasing doses of CBZ-SR (Table 2). In contrast to AUC and C_{max}, the mean T_{max} for each dose administered did not increase sequentially with increasing doses of CBZ-SR. The lowest mean T_{max} value was 34.3 ± 8.8 hours at the 300 mg dose, and the highest T_{max} was 38.6± 5.9 hours occurred at the 800 mg dose. The differences in T_{max} among these doses were not statistically significant (p=0.4196). The plasma half-life of CBZE was not constant with increasing doses of CBZ-SR. The longest half-life occurred at the 200 mg

dose (35.8 ± 9.1 hours) and this value decreased sequentially with increasing doses such that the half-life at the 800 mg dose was 27.3 ± 5.9 hours.

The $AUC_{0\text{-inf}}$ and C_{max} of CBZE was less than 10% compared to CBZ at the dose range of 200-800 mg of CBZ.

TABLE 2

Dose Administered (CBZ-SR)	$AUC_{0\text{-inf}}$ µg*hr/mL	C_{max} ng/mL	T_{max} hrs	$T_{1/2}$ hrs
200 mg	8.5 ± 1.5	108 ± 12	36.2 ± 6.3	33.7 ± 9.1
300 mg	12.8 ± 1.5	167 ± 31	34.3 ± 8.8	35.7 ± 6.1
400 mg	17 ± 3.0	225 ± 30	35.7 ± 5.8	31.1 ± 4.2
500 mg	20.7 ± 4.0	279 ± 58	38.4 ± 5.5	31.0 ± 6.7
600 mg	25.7 ± 5.0	355 ± 92	35.5 ± 8.1	27.9 ± 4.6
800 mg	34.4 ± 6.6	472 ± 104	38.6 ± 5.9	27.3 ± 5.9

Mean ± sd

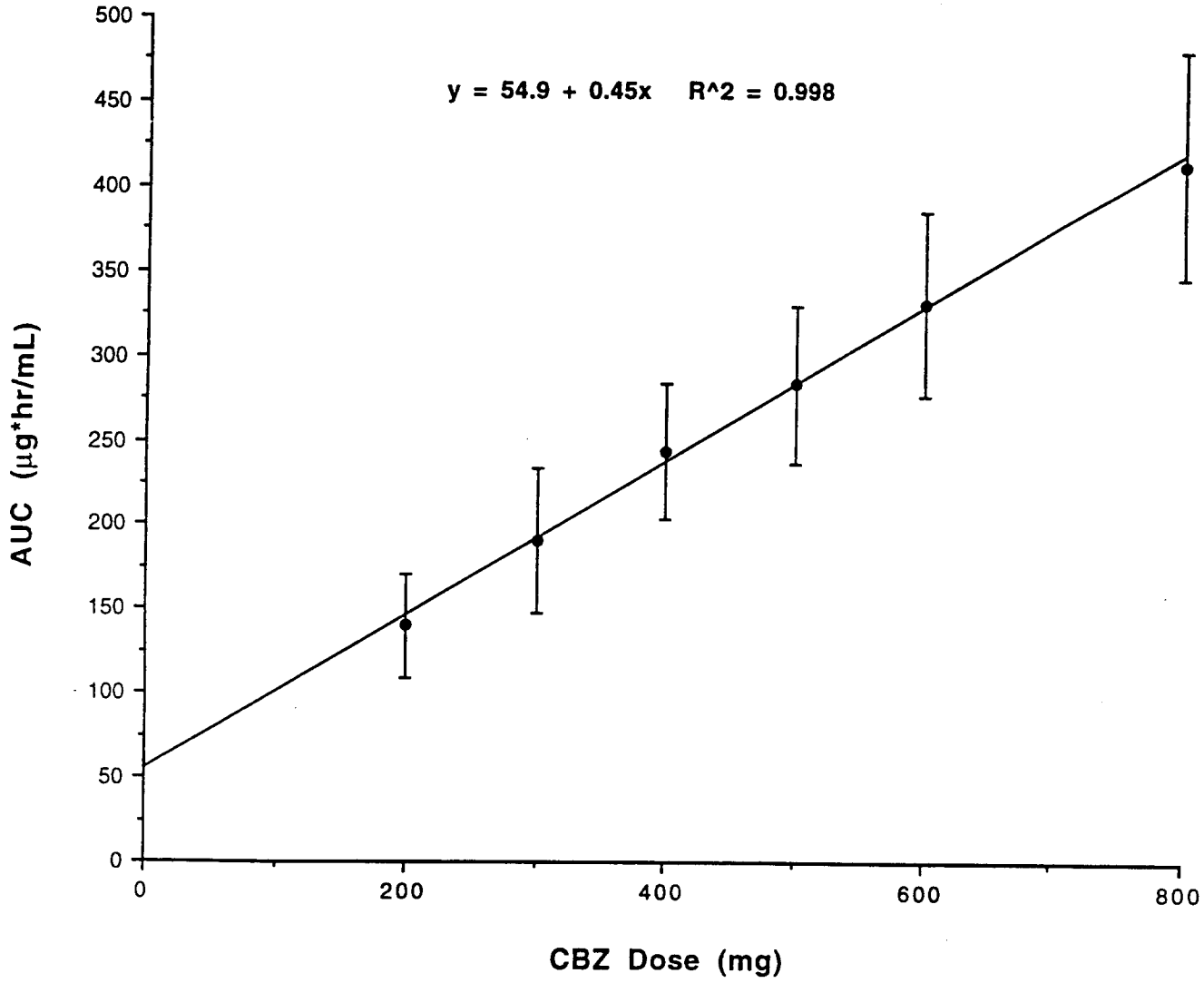
Conclusion:

In summary, the data suggest that carbamazepine and carbamazepine-10,11-epoxide follow linear kinetics at the dose range of 200-800 mg given as CBZ-SR.

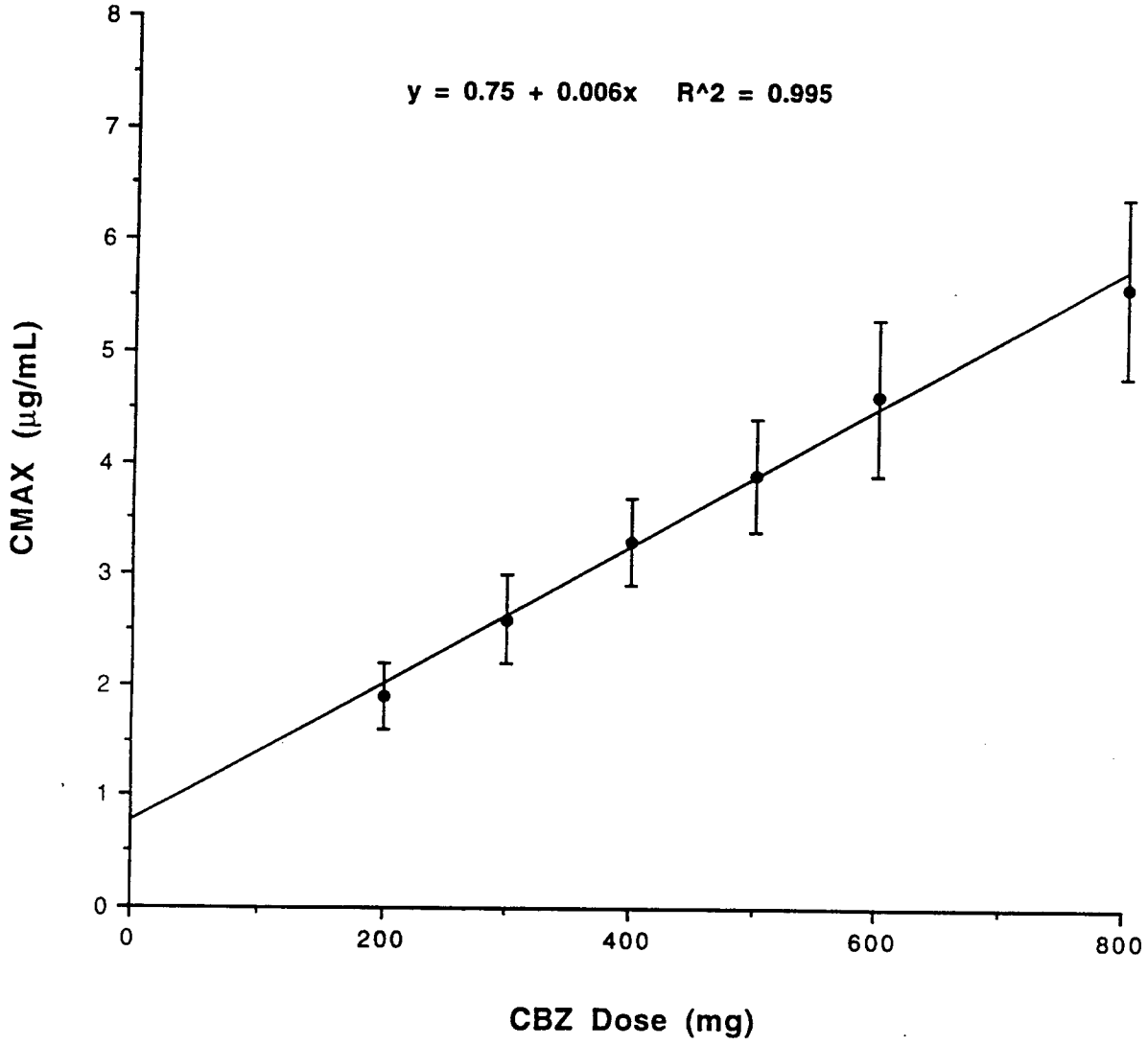
Table 11 The Relationship between Mean Bioavailability of Carbamazepine, Carbamazepine Epoxide and Dose Administered.

Dose (mg)	CBZE $AUC_{0-\infty}$ (µg·hr/mL)	CBZ $AUC_{0-\infty}$ (µg·hr/mL)	Metabolite (% of drug)
200	8.5	140.3	6.1
300	12.8	190.9	6.7
400	17.0	243.7	7.0
500	20.7	283.3	7.3
600	25.6	330.4	7.7
800	34.4	413.5	8.3

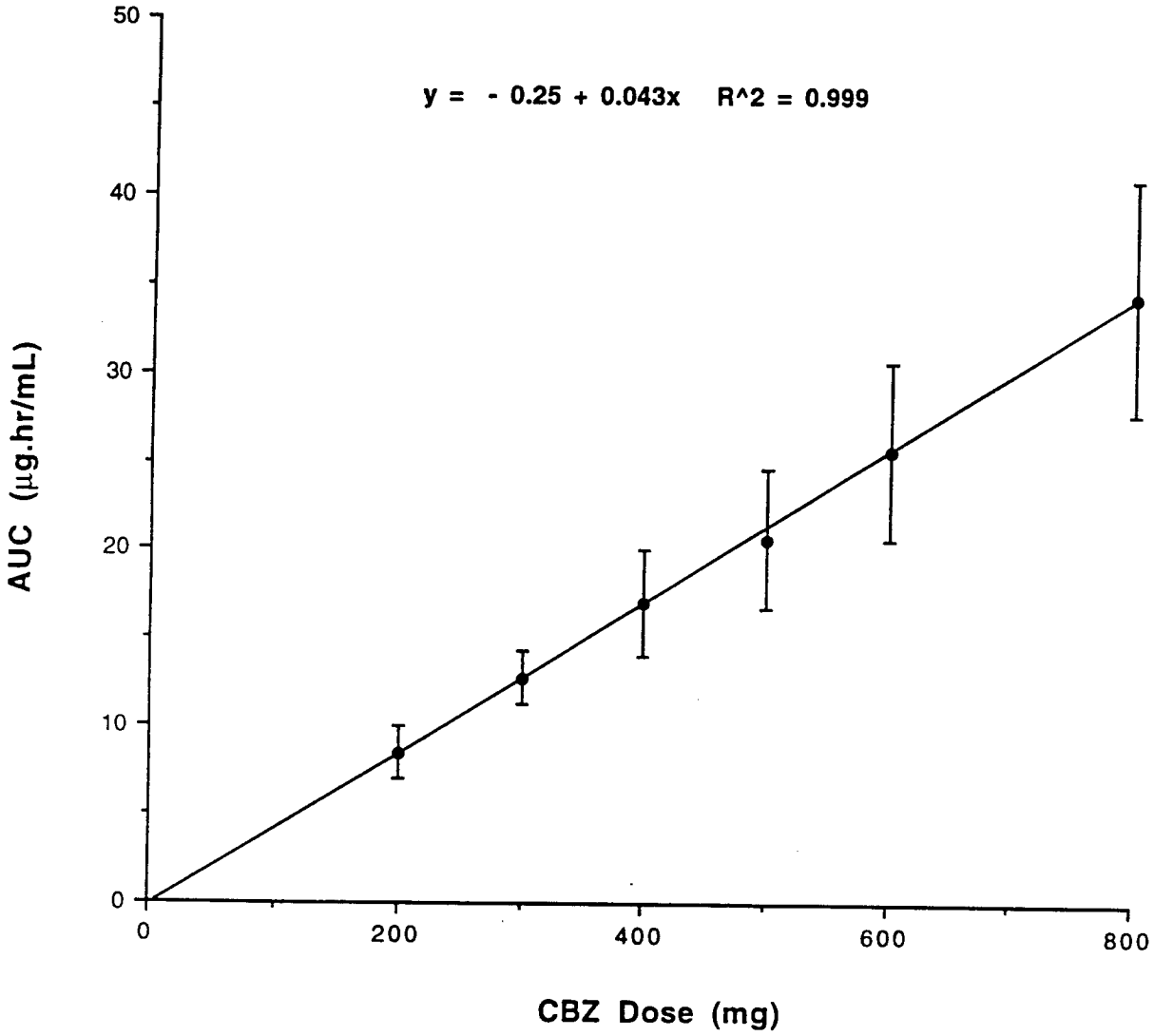
Dose vs AUC (CBZ)



Dose vs Cmax (CBZ)



Dose vs AUC (CBZE)



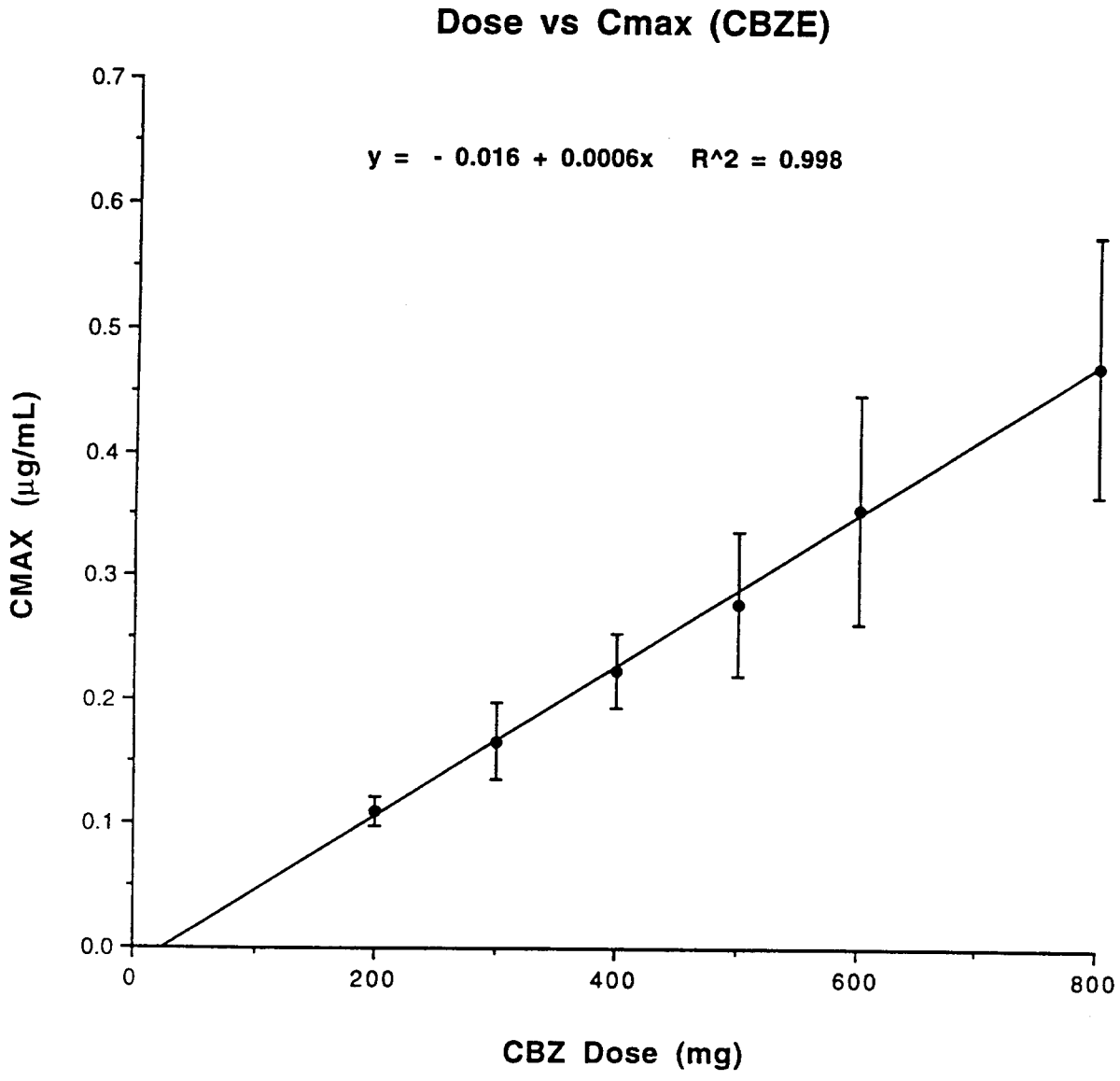

Dose vs Cmax (CBZE)
y = - 0.016 + 0.0006x R^2 = 0.998
CMAX (µg/mL)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
200
400
600
800
CBZ Dose (mg)

Figure 1.7 Average Plasma Concentration-Time Plots: CBZ

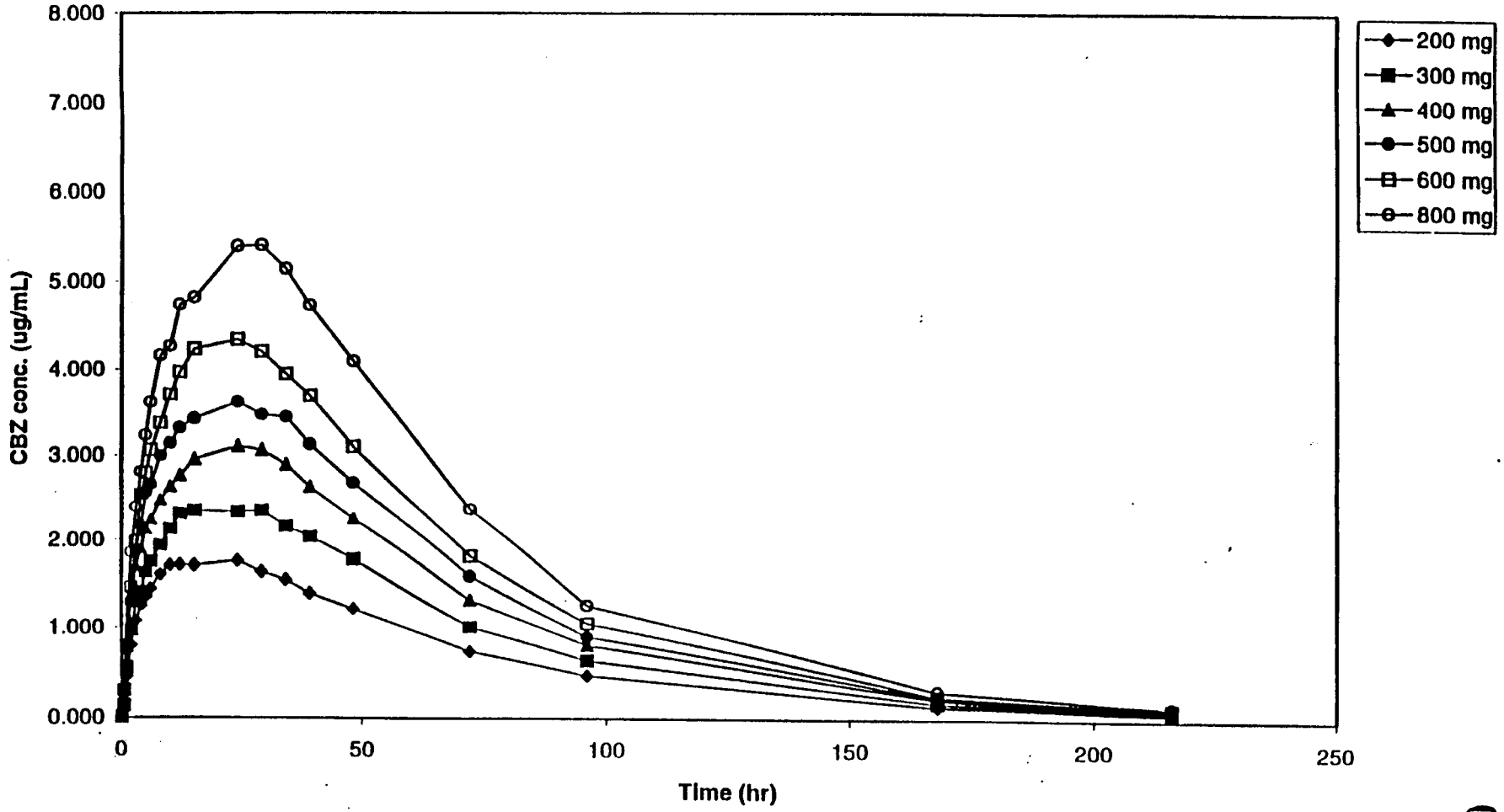
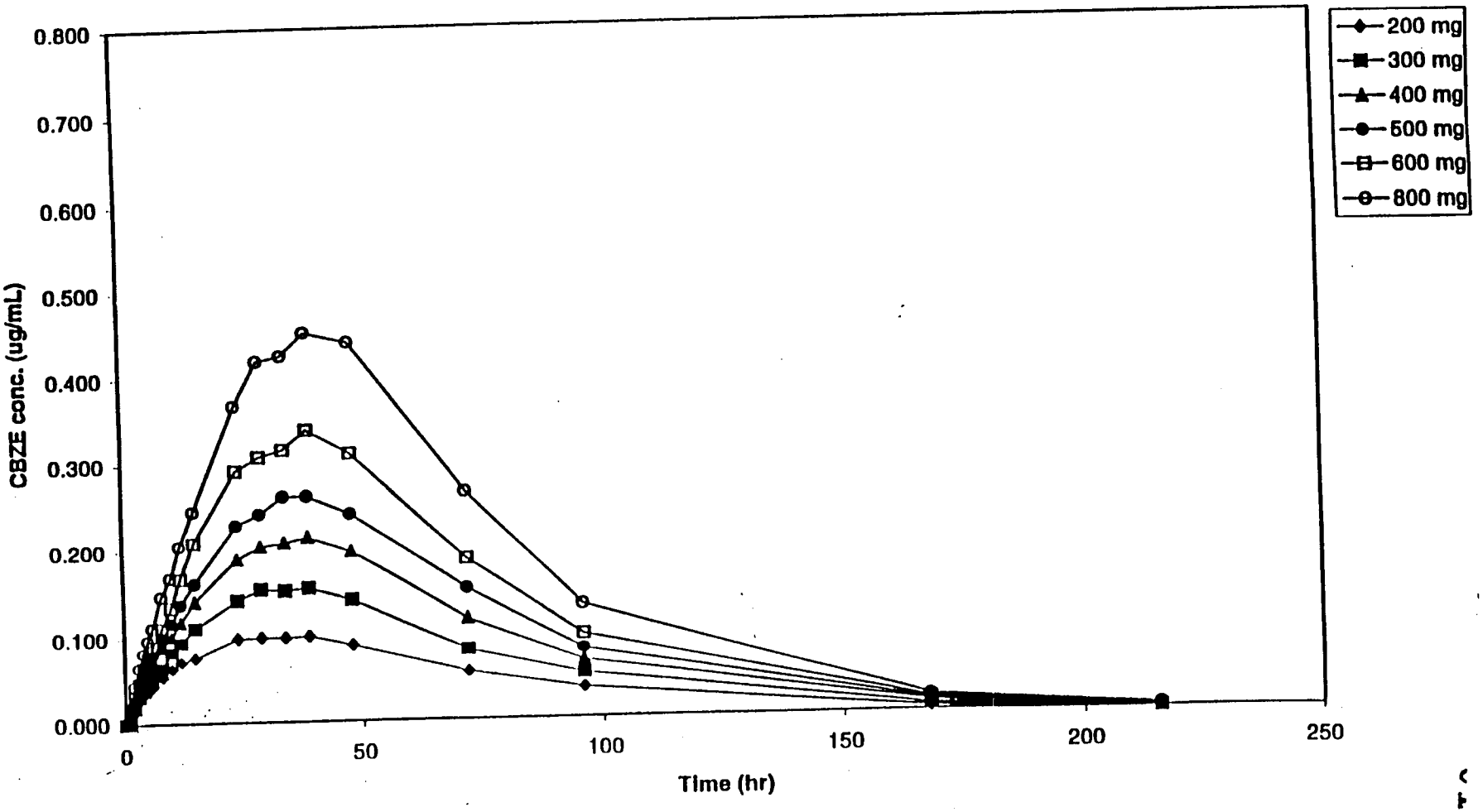


Figure 2.7 Average Plasma Concentration-Time Plots: CBZE



Study #4

Title: A Three Formulation Comparison Study of CARBATROL (Protocol PI 101.112).

Objective:

The objective of this study was to compare the bioavailability of the product intended for marketing (gamma) with the two drug lots used in previous studies (alpha and beta).

Study Design:

The study was a randomized, three-way cross-over study, in which 12 normal male volunteers received a single 400 mg dose from each of three separate lots of carbamazepine-sustained-release capsules. The subjects were fasted prior to receiving drug. All subjects were white with ages ranging from 23-44 years (mean 34.4 years). The washout period between each formulation administered was at least 14 days. Blood samples were collected 5 minutes before drug administration and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 29, 34, 39, 48, 72, 96, 168, and 216 hours after administration. Blood samples were immediately centrifuged, and the separated plasma was then stored at -20^{0}C. Carbamazepine and carbamazepine-10,11-epoxide plasma levels were determined by [redacted]. The limit of detection for carbamazepine and carbamazepine-10,11-epoxide was 0.02 - 6 µg/mL and 0.01 - 0.6 µg/mL, respectively.

Drug Administration:

Each subject received 400 mg (2 x 200 mg) of carbamazepine sustained-release capsules from each manufactured lot.

Alpha (1993)	200 mg capsules	930002A
Beta (1994)	200 mg capsules	940001A
Gamma (1995)	200 mg capsules	950026

Results:

The results of this study has been summarized in the following Tables (90% confidence interval on a log-normalized data).

TABLE 1

Pharmacokinetic Parameters **(CBZ)**	Ratio Estimate	90% Confidence Interval of Ratio (ANOVA)
	(Beta to Alpha)	
$AUC_{0\text{-inf}}$	1.07	0.97-1.18
C_{max}	1.17	1.05-1.32
	(Gamma to Alpha)	
$AUC_{0\text{-inf}}$	0.98	**0.89-1.08**
C_{max}	0.98	**0.87-1.09**
	(Gamma to Beta)	
$AUC_{0\text{-inf}}$	0.91	0.83-1.01
C_{max}	0.83	0.74-0.93

TABLE 2

Pharmacokinetic Parameters **(CBZE)**	Ratio Estimate	90% Confidence Interval of Ratio (ANOVA)
	(Beta to Alpha)	
$AUC_{0\text{-inf}}$	1.11	0.97-1.27
C_{max}	1.16	1.0-1.36
	(Gamma to Alpha)	
$AUC_{0\text{-inf}}$	1.0	**0.88-1.15**
C_{max}	0.97	**0.83-1.13**
	(Gamma to Beta)	
$AUC_{0\text{-inf}}$	0.90	0.79-1.03
C_{max}	0.83	0.71-0.97

The results of this single dose, three-way cross-over study demonstrate the drug product intended for marketing (gamma batch) was bioequivalent to the drug product

manufactured from the alpha batch in terms of AUC and C_{max} (both for carbamazepine and carbamazepine-10,11-epoxide). Furthermore, the drug product intended for marketing (gamma) was equivalent to the beta batch in terms of AUC for carbamazepine, but fell outside the limits for C_{max}, whereas CBZE failed to meet bioequivalence criteria for both AUC (although marginally) and C_{max}. The beta batch was equivalent to alpha batch in terms of AUC for CBZ, but C_{max} was outside the recommended confidence interval, whereas CBZE failed to meet bioequivalence criteria for both AUC and C_{max}.

Plasma Concentrations of CBZ plus CBZE:

Pharmacokinetic parameters of $AUC_{0\text{-inf}}$, and C_{max} obtained for **CBZ plus CBZE** (µg/ml) are shown in the following Table.

Table 3.

Pharmacokinetic Parameters (**CBZ plus CBZE**)	Ratio Estimate	90% Confidence Interval of Ratio (ANOVA)
	(Beta to Alpha)	
$AUC_{0\text{-inf}}$	1.08	0.98-1.19
C_{max}	1.17	1.05-1.32
	(Gamma to Alpha)	
$AUC_{0\text{-inf}}$	0.98	**0.89-1.09**
C_{max}	0.97	**0.87-1.09**
	(Gamma to Beta)	
$AUC_{0\text{-inf}}$	0.91	0.83-1.01
C_{max}	0.83	0.74-0.93

Plasma Concentrations of Unbound CBZ plus Unbound CBZE:

Pharmacokinetic parameters of $AUC_{0\text{-inf}}$ and C_{max} obtained for **unbound CBZ plus unbound CBZE** (μg/ml) are shown in the following Table.

TABLE 4

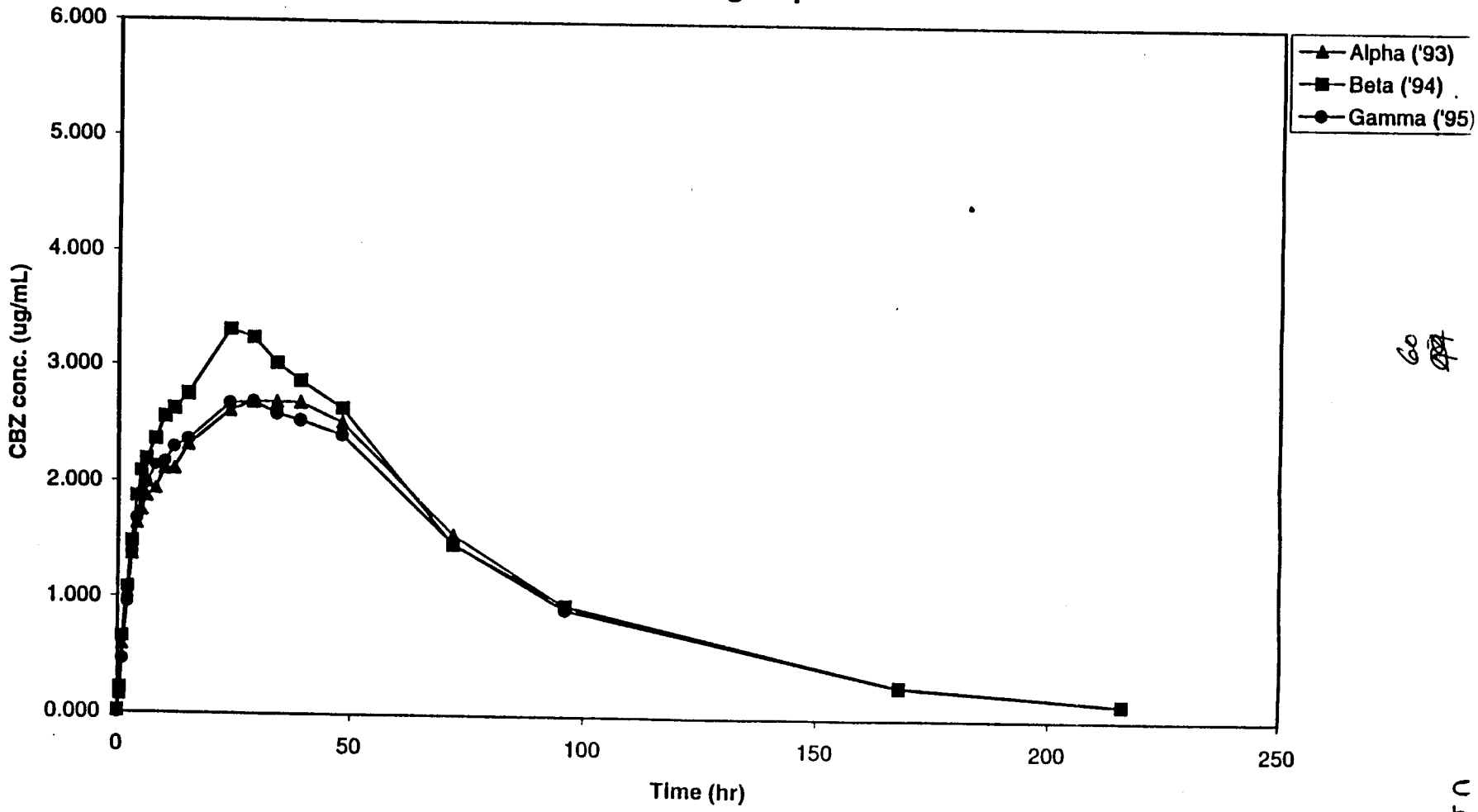
Pharmacokinetic Parameters (**unbound CBZ plus unbound CBZE**)	Ratio Estimate (Beta to Alpha)	90% Confidence Interval of Ratio (ANOVA)
$AUC_{0\text{-inf}}$	1.08	0.98-1.19
C_{max}	1.18	1.05-1.32
	(Gamma to Alpha)	
$AUC_{0\text{-inf}}$	0.99	**0.89-1.09**
C_{max}	0.98	**0.87-1.10**
	(Gamma to Beta)	
$AUC_{0\text{-inf}}$	0.91	0.83-1.01
C_{max}	0.83	0.74-0.93

The results of bioequivalence analysis of plasma concentrations of both total and unbound **CBZ plus CBZE** followed the same pattern as the bioequivalence analysis of CBZ and CBZE.

Conclusion:

The results of this study demonstrate that the drug product intended for marketing (gamma batch) was bioequivalent to the drug product manufactured from the alpha batch for both CBZ, CBZE and CBZ plus CBZE. However, beta to alpha and gamma to beta batches were not bioequivalent.

Figure 1.4 CBZ Average Plasma Concentration-Time Plots for Carbatrol Formulation of 200mg Capsules



Study #5

Title: A Dose Equivalency Study of CARBATROL (Protocol PI 101.110).

Objective: The objective of this study was to compare the bioavailability of CBZ-SR when administered as 200 mg and 300 mg capsules.

Study Design:

The study was an outpatient, open-labeled, randomized, two-phase cross-over study, in 12 normal male volunteers. The subjects were Caucasian, and their age ranged from 24 to 47 years (mean 36.5 years). Each subject received a single 600 mg oral dose of Carbatrol either in the form of 3x200 mg capsules or 2x300 mg capsules after overnight fasting. The washout period between each dose was 14 days. On the dosing day of each phase, blood samples were collected 5 minutes prior to drug administration and up to 216 hour to determine carbamazepine and carbamazepine-10,11-epoxide levels. The blood samples were immediately centrifuged, and the separated plasma was stored at -20^{0}C. Carbamazepine (CBZ) and carbamazepine-10,11-epoxide (CBZE) plasma concentrations were determined by] The limit of detection for carbamazepine and carbamazepine-10,11-epoxide was 0.02 - 10 µg/mL and 0.01 - 1.0 µg/mL, respectively.

Drug Administration:

Each subject received 600 mg of each carbamazepine formulation (3x200mg and 2x300mg).

Dosage Form	Lot Numbers
200 mg capsules	940002A
300 mg capsules	940004A

Results:

The bioequivalence analysis (log transformed) was performed on CBZ, CBZE and by summing plasma concentrations of carbamazepine and carbamazepine-10,11-epoxide prior to determining the pharmacokinetic parameters of C_{max} and T_{max}, and added up the AUC values of CBZ and CBZE to determine the corresponding $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ for **CBZ plus CBZE.**

Plasma Concentrations of Unbound CBZ plus Unbound CBZE:

Approximately 25% of CBZ and 50% of CBZE are considered to be unbound to plasma proteins. The unbound concentrations of CBZ and CBZE was estimated using unbound fraction of CBZ (25%) and CBZE (50%).

Logrithmic transformation of AUC and C_{max} values of CBZ, CBZE and CBZ plus CBZE indicated that the 90% confidence intervals of the ratio of the 2x300 mg capsules and 3x200 mg capsules fell within the recommended limits of bioequivalence (0.80-1.25). The attached Tables summarize the results of this study.

Conclusions:

The study demonstrates that 3x200 mg CBZ-SR capsules are bioequivalent to 2x300 mg CBZ-SR capsules.

TABLE

Bioequivalence of Carbatrol 2x300 mg capsules to 3x200 mg capsules for CBZ and CBZE

		(mean ± s.d.) (3x200mg)	(2x300mg)	90% Confidence Interval or (p value)
$AUC_{(0\text{-}inf)}$ ($\mu g \cdot hr/ml$)	carbamazepine	372.175±72.127	332.717±64.922	(0.81 - 0.98)*
	CBZE	27.583±7.277	24.275±5.244	(0.80 - 0.99)*
$AUC_{(0\text{-}t)}$ ($\mu g \cdot hr/ml$)	carbamazepine	360.292±61.308	324.914±60.609	(0.82 - 0.98)*
	CBZE	26.075±7.750	23.371±5.339	(0.82 - 1.02)*
C_{max} ($\mu g/ml$)	carbamazepine	4.472±0.565	4.427±0.708	(0.90 - 1.08)*
	CBZE	0.344±0.110	0.326±0.098	(0.84 - 1.09)*
T_{max} (hr)	carbamazepine	29.417±4.981	24.917±9.376	p=0.107
	CBZE	46.167±10.179	40.917±9.160	p=0.182
$t_{1/2}$ (hr)	carbamazepine	36.692±9.289	35.067±8.092	p=0.084
	CBZE	31.217±6.123	30.067±5.280	p=0.266

* denotes 90% confidence interval fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on a logarithmic scale.

Table 2.1 < PI 101.110 > Bioequivalence of Carbatrol 2x300mg Capsules to 3x200mg Capsules for CBZ plus CBZ-epoxide: Total

A parametric approach of ANOVA model with log-transformation

PK Parameters	2x300mg (mean)	3x200mg (mean)	Mean % (2x300mg to 3x200mg)	Ratio Estimate (2x300mg to 3x200mg)	90% CI of ratio (ANOVA model)
AUC (0-inf)	356.992	399.758	90.8	0.89	(0.81 - 0.98)*
AUC (0-t hr)	348.292	386.367	91.5	0.90	(0.82 - 0.99)*
C max	4.700	4.768	99.5	0.98	(0.89 - 1.08)*

* : The 90% CI fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on log scale
AUC (0-t hr) = Area under the curve from zero to the last measurable time point
Measurement: AUC in ug.hr/mL; C max in ug/mL

Table 2.2 < PI 101.110 > Bioequivalence of Carbatrol 2x300mg Capsules to 3x200mg Capsules for CBZ plus CBZ-epoxide: Unbound

A parametric approach of ANOVA model with log-transformation

PK Parameters	2x300mg (mean)	3x200mg (mean)	Mean % (2x300mg to 3x200mg)	Ratio Estimate (2x300mg to 3x200mg)	90% CI of ratio (ANOVA model)
AUC (0-inf)	95.325	106.850	90.8	0.89	(0.81 - 0.98)*
AUC (0-t hr)	92.925	103.125	91.6	0.90	(0.82 - 0.99)*
C max	1.247	1.269	99.4	0.98	(0.89 - 1.08)*

* : The 90% CI fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on log scale
AUC (0-t hr) = Area under the curve from zero to the last measurable time point
Measurement: AUC in ug.hr/mL; C max in ug/mL
25% CBZ and 50% CBZ-epoxide was considered unbound or free in calculation

Figure 1.3 Average Plasma Concentration-Time Plots: CBZ

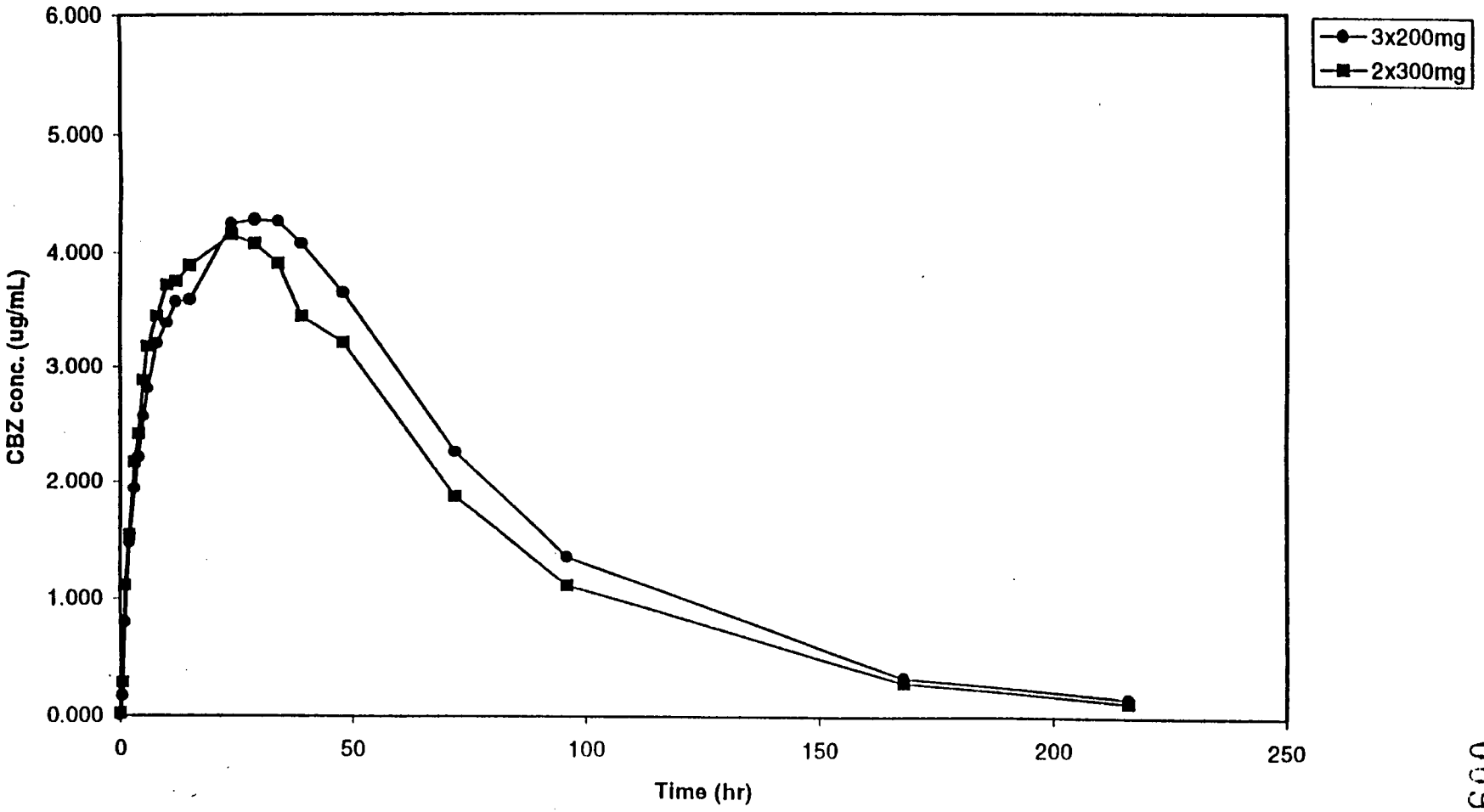
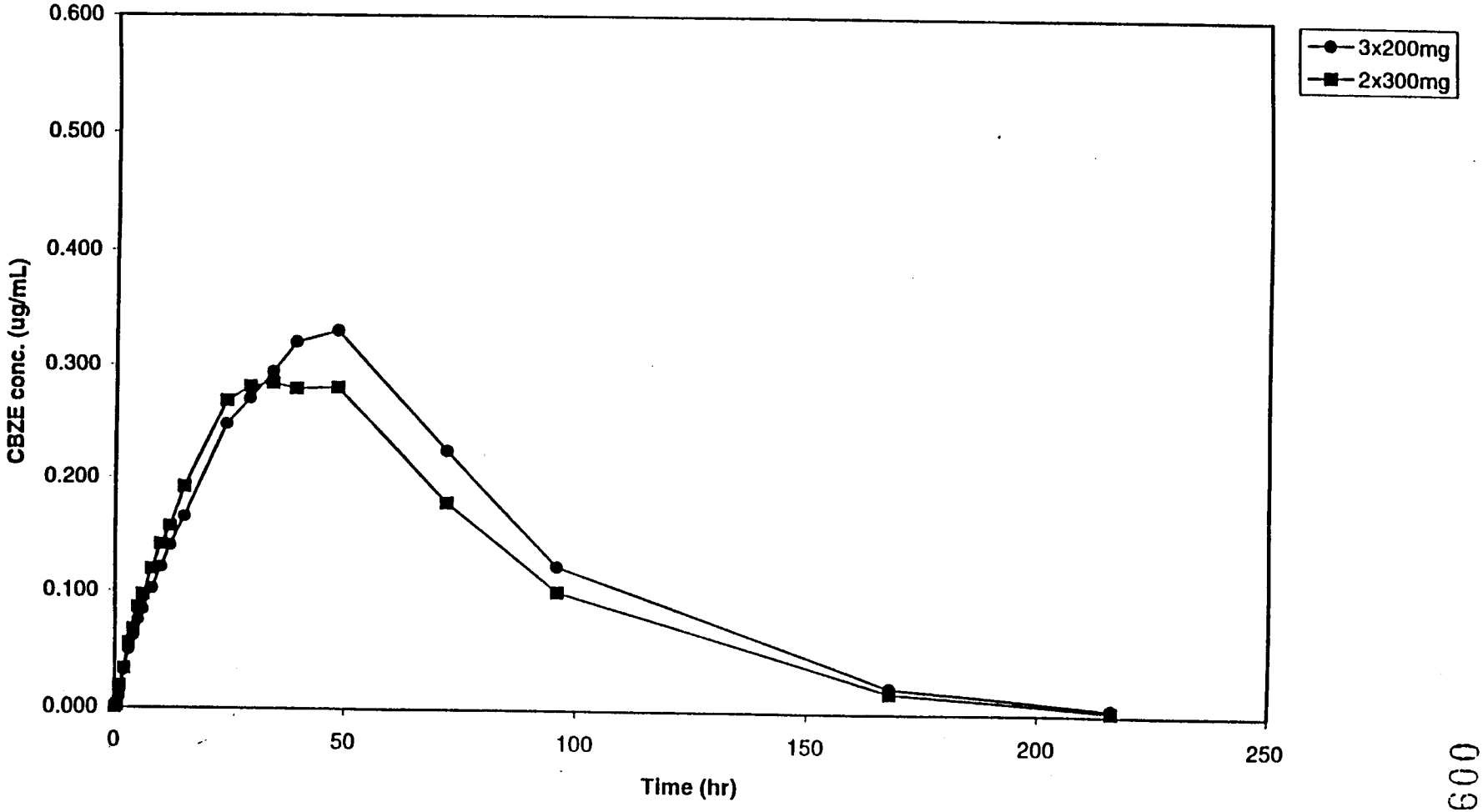


Figure 2.3 Average Plasma Concentration-Time Plots: CBZ-epoxide



Study #6

Title: A Bioavailability Study of Two Batches of CARBATROL (Protocol PI 101.107).

Objective:

The objective of this study was to compare the bioavailability of two different batches (1993 and 1994 batches) of the sustained-release, multi-unit form of carbamazepine (CARBATROL; CBZ-SR).

Study Design:

The study was an open-label, single dose, fasting, randomized, balanced cross-over study with two treatment arms, in which 12 normal male volunteers (10 Caucasian, 1 African American, and 1 Hispanic) received a single 400 mg (2 x 200 mg) dose of CBZ-SR manufactured from each of the 1993 and 1994 batches of drug. The mean age of the subjects was 32.6 years (range 23-47 years). The washout period between each formulation administered was at least 14 days. Blood samples were collected 5 minutes before drug administration (0-hour) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 29, 34, 48, 72, 96, 168, and 216 hours after administering CBZ-SR. The blood samples were immediately centrifuged, and the separated plasma was then stored at -20°C. Carbamazepine and carbamazepine-10,11-epoxide plasma levels were determined by [illegible] detection. The limit of detection for carbamazepine and carbamazepine-10,11-epoxide was 0.02 - 10 μg/mL and 0.01 - 1.0 μg/mL, respectively.

Drug Administration:

Each subject received 400 mg (2 x 200 mg) of the 1993 or 1994 batch of CBZ-SR.

CBZ-SR

Treatment 1 (clinical/1993 batch)	200 mg capsules	(Lot #930002A)
Treatment 2 (manufacturing/1994 batch)	200 mg capsules	(Lot #940002A)

Results:

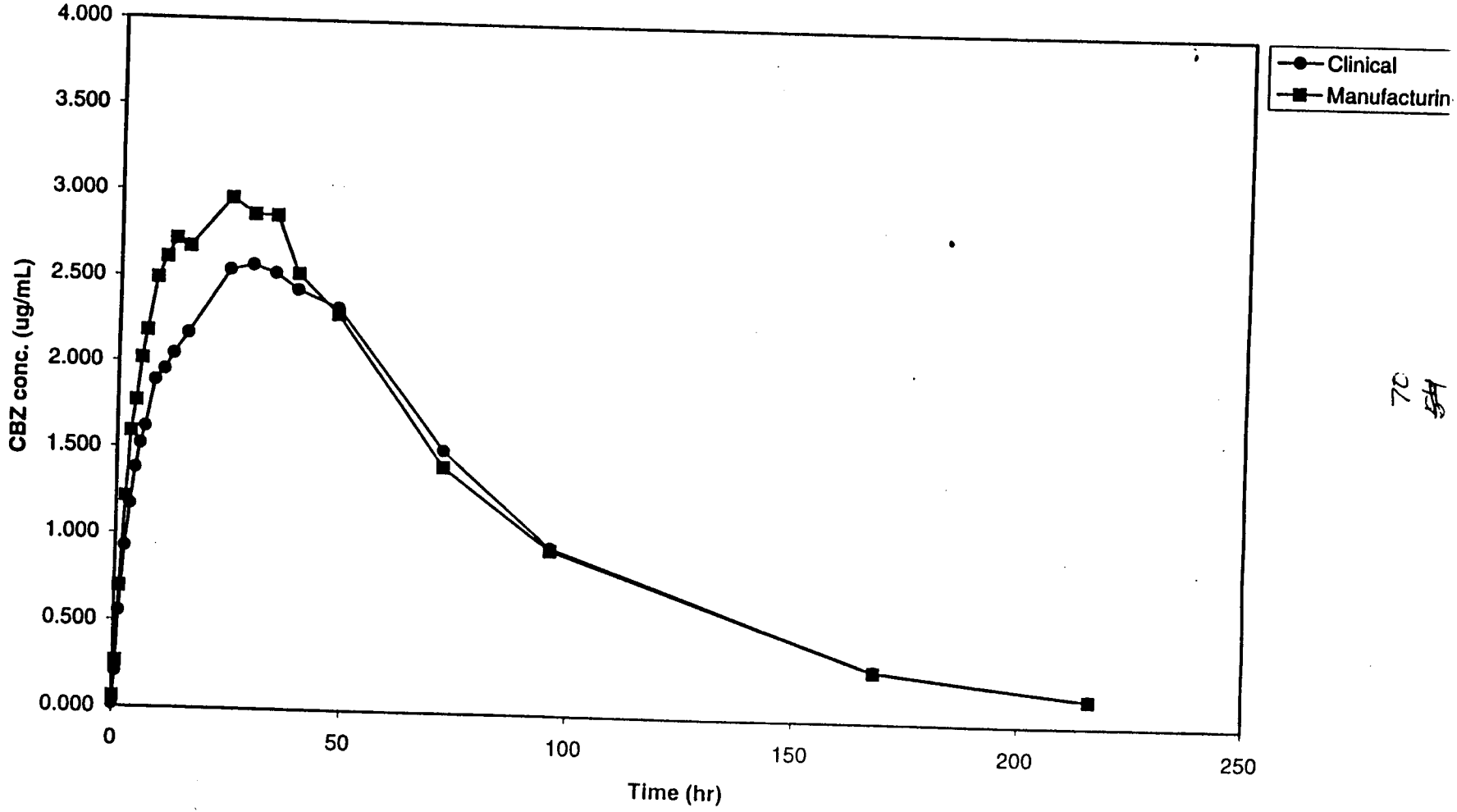
		1994 Batch	1993 Batch	90% CI
AUC	carbamazepine	259.567±60.157	247.458±50.850	(0.99 - 1.10)
(μg·hr/ml)	CBZE	16.808±2.668	15.758±2.275	(0.99 - 1.14)
C_{max}	carbamazepine	3.121±0.300	2.764±0.342	(1.07 - 1.20)
(μg/ml)	CBZE	0.199±0.026	0.172±0.029	(1.07 - **1.26**)
$t_{1/2}$	carbamazepine	42.533±10.024	43.792±9.611	
(hr)	CBZE	36.350±5.922	39.175±6.657	

This study demonstrated comparable bioavailability and pharmacokinetic profiles for CBZ-SR manufactured from the 1993 and 1994 batches of drug. The plasma levels of carbamazepine were bioequivalent as determined from AUC and C_{max}. The metabolite, carbamazepine-10,11-epoxide, was bioequivalent in terms of AUC but C_{max} failed to meet the bioequivalence criteria by a very narrow margin (1.07 - 1.26).

Conclusions:

The study demonstrates that the batches of 1993 and 1994 of the sustained-release, multi-unit form of carbamazepine could be considered to be bioequivalent.

Figure 1.1 CBZ Average Plasma Concentration-Time Plots for Individual Batches



DISSOLUTION

ATTACHMENT F

Proposed Dissolution Method and Specifications for Carbatrol™ Capsules (Carbamazepine Sustained-Release Capsules)

1) Dosage Form: Capsule

2) Strengths: 200 mg and 300 mg strengths

3) Apparatus Type:

4) Media:

5) Volume:

6) Speed of Rotation

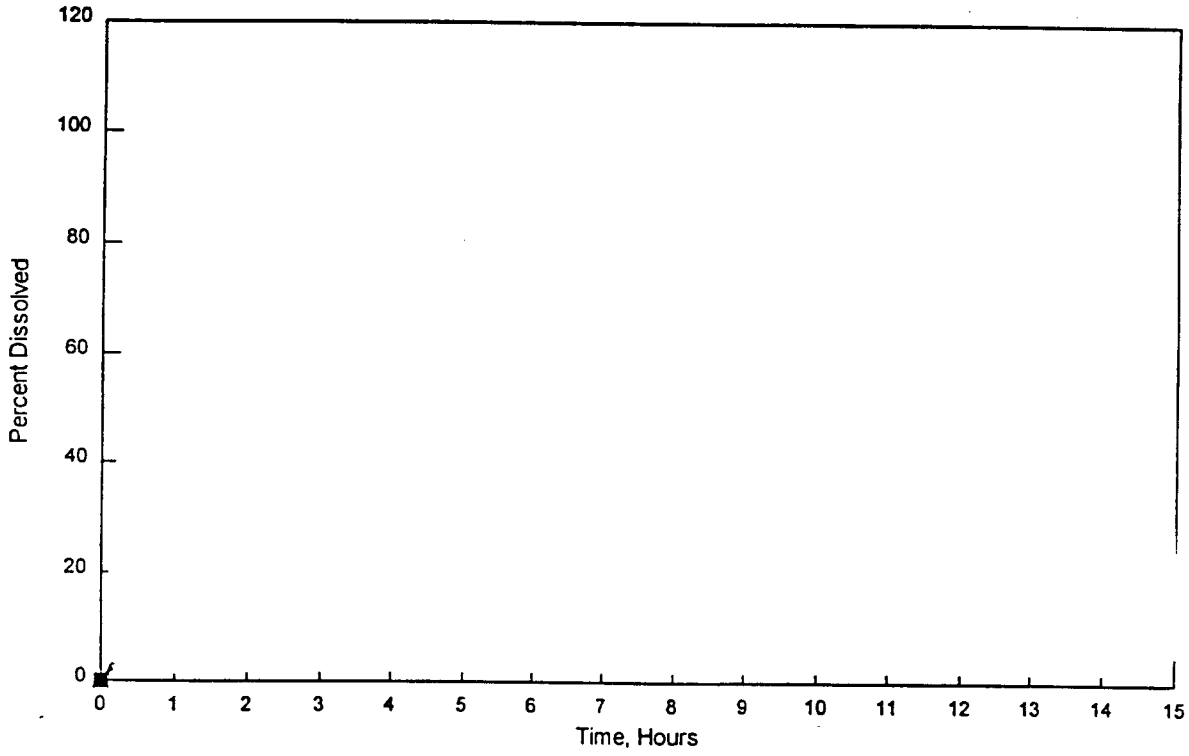
7) Sampling Times (hrs):

8) Brief Description of Dissolution Analytical Method:

9) Recommended Dissolution Specifications:

Time (hr)	% Dissolved
1.0	
4.0	
6.0	
12.0	

Carbatrol Dissolution Profiles



ATTACHMENT E: Summary of Drug Product Dissolution Testing

The following data is for composite capsules that were used in clinical studies to provide information on our final formulation.

Date of Test / Notebook Reference	Dosage Form and Strength	Lot Number	Dissolution Apparatus (USP)	Media / Temperature	Speed of Rotation	Collection Times (Hrs)	Units Tested	Range	Mean % Dissolved	Percent RSD
9-Mar-93 AL-0026/95 31-Mar-93 AL-0027/54	Composite Capsule 200 mg	930002							21.0	4.1%
									32.3	2.9%
									45.5	2.9%
									60.0	4.0%
									70.7	4.0%
									86.3	5.3%
									98.2	2.8%
									101.3	2.4%
									102.5	2.2%
15-Sep-94 AL-0093/72 19-Sep-94 AL-0093/94	Composite Capsule 200 mg	940001A						-	20.7	14.4%
									33.0	9.2%
									46.8	4.4%
									66.2	2.8%
									77.8	3.3%
									90.8	2.6%
									96.8	2.2%
									99.9	1.9%
									103.2	1.5%
22-Sep-94 AL-0092/31 30-Sep-94 AL-0092/55	Composite Capsule 200 mg	940002A						-	22.7	16.5%
									36.1	12.1%
									49.1	6.1%
									71.1	4.6%
									81.8	4.0%
									91.4	3.0%
									96.0	2.6%
									98.9	2.3%
									102.1	1.8%
19-Sep-94 AL-0097/2 19-Sep-94 AL-0097/6	Composite Capsule 300 mg	940004A						-	22.6	16.2%
									32.6	11.9%
									42.5	8.6%
									64.9	5.5%
									75.8	4.4%
									86.0	3.7%
									90.0	3.5%
									92.0	3.2%
									93.8	4.2%
19-Jul-95 AL-0153/9 25-Jul-95 AL-0153/46	Composite Capsule 200 mg	950026						-	17.2	19.3%
									28.4	14.7%
									42.3	10.8%
									63.3	6.6%
									76.5	5.9%
									91.5	4.7%
									98.6	3.3%
									102.2	2.5%
									104.3	2.1%
25-Jul-95 AL-0152/54 25-Jul-95 AL-0153/50	Composite Capsule 300 mg	950027						-	15.5	15.8%
									25.0	11.9%
									37.8	8.1%
									56.6	5.6%
									68.3	6.2%
									82.0	4.5%
									91.2	3.1%
									97.4	2.5%
									101.2*	1.8%*

* This value based on 11 units tested due to sampler error.

6 0051

Date of Test / Notebook Reference	Dosage Form and Strength	Lot Number	Dissolution Apparatus (USP)	Media / Temperature	Speed of Rotation	Collection Times (Hrs)	Units Tested	Range	Mean % Dissolved	Percent RSD
25-Feb-92 AAI Document campwrg64.fdl	Immediate-Release Pellet Capsule 200 mg	920001							14.1	21.2%
									26.0	11.7%
									34.2	9.9%
									49.6	9.3%
									60.5	8.6%
									68.4	8.5%
									96.6	7.3%
12-Feb-92 AAI Document campwrf07.cds	Sustained-Release Pellet Capsule 200 mg	920002							2.9	27.6%
									8.2	24.4%
									25.4	18.9%
									67.9	8.1%
									93.6	6.1%
									102.2	3.6%
12-Feb-92 AAI Document campwrf05.cds	Enteric-Release Pellet Capsule 200 mg	920003							3.2	28.1%
									5.1	15.7%
									7.4	16.2%
									56.2	10.6%
									80.1	6.7%
									90.3	2.0%
									92.5	1.6%
									94.8	1.9%
									96.2	1.8%
8-Jun-92 AL-0002/17	Sustained-Release Pellet Capsule 200 mg	920033							41.3	7.1%
									79.4	4.6%
									99.8	1.8%
									101.3	2.1%
									101.1	2.0%
									102.0	1.0%
									102.1	1.9%
									103.2	1.6%
									102.3	2.4%
10-Jun-92 AL-0002/21	Sustained-Release Pellet Capsule 200 mg	920034							26.3	8.8%
									61.6	9.2%
									93.9	3.3%
									98.7	2.0%
									99.4	1.4%
									99.9	1.9%
									100.5	1.4%
									101.5	1.7%
									101.3	1.8%
4-Dec-92 AL-0017/93	Sustained-Release Pellet Capsule 200 mg	920094							25.2	5.5%
									47.7	4.7%
									75.7	2.9%
									89.3	2.3%
									94.4	2.0%
									98.1	1.9%
									99.7	1.5%
25-Nov-92 AL-0017/38	Sustained-Release Pellet Capsule 200 mg	920095							22.3	13.5%
									47.1	7.1%
									77.9	4.6%
									93.6	3.5%
									100.3	3.4%
									105.5	3.4%
									107.5	3.9%
23-Oct-92 AL-0015/91	Immediate-Release Pellet Capsule 200 mg	920077							10.6	8.2%
									16.9	6.1%
									33.0	4.9%
									46.5	4.1%
									56.9	3.5%
									71.9	2.9%
									81.4	2.9%
									91.1	2.5%
									95.8	2.4%
									102.0	3.0%
8-Oct-92 AL-0015/19	Sustained-Release Pellet Capsule 200 mg	920074							14.6	6.3%
									38.5	4.6%
									72.0	2.8%
									94.2	5.1%
									100.0	2.3%
									95.7	3.9%
									101.9	2.0%
									97.8	2.8%
									107.7	1.9%
22-Oct-92 AL-0015/95	Enteric-Release Pellet Capsule 200 mg	920076							0.8	3.9%
									1.5	7.2%
									2.6	6.0%
									32.4	5.9%
									54.1	4.9%
									79.7	4.5%
									94.9	3.1%
									99.3	2.7%
									100.3	2.3%

* mixing represents 15 minutes of operation at a rotation speed of 250 rpm

6 0052

ANALYTICAL METHOD

2 pages
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DOSAGE FORMS

Dosage Forms

Pharmavene, Inc. has developed a multi-unit extended-release capsule formulation of carbamazepine (CARBATROL; CBZ-SR; carbamazepine sustained-release) designed to enable twice daily administration in patients with epilepsy. The multi-unit is composed of three types of pellet, with each pellet type being combined in a specific ratio within one capsule. The three types of pellets consist of immediate-release, sustained-release, and enteric-release pellets, with each capsule containing many pellets of each type. The ratios of the immediate-release, sustained-release, and enteric-release pellets are identical for each dosage strength as shown below:

Dosage Strength	% of pellets within each CBZ Extended-Release capsule		
	Immediate-release	Sustained-release	Enteric-release
200 mg capsule			
300 mg capsule			

The composition of CBZ Immediate-Release, Sustained-Release and Enteric-Release pellets, Amount of drug substance and other ingredients contained in the drug product CBZ Sustained-Release 200 and 300 mg Capsules, Process Overview, and Drug Formulation Development Summary can be found in the attached Tables.

CMC Summary Table III. The composition of Carbamazepine Immediate-Release, Sustained-Release and Enteric-Release Pellets

	Percentage of Ingredient			
	Intermediates			
Ingredients	Immediate-Release	Sustained-Release	Enteric-Release	Composite Capsule
Carbamazepine, USP	80.0	69.0	69.0	71.7
Lactose, NF (Monohydrate)				
Citric Acid, USP (Anhydrous)				
Povidone, USP				
Talc, USP				
Povidone, USP				
Microcrystalline Cellulose, NF				
Triethyl Citrate				
Sodium Lauryl Sulfate, NF				
Polyethylene Glycol 400, NF				
Colloidal Silicon Dioxide, NF				
Total				
Percentage of Composite Capsule				

CMC Summary Table IV. Amount of drug substance and other ingredients contained in the drug product Carbamazepine Sustained-Release Capsules, 200 mg

Ingredient	Amount (mg/capsule)	% per Capsule
Carbamazepine, USP	200.0	
Lactose Monohydrate, NF		
Citric Acid, USP (Anhydrous)		
Povidone, USP		
Talc, USP		
Povidone, USP		
Microcrystalline Cellulose, NF		
Triethyl Citrate, NF		
Sodium Lauryl Sulfate, NF		
Polyethylene Glycol 400, NF		
Colloidal Silicon Dioxide, NF		
Purified Water, USP		
Hard Gelatin Capsule		
Total[1]		

*Removed During Processing

**Excluded from percent calculation

[1]For purposes of manufacturing, total was rounded to nearest whole number

CMC Summary Table V. Amount and percent of drug substance and other ingredients contained in the drug product Carbamazepine Sustained-Release Capsules, 300 mg.

Ingredient	Amount (mg/capsule)	% per Capsule
Carbamazepine, USP	300.0	
Lactose Monohydrate, NF		
Citric Acid, USP (Anhydrous)		
Povidone, USP		
Talc, USP		
Povidone, USP		
Microcrystalline Cellulose, NF		
Triethyl Citrate, NF		
Sodium Lauryl Sulfate, NF		
Polyethylene Glycol 400, NF		
Colloidal Silicon Dioxide, NF		
Purified Water, USP		
Hard Gelatin Capsule		
Total[1]		

*Removed During Processing

**Excluded from percent calculation

[1]For purposes of manufacturing, total was rounded to nearest whole number

4. Process Overview

Carbamazepine Sustained-Release Capsules are composed of three different pellet formulations. The three pellet formulations are Immediate-Release (IR), Sustained-Release (SR), and Enteric-Release (ER). . The Sustained-Release and Enteric-Release Pellets are made by coating the Immediate-Release Pellets with sustained-release and enteric-release coatings.

The intermediate bulk pellets for each of the three pellet formulations are manufactured at . The manufacturing process

Figure 1

Process Overview

ATTACHMENT C

DRUG FORMULATION DEVELOPMENT SUMMARY (Cont'd)

Clinical Study Number	Product	Finished Product Batch Number	Packaged Product Batch Number	Dosage Form and Strength	Batch Size	Formulation or Significant Manufacturing Change (if any) and reason for Change	Effect of Change
101.106	CBZ SR Capsule	940002	940002A	200 mg capsule			
	CBZ SR Capsule	940004	940004A	300 mg capsule			
101.107	CBZ SR Capsule	940002	940002A	200 mg capsule			
	CBZ SR Capsule	930002	930002A	200 mg capsule			
101.108	CBZ SR Capsule	940002	940002A	200 mg capsule			
101.109	CBZ SR Capsule	940002	940002A	200 mg capsule			
	CBZ SR Capsule	940004	940004A	300 mg capsule			
101.110	CBZ SR Capsule	940002	940002A	200 mg capsule			
	CBZ SR Capsule	940004	940004A	300 mg capsule			
101.112	CBZ SR Capsule	930002	930002A	200 mg capsule			
	CBZ SR Capsule	940001	940001A	200 mg capsule			
	CBZ SR Capsule	950026	950026	200 mg capsule			
101.113	CBZ SR Capsule	940004	940004A	300 mg capsule			
	CBZ SR Capsule	950027	950027	300 mg capsule			

ATTACHMENT C

DRUG FORMULATION DEVELOPMENT SUMMARY

Clinical Study Number	Product	Finished Product Batch Number	Packaged Product Batch Number	Dosage Form and Strength	Batch Size	Formulation or Significant Manufacturing Change (if any) and reason for Change	Effect of Change
101.101	IR Pellet	92015	92001	200 mg capsule			
	SR Pellet	92018	92002	200 mg capsule			
	ER Pellet	92021	92003	200 mg capsule			
101.101B	SR Pellet	920033	920033	200 mg capsule			
	SR Pellet	920034	920034	200 mg capsule			
101.101C	SR Pellet	920094	920094	200 mg capsule			
	SR Pellet	920095	920095	200 mg capsule			
101.102	Tegretol	None	920078	200 mg tablet			
	IR Pellet	920077	920077	200 mg capsule			
	SR Pellet	920072	920072	200 mg capsule			
	ER Pellet	920076	920076	200 mg capsule			
101.103	Tegretol Placebo	930006 930019	930021	200 mg capsule 800 mg dose			
	Tegretol Placebo Placebo	930006 930017 930019	930022	200 mg capsule 1200 mg dose			
	Tegretol Placebo	930020 930019	930023	200 mg capsule 1600 mg dose			
	CBZ SR Capsule Placebo	930002 930019	930024	200 mg capsule 800 mg dose			
	CBZ SR Capsule Placebo	930002 930019	930025	200 mg capsule 1200 mg dose			
	CBZ SR Capsule Placebo	930002 930019	930026	200 mg capsule 1600 mg dose			
101.104	CBZ SR Capsule	930002	930039	200 mg capsule			
	Depakote Sprinkle	930038	930040	125 mg capsule			

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IN-VITRO/IN-VIVO CORRELATION

G. *In Vitro-in Vivo* Correlation Study

a. Introduction

Pharmavene has developed and is seeking approval for a sustained-released dosage form of carbamazepine: Carbamazepine Sustained-Release Capsules. The dosage form is a capsule that contains a mixture of three types of components, each demonstrating different release characteristics. One component is made up of Immediate-Release Pellets, the second is made up of Sustained-Release Pellets, and the third is made up of Enteric-Release Pellets. Two strengths have been developed - 200 mg and 300 mg.

An analysis was undertaken to establish the relationship between the 12 hour *in vitro* dissolution release profile of the drug and the 72 hour *in vivo* fraction absorbed profile of the drug from the Carbamazepine Sustained-Released Capsules. The *in vitro* data were generated by a discriminating dissolution procedure. This dissolution procedure demonstrates both the extended-release properties of the formulation and is sufficiently discriminating to assess the quality of the product. The *in vivo* data were obtained from several single dose pharmacokinetic studies, which were conducted to evaluate the bioavailability of the Carbamazepine Sustained-Released Capsules. The *in vivo* fraction absorbed results are correlated on a point-to-point basis with the *in vitro* dissolution release data at five timepoints over the profiles. The *in vivo* profile time is divided by six to make it superimposable with the *in vitro* dissolution profile and provide an USP Level A correlation.

b. Dissolution Methodology

The dissolution procedure for Carbamazepine Sustained-Release Capsules is carried out

Table III lists the correlation results for each of the lots evaluated. Table IV lists the *in vitro* fraction released and the *in vivo* fraction absorbed results for each of the drug product lots used in the evaluation. Figures 3 through 22 are plots of the *in vitro* Fraction Released and *in vivo* Fraction Absorbed (time divided by six) versus time and plots of Fraction Absorbed (time divided by six) versus Fraction Released. The correlation results of the composite Carbamazepine Sustained-Released Capsules, 200 mg and 300 mg and SR pellet lots 920094 and 920095 indicate that a Level A correlation may be achieved according to the USP criteria. SR Pellet lots 920033 and 920034 (see Figures 19 through 22) show a poor correlation, particularly through the first 4 hours. These lots were poorly absorbed and were not acceptable as components in the composite dosage formulation.

e. Conclusions

Analysis of the *in vitro* dissolution data with the *in vivo* drug plasma time profile for the Carbamazepine Sustained-Released Capsules confirms a Level A correlation according to the USP criteria. Validation of the manufacturing process at full production scale, accompanied with future analyses as manufacturing experience is obtained, will provide the opportunity for confirmation of the results reported in this study. As future manufacturing changes are proposed, the *in vitro* dissolution method may be a potentially useful predictive tool for the *in vivo* performance of the Carbamazepine Sustained-Released Capsules.

Table IV. *In vitro* Fraction Released and *in vivo* Fraction Absorbed (Time Transformed t/6) Data for Various Lots of Carbamazepine Sustained-Released Capsules, 200 mg and 300 mg (Composite) and Investigational Formulations (SR Pellets)

Date of Test / Notebook Reference	Dosage Form and Strength	Lot Number	Collection Times (hr)	Units Tested	Fraction Released	Fraction Absorbed Time Transformed (t/6)
9-Mar-93 AL-0026/95 31-Mar-93 AL-0027/54	Composite Carbamazepine Sustained-Release Capsule, 200 mg	930002 107	0 1 2 4 8 12	12		
22-Sep-94 AL-0092/31 30-Sep-94 AL-0092/55	Composite Carbamazepine Sustained-Release Capsule, 200 mg	940002 107	0 1 2 4 8 12	12		
15-Sep-94 AL-0093/72 19-Sep-94 AL-0093/94	Composite Carbamazepine Sustained-Release Capsule, 200 mg	940001 112	0 1 2 4 8 12	12		
19-Jul-95 AL-0153/9 25-Jul-95 AL-0153/46	Carbamazepine Sustained-Release Capsule, 200 mg	950026 112	0 1 2 4 8 12	12		
19-Sep-94 AL-0097/2 19-Sep-94 AL-0097/6	Carbamazepine Sustained-Release Capsule, 300 mg	940004 113	0 1 2 4 8 12	12		

Continued...

Figure 1. Mean Plasma Level plot for Lot 930002, Pharmacokinetic Study 101.107

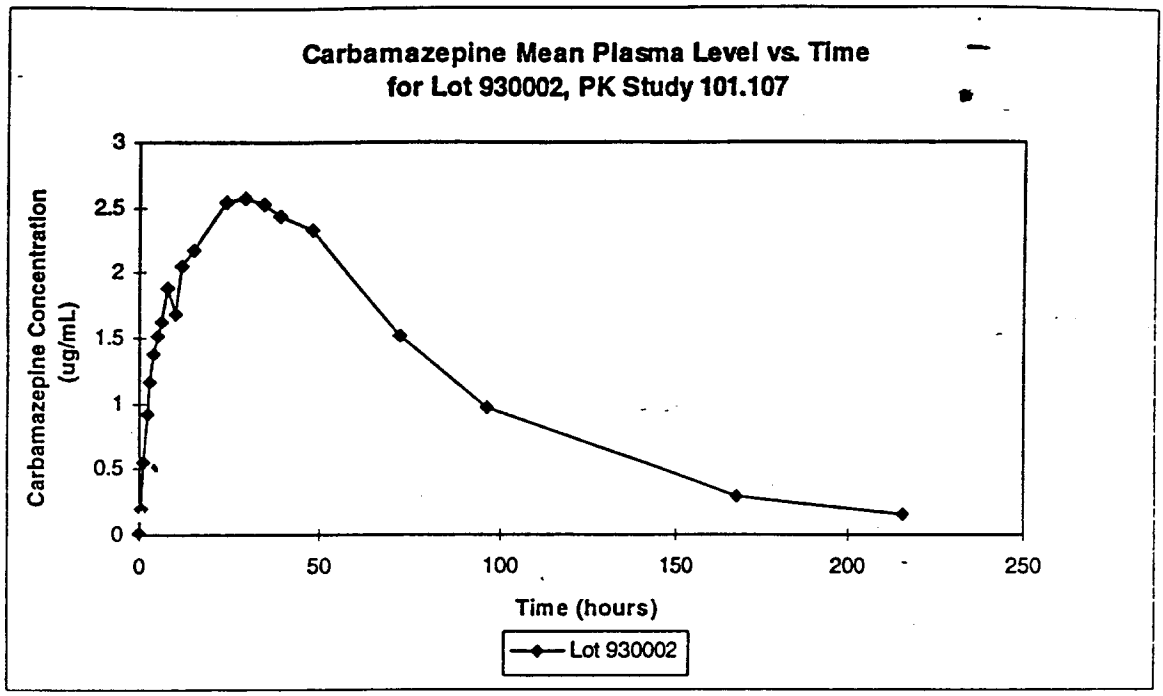


Figure 2. Wagner-Nelson Plot of Lot 930002, Pharmacokinetic Study 101.107

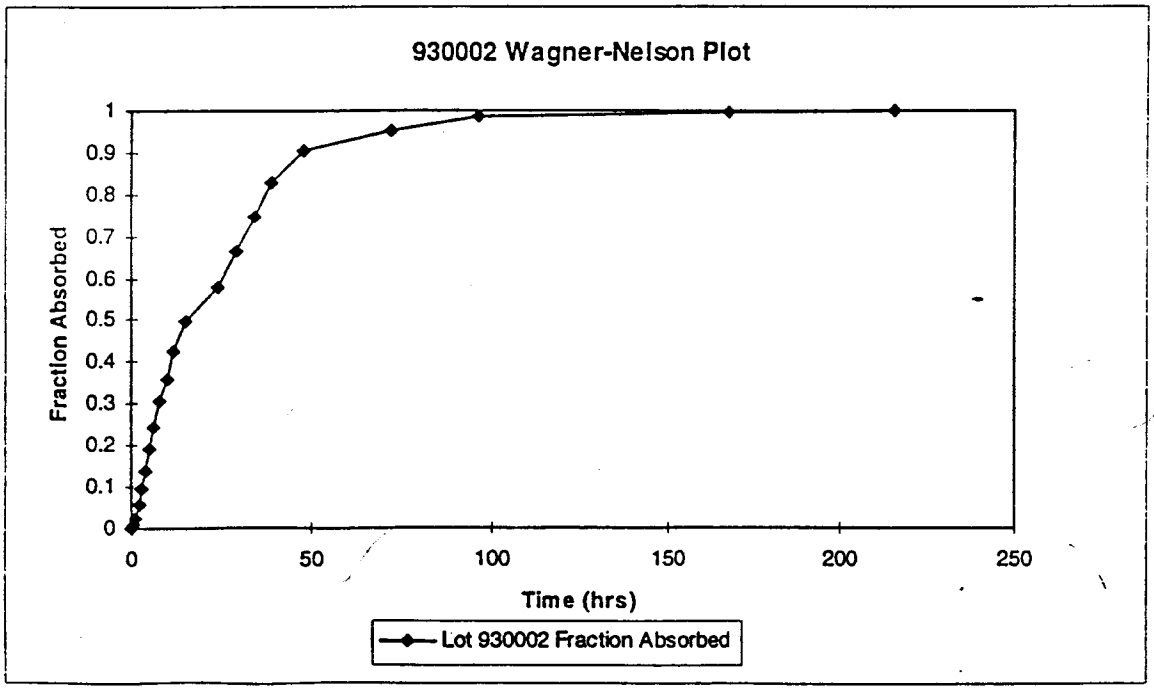


Figure 5. *In vitro-in vivo* Plot of Lot 940002, Pharmacokinetic Study 101.107

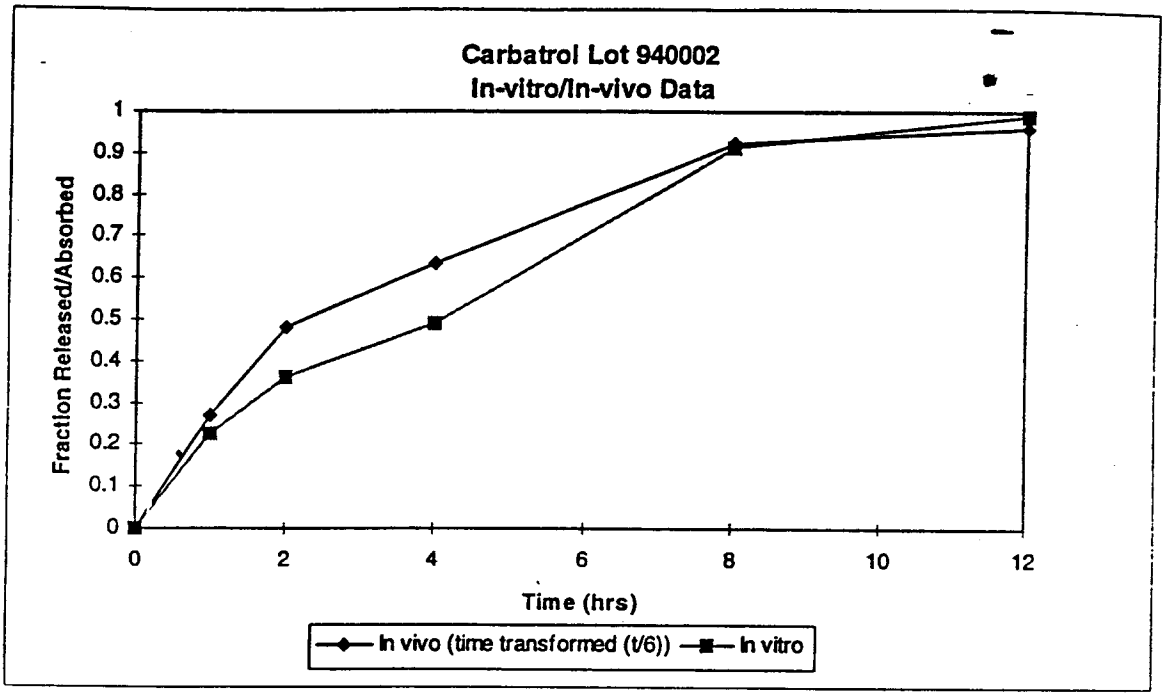


Figure 6. Fraction Absorbed vs. Fraction Released, Lot 940002, Pharmacokinetic Study 101.107

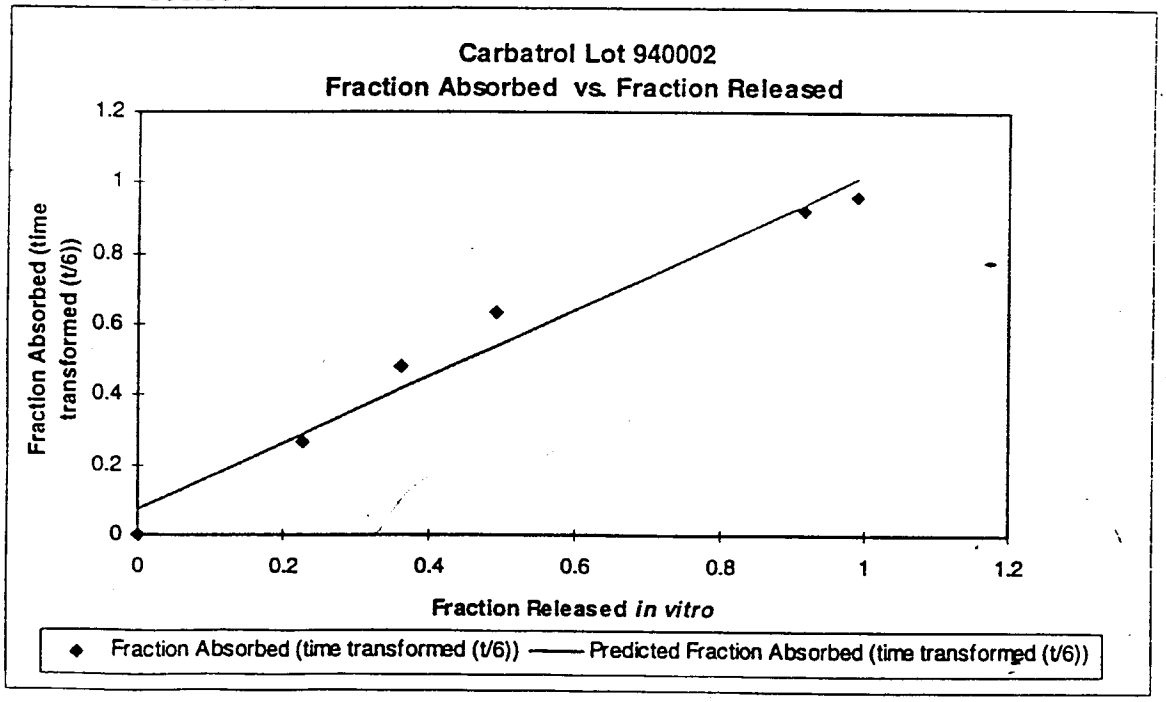


Figure 9. *In vitro-in vivo* Plot of Lot 950026, Pharmacokinetic Study 101.112

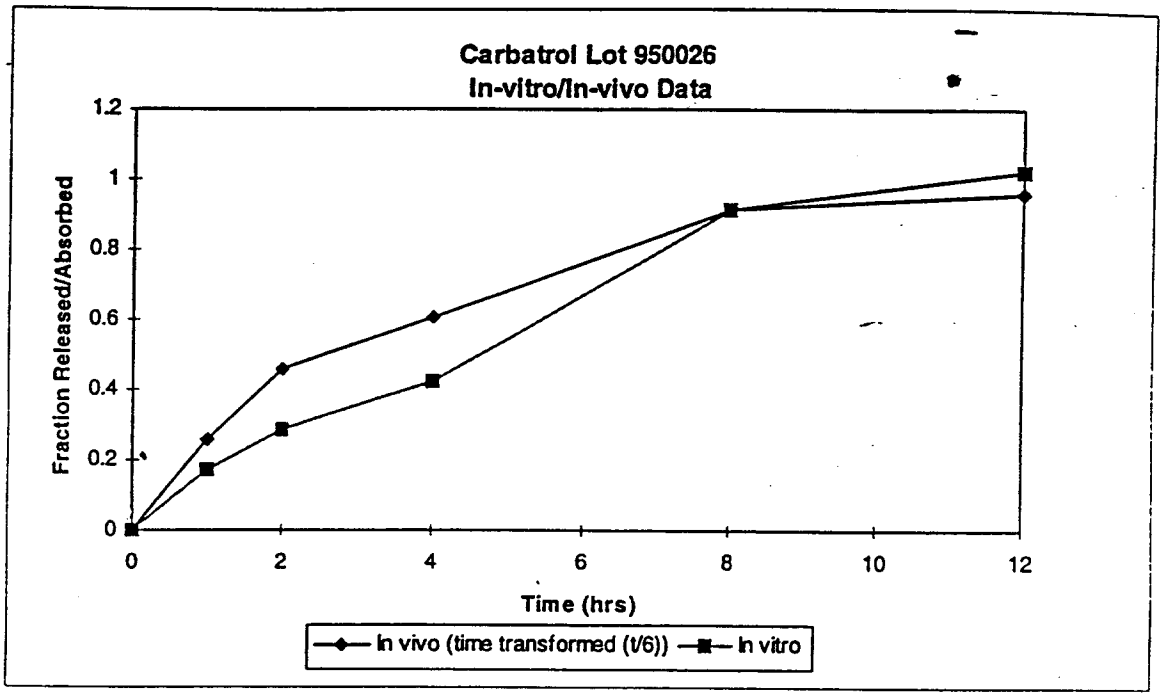


Figure 10. Fraction Absorbed vs. Fraction Released, Lot 950026, Pharmacokinetic Study 101.112

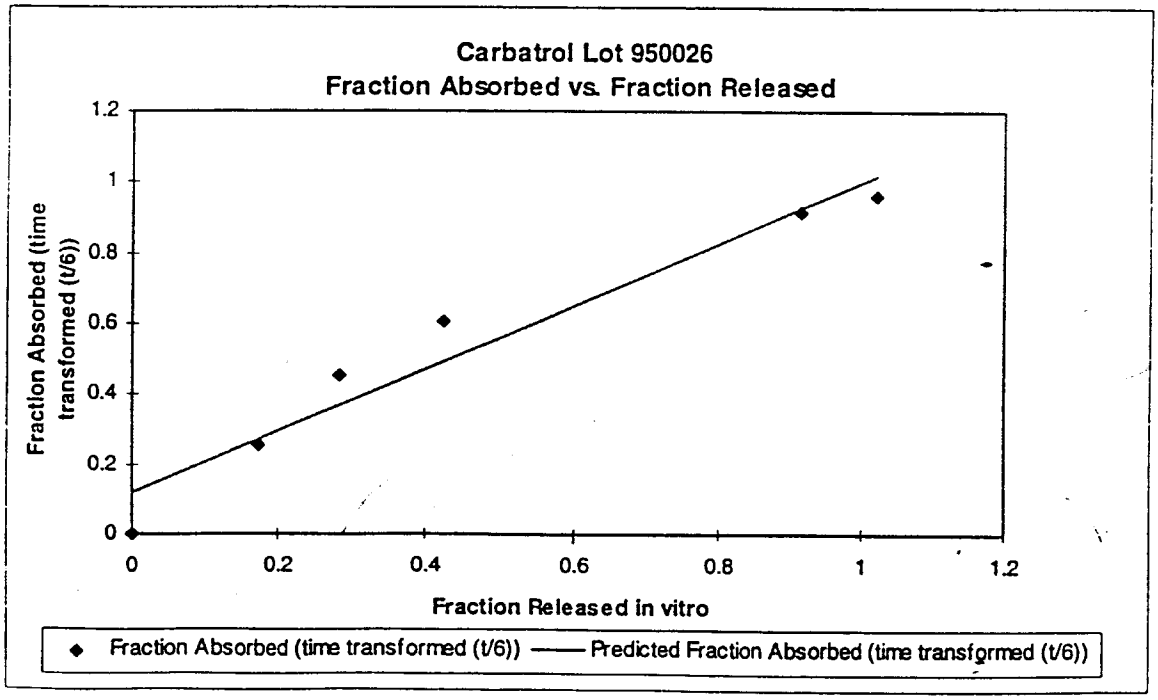


Figure 13. *In vitro-in vivo* Plot of Lot 950027, Pharmacokinetic Study 101.113

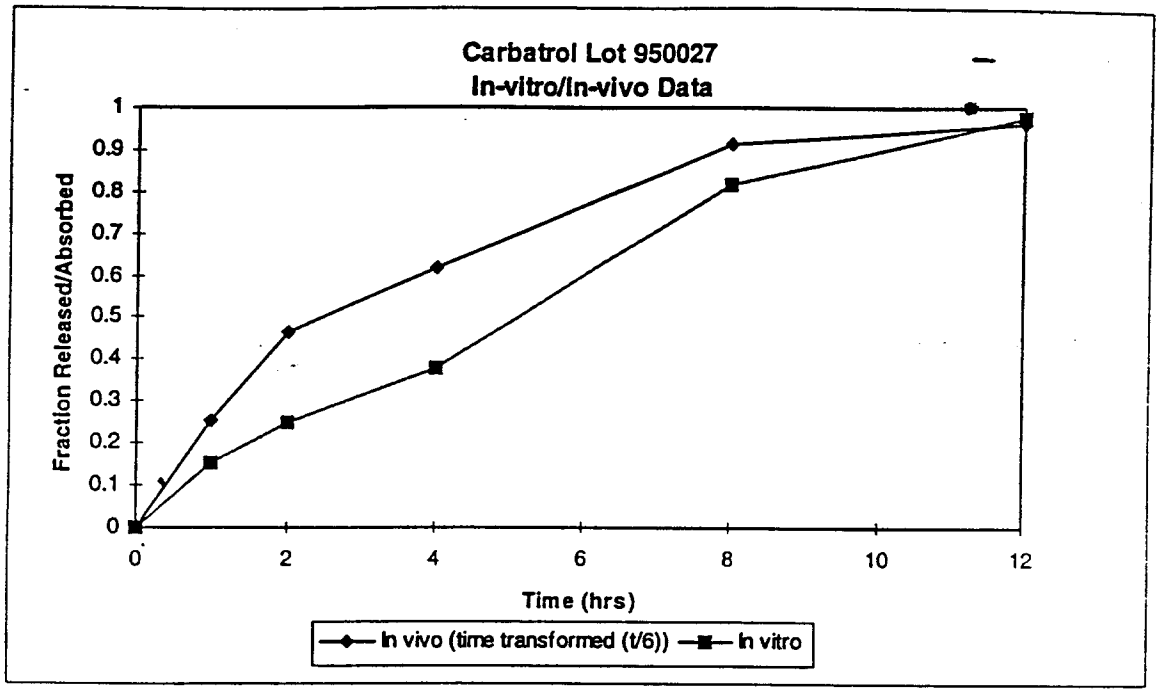


Figure 14. Fraction Absorbed vs. Fraction Released, Lot 950027, Pharmacokinetic Study 101.113

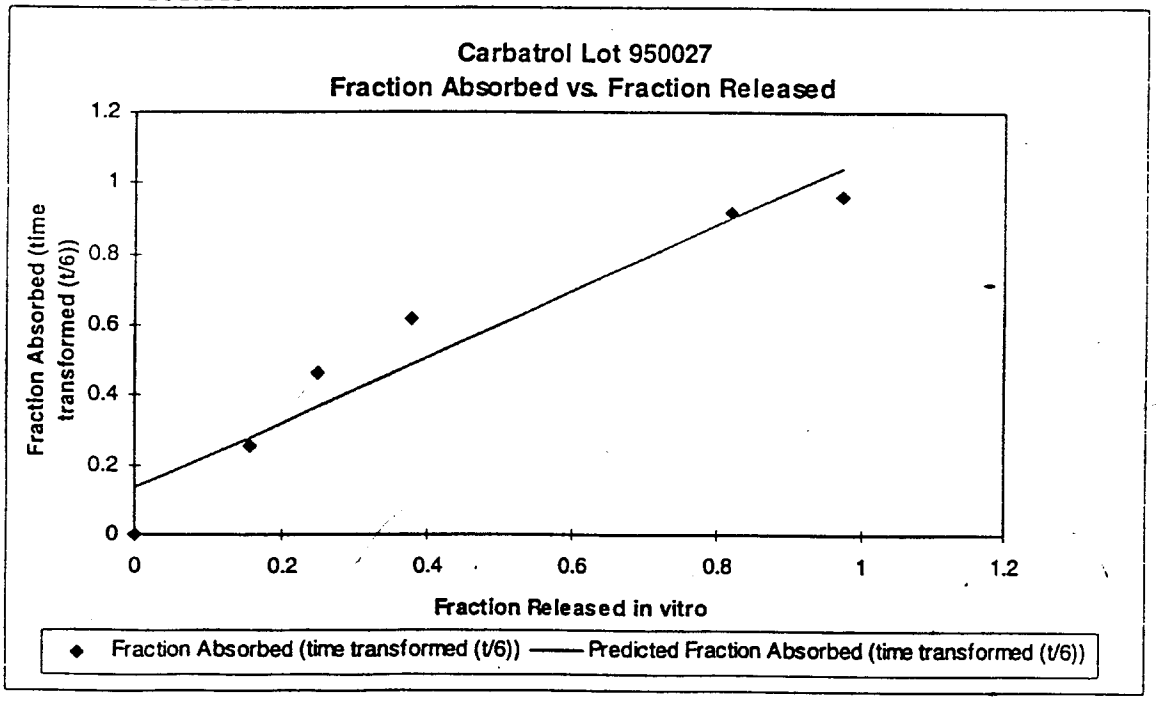


Figure 17. *In vitro-in vivo* Plot of Lot 920095, Pharmacokinetic Study 101.101C

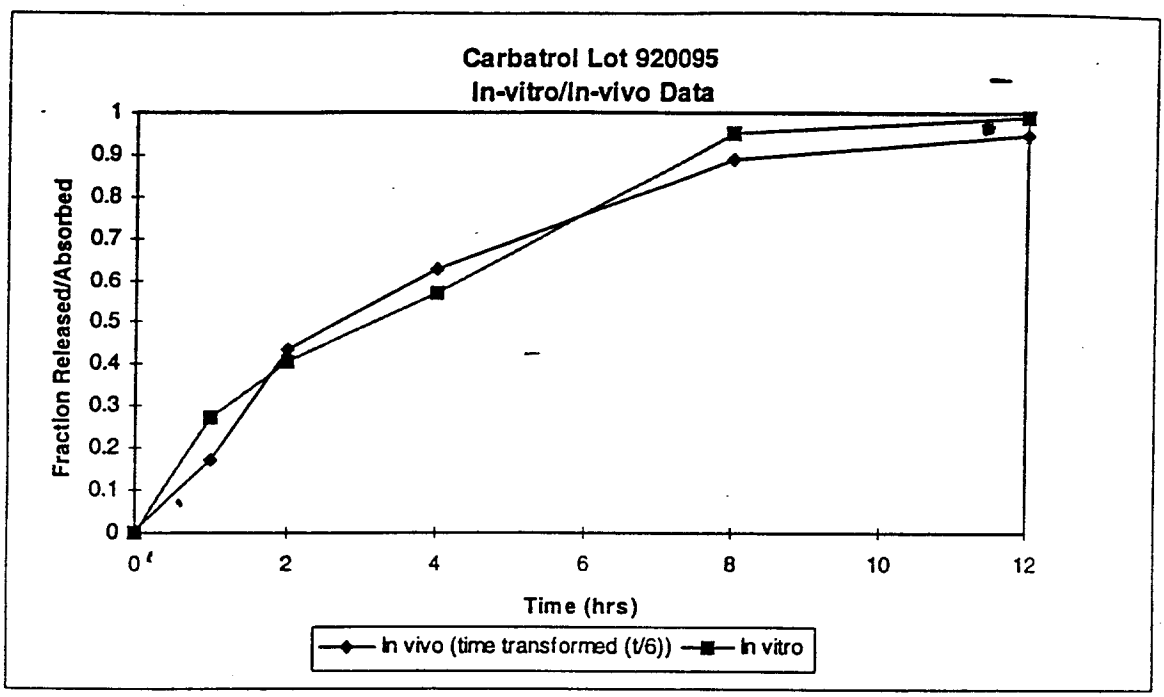


Figure 18. Fraction Absorbed vs. Fraction Released, Lot 920095, Pharmacokinetic Study 101.101C

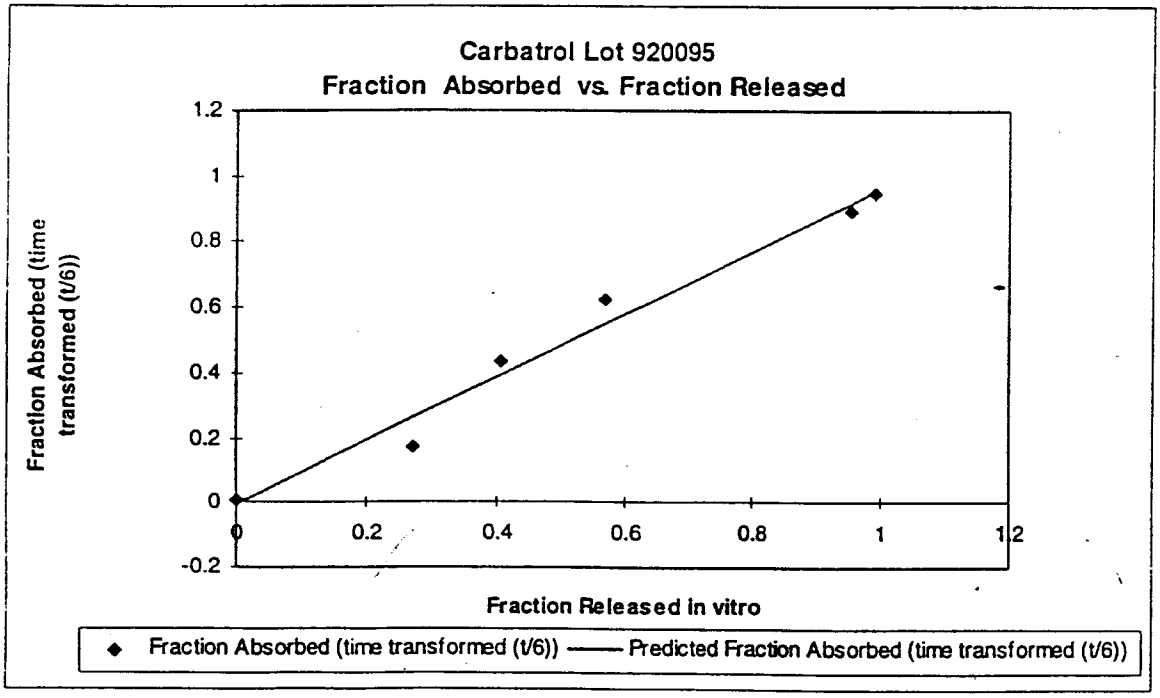


Figure 21. *In vitro-in vivo* Plot of Lot 920034, Pharmacokinetic Study 101.101B

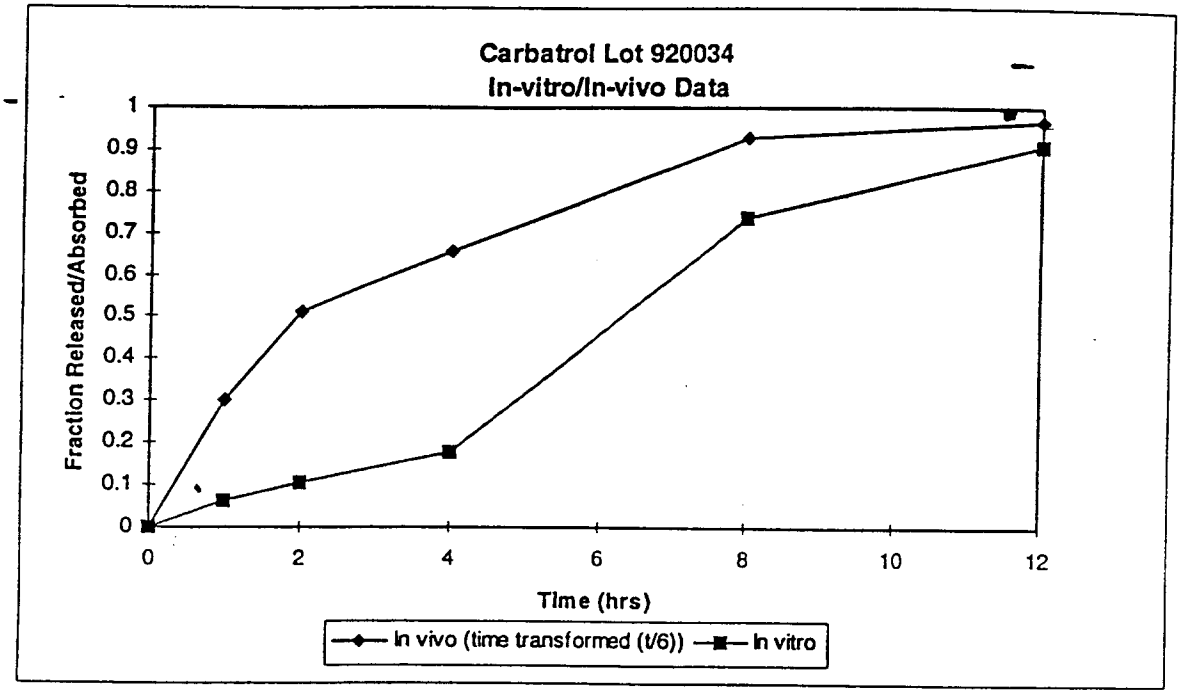
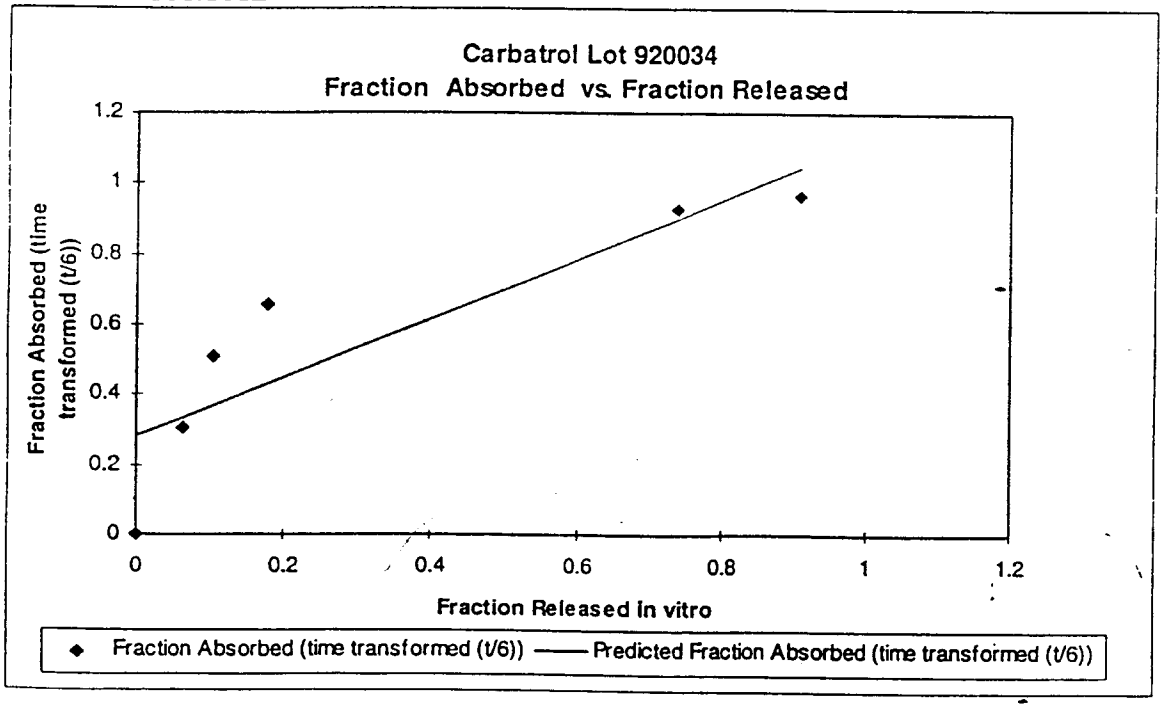
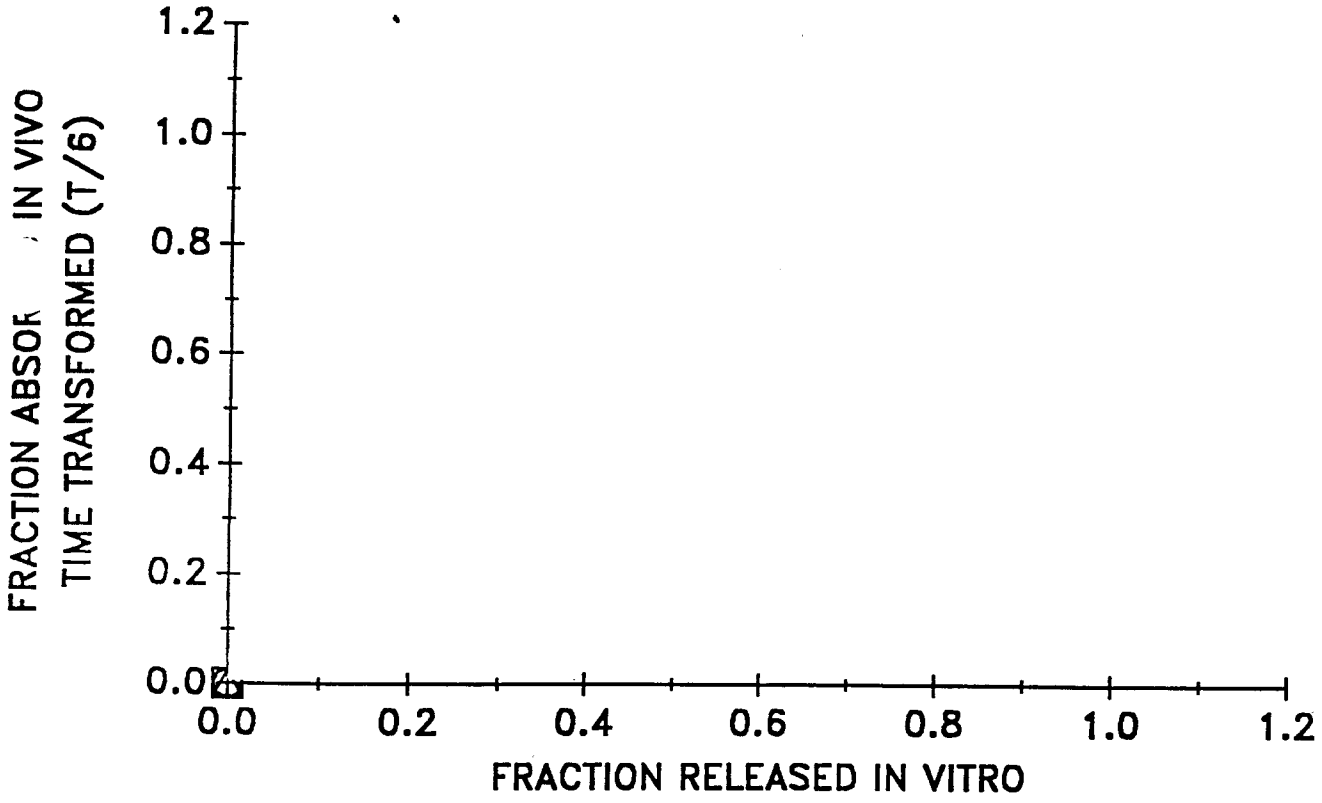


Figure 22. Fraction Absorbed vs. Fraction Released, Lot 920034, Pharmacokinetic Study 101.101B

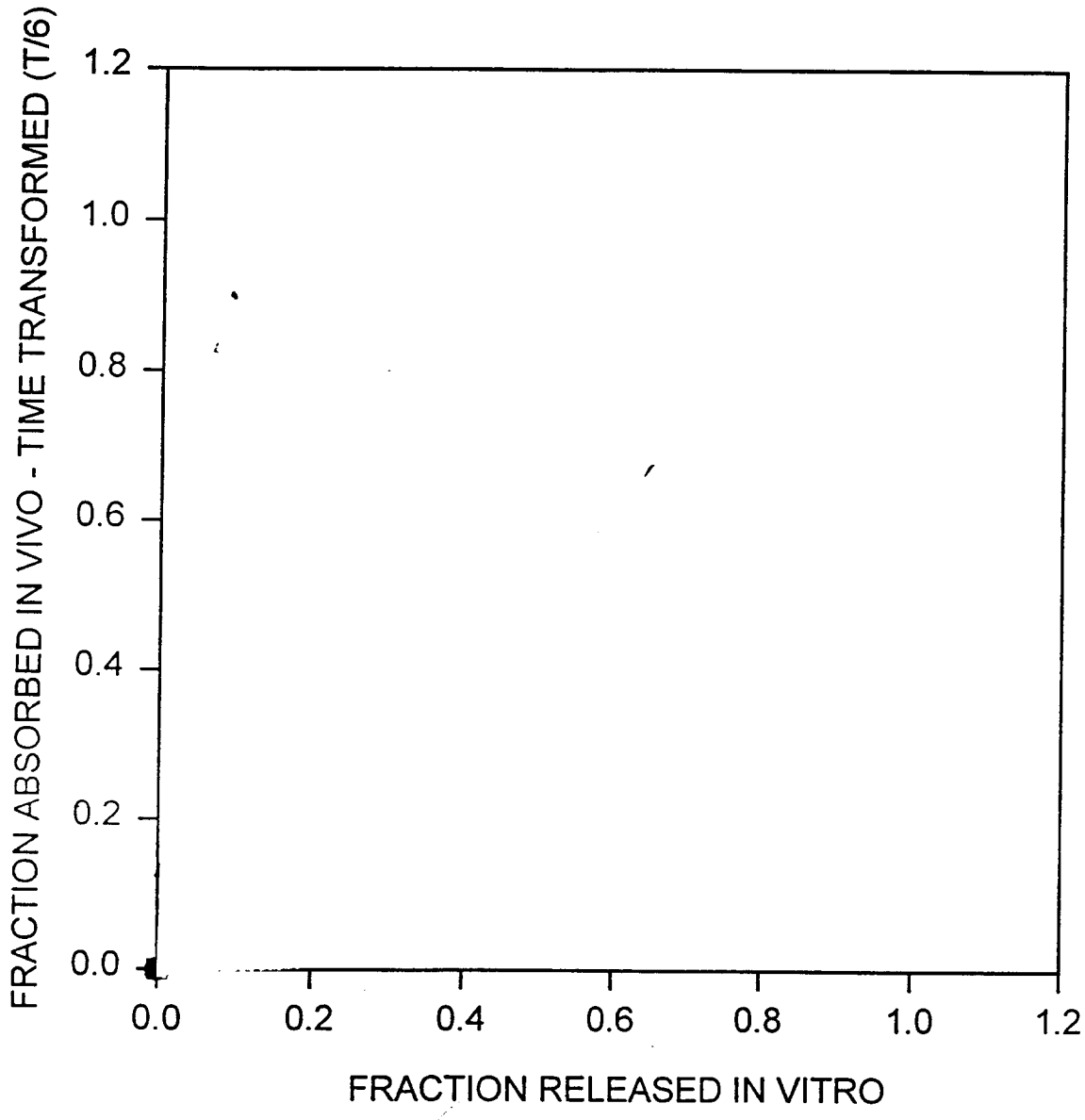


FDA ANALYSIS

CARBAMAZEPINE SR COMPOSITE PELLET FORMULA (IR+SR+EC)
STUDY PI 101.112 – A Three Formulation Comparison Study



CARBAMAZEPINE SR COMPOSITE FORMULA (IR+SR+EC)



ATTACHMENT A

BIOPHARMACEUTICS STUDY SUMMARY

Bioequivalence Study (Bio-batch)

Protocol No./ Status	Protocol Title	Study Design	Subjects/ Patients	Parameter Evaluated	Status	Summary of Results
101.103 Complete	Multidose Evaluation of Pharmacokinetics and Safety of a Multi-unit Dose of Carbamazepine in Epileptic Patients	Multiple dose of CARBATROL (every 12 hours) vs. Tegretol (every 6 hours) (4 weeks)	24 patients	AUC Cmax Cmin Tmax Epoxide	Completed 12/19/93 Prelim. Report IND Ser. # 014	CARBATROL given every 12 hours is bioequivalent to Tegretol given every 6 hours. The results indicate it is safe to switch from one formulation and dosage regimen to the other without risking worsening of seizures.

Clinical Pharmacokinetics/Bioequivalence Studies

101.112 Complete	A Three Formulation Comparison Study of CARBATROL	Open label, single dose, fasting, randomized, balanced, cross-over with 3 phases: optimized manufacturing Vs. manufacturing Vs. clinical batches (200 mg capsules)	12 subjects	AUC Cmax Tmax t1/2 Epoxide	Completed	Bioavailability of batches used in clinical trials were the same as bioavailability of batches intended for marketing. This study showed that the product intended for marketing was bioequivalent to the Bio-batch (see 101.103 above).
101.108 Complete	A "Food Effect" Bioavailability Study of CARBATROL	Open label, single dose randomized, balanced cross-over design with 3 phases: - with food; - without food; - and sprinkled on food	12 subjects	AUC Cmax Tmax t1/2 Epoxide	Completed 12/7/95	Bioavailability of CARBATROL was similar between the "without food" and the "sprinkled on food" groups. This study shows that sprinkling the contents of the CBZ-SR capsule over food is an acceptable method of drug administration.
101.109 Complete	A Dose Proportionality Study of CARBATROL	Open label, six-phase, single-dose, cross-over study; 200, 300, 400, 500, 600, and 800 mg	12 subjects	AUC Cmax Tmax t1/2 Epoxide	Completed 04/13/95	Plasma levels of carbamazepine were found to be proportional to the dose administered.
101.110 Complete	A Dose Equivalency Study of CARBATROL	Open label, single dose, fasting, randomized, balanced, cross-over with 2 phases: 2 x 300 mg Vs. 3 x 200 mg	12 subjects	AUC Cmax Tmax t1/2 Epoxide	Completed 11/2/95	600 mg of carbamazepine delivered as 2x300 mg capsules was bioequivalent to 600 mg of carbamazepine delivered as 3x200 mg capsules.

Cont'd

ATTACHMENT A (Cont'd)

Experimental Formulation Studies

Protocol No./ Status	Protocol Title	Study Design	Subjects/ Patients	Parameter Evaluated	Status	Summary of Results
101.101 Complete	Comparison of Absorption of Three Different Formulations of Carbamazepine (A, B1, and C)	Single dose, crossover with comparing the bioavailability of 3 pellets, A (rapid), B1 (intermediate), C (slow) (400 mg)	12 subjects	AUC Cmax Tmax t1/2 Epoxide	Completed 04/23/92 Prelim. Report 09/23/92 IND Ser. # 007	The data suggested no measurable difference in the absorption of carbamazepine from formulations A and C. The extent of absorption for formulation B1 was approximately 13% compared to formulation A. This study confirmed viability of A and C components, but the B component required further examination.
101.101B Complete	Comparison of Absorption of Two Different Formulations of Carbamazepine (B2 and B3)	Single dose, two-way crossover comparing the bioavailability of pellets B2 and B3 (400 mg)	12 subjects	AUC Cmax Tmax t1/2 Epoxide	Completed 09/23/92 Prelim. Report IND Ser. # 009	B2 absorbed (60%) better than B3 compared to A in study 101.101. This study confirmed discriminating ability of dissolution assay, but the sponsor determined the absorption of both B components to be unacceptable.
101.101C Complete	Comparison of Absorption of Two Different Formulations of Carbamazepine (B16 and B17)	Single dose, two-way crossover comparing the bioavailability of pellets B17 and B16 (400 mg)	6 subjects	AUC Cmax Tmax t1/2	Completed 12/16/92 Prelim. Report IND Ser. # 011	B17 significantly better absorbed than B16, but rate did not differ. This study confirmed the viability of the B17 component, which was used in later studies, including study 101.103.
101.102 Complete	Comparison of the Absorption of Three Different Components of Carbamazepine to Tegretol in Normal Volunteers	Single dose, crossover. compared the bioavailabilty of pellets A, B, and C, to Tegretol (400 mg of each)	12 subjects	AUC Cmax Tmax t1/2 Epoxide	Completed 12/23/92 Prelim. Report IND Ser. # 011	Pellets A and C were absorbed to the same extent as Tegretol. Absorption of B was lower.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20712

ADMINISTRATIVE DOCUMENTS

CARBAMAZEPINE SUSTAINED-RELEASE CAPSULES
PATENT CERTIFICATION STATEMENT

U.S. Patent No. 5,326,570

U.S. Patent No. 5,326,570 (issued July 5, 1994) covers the concept of Pharmavene's product, Carbamazepine Sustained-Release Capsules. This patent was issued before GATT regulations came into effect on June 7, 1995. The ultimate patent term is uncertain at this time, but it will be in force until at least July 5, 2011, and possibly until July 23, 2011. In addition, a Continuation-in-Part, extending the claims of the original patent was filed with the United States Patent and Trademark Office on April 21, 1995 and is pending.

US005326570A

United States Patent [19]

Rudnic et al.

[11] Patent Number: 5,326,570

[45] Date of Patent: Jul. 5, 1994

[54] **ADVANCED DRUG DELIVERY SYSTEM AND METHOD OF TREATING PSYCHIATRIC, NEUROLOGICAL AND OTHER DISORDERS WITH CARBAMAZEPINE**

[75] Inventors: **Edward M. Rudnic**, Gaithersburg; **George W. Belendiuk**, Potomac, both of Md.

[73] Assignee: **Pharmavene, Inc.**, Gaithersburg, Md.

[21] Appl. No.: **734,541**

[22] Filed: **Jul. 23, 1991**

[51] Int. Cl.[5] **A61K 9/54**

[52] U.S. Cl. **424/458**; 424/451; 424/452; 424/457; 424/459; 424/465; 424/468; 424/469; 424/489; 424/490

[58] Field of Search 424/451, 465, 457, 489, 424/459, 458, 468, 469, 490, 452; 544/152

[56] **References Cited**

U.S. PATENT DOCUMENTS

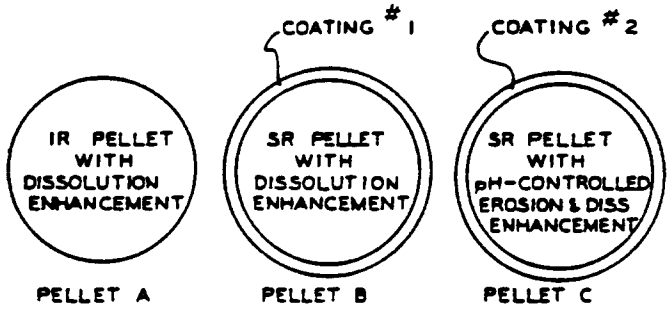
4,606,909	8/1986	Bechgaard et al.	424/481
4,794,001	12/1988	Mehta et al.	424/457
4,801,460	1/1989	Goertz et al.	424/465
4,857,336	8/1989	Khanna et al.	424/486
4,942,182	7/1990	Weiss et al.	424/10
4,980,170	12/1990	Schneider et al.	424/451
5,009,894	4/1991	Hsiao	424/451
5,023,272	6/1991	Burch et al.	544/152

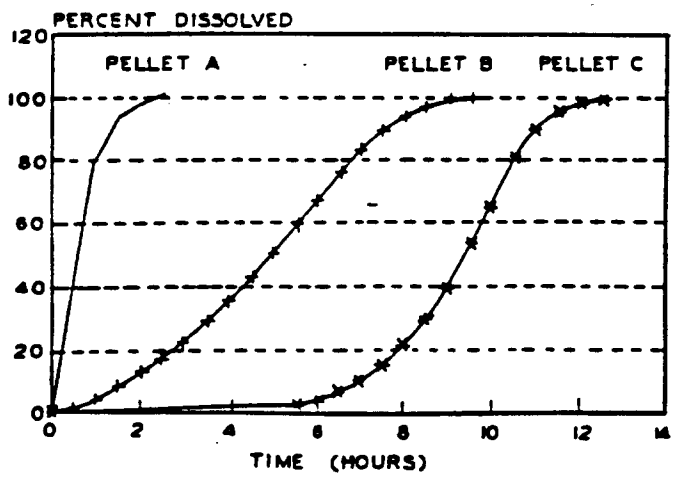
Primary Examiner—Thurman K. Page
Assistant Examiner—James M. Spear
Attorney, Agent, or Firm—Elliot M. Olstein; Susan A. Capello

[57] **ABSTRACT**

The present invention relates to a composition and method of treating a patient by administering carbamazepine in a pharmaceutical dosage form capable of maintaining the patient's blood concentration at from about 4 μg/ml to about 12 μg/ml over at least a 12 hour period, where the blood concentration of carbamazepine does not vary by more than 60 percent.

25 Claims, 1 Drawing Sheet





DOSAGE FORM COMPONENTS AND TARGET DISSOLUTION

Consult #694 (HFD-120)

CARBATROL carbamazepine sustained release capsules

The Committee notes the following look-alike/sound-alike conflicts with the proposed proprietary name: CAPITROL, CARTROL, carbachol. However, these other medications are available either OTC, in other dosage forms, or in different strengths therefore little confusion is expected. The USP no longer lists sustained release as a dosage form descriptor and instead is using "extended release". The appropriate established name for the drug should be (cabamazepine extended release capsules).

The Committee has no reason to find the proposed proprietary name unacceptable.

D L Boring 11/18/96, Chair
CDER Labeling and Nomenclature Committee

EXCLUSIVITY SUMMARY for NDA # 20-712 SUPPL # _____

Trade Name Carbatrol® Generic Name: carbamazepine extended release capsules

Applicant Name Pharmavene Inc. HFD-120

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /_X_/ NO /___/

   Please note that this application was submitted pursuant to CFR 314.50 as a 505(b)(2) application with cross-reference to NDA 16-608 (Tegretol tablets).

   b) Is it an effectiveness supplement?

   YES /___/ **NO /_X_/**

   If yes, what type? (SE1, SE2, etc.) ____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /__/ **NO /_X_/**

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   d) Did the applicant request exclusivity?

   YES /___/ **NO /_X_/**

   If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

   _____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for

YES /__/ **NO /_X_/**

Please note that Tegretol XR Tablets (NDA 20-234; approved 3/25/96)) is similar. It contains the same active ingredient, has 1 same strength (200mg), is orally admininistered, and has the same dosing schedule as Carbatrol. The difference between the 2 products is the dosage form. The Carbatrol dosage form is capsule; Tegretol XR is tablet.

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ **NO /_X_/**

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 16-608 Tegretol tablets

NDA # 18-281 Tegretol Chewable tablets

NDA # 18-927 Tegretol Suspension

NDA # 20-234 Tegretol XR tablets

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ **NO /_X_/**

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__/ **NO /_X_/**

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

This is a bioequivalency based approval.

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /__/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /__/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____
Investigation #2, Study # _____
Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /__/

Investigation #2 YES /___/ NO /__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

"No" is the answer for both investigations.

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /__/

Investigation #2 YES /___/ NO /_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

"No" is the answer for both investigations.

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1,Study # _____

Investigation #2, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 AN094-001

IND # _____ YES /__ / NO /___ /

Explain: _____

Investigation #2 AN094-003

IND #_____ YES /__/ NO /___/

Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

YES /__ / NO /___ /

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

Jacqueline H Ware

Jacqueline H. Ware, Pharm.D.
Project Manager, NDA 20-648

2/28/97
Date

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products

3/20/97
Date

cc: Original NDA 20-648
HFD-120/Division File
HFD-85 Mary Ann Holovac

file:c:\carbexcl.wpc

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA # 20-712 **Supplement # ____Circle one: SE1, SE2, SE3, SE4, SE5, SE6**

HFD-120 Trade (generic) name/dosage form: Carbatrol® (carbamazepine sustained release) Capsules

Action: AP AE NA **Applicant** Pharmavene Inc. **Therapeutic Class** 3S

Indication(s) previously approved: None

Pediatric labeling of approved indication(s) is adequate X **inadequate** ___

Indication in this application: Epilepsy - partial seizures with complex symptomatology (psychomotor, temporal lobe), generalized tonic-clonic seizures, and mixed seizure patterns which include the above, or other partial or generalized seizures.

(For supplements, answer the following questions in relation to the proposed indication.)

X 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

__ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- __ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- __ b. The applicant has committed to doing such stuilies as will be required.
  - ___ (1) Studies are ongoing.
  - ___ (2) Protocols were submitted and approved.
  - ___ (3) Protocols were submitted and are under review.
  - ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.
- __ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

__ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Cynthia G. McCormick MD — **Signature of Preparer and Title (PM, CSO, MD, other)**

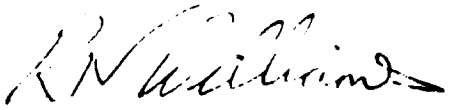
2/7/97 — **Date**

cc:Orig NDA
HFD-120/Div File
NDA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.
3/96

CARBATROL
(CARBAMAZEPINE SUSTAINED-RELEASE CAPSULES)
DERBARMENT CERTIFICATION STATEMENT

In the opinion and to the best knowledge of Pharmavene, Inc., there are no investigators, or any other individuals, that were involved with the submission of this New Drug Application who have been the subject of debarment activity by the Food and Drug Administration.



April 18, 1996

Richard N. Williams, Ph.D.
Director, Regulatory Affairs

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: March 19, 1997

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Carbatrol NDA Approvable Action

TO: File NDA 20-712

This memorandum conveys and explicates for the file the basis for the Division's decision to declare Pharmavene's NDA 20-712 for Carbatrol (a "sustained release" formulation of carbamazepine) approvable for use as in the management of epilepsy and trigeminal neuralgia. The NDA has been evaluated under the provisions of Section 505[b][2] of the FD&C Act.

Background:

A number of carbamazepine containing products (oral immediate release, oral chewable, and an oral suspension) are marketed for use in the management of epilepsy and trigeminal neuralgia. Ciba Geigy's Tegretol Tablet [NDA 16608] is the innovator product(1974 approval); generic versions of the tablet and chewable tablet have been available for 11 and 9 years respectively. A "sustained release" formulation of CBZ, Tegretol XR, is also marketed, approved on the basis of clinical pharmacokinetic studies that were deemed to show it 'bioequivalent' to the innovator product.

Following oral administration, CBZ and CBZE (carbamazepine 10,11-epoxide) appear in the systemic circulation. Based on findings in animal PD models, the two species are believed to have equal antiepileptic potency on a molar basis. Accordingly, in regard to therapeutic

equivalence[1] at least, the clinician would be largely indifferent as to the proportion of each species present as long as the sum of CBZ and CBZE were the same[2]. It is of relevance to the current application that this logic was relied upon in evaluating the evidence bearing on the approval of Tegretol XR. Although the 90% CI for the ratio of CBZE concentration following Tegretol XR to that following Tegretol for both Cmax and Cmin fell below the lower limit ordinarily required to declare two products bioequivalent(within the limits of 0.8 to 1.25), Tegretol XR was deemed bioequivalent because the sum of the concentrations of CBZ+CBZE for the two products were within the limits specified for considering them indistinguishable).

When its determination concerning Tegretol XR was made, however, the Office was unaware (as was the Division) that OGD's strategy for evaluating generic CBZ formulations considers only their capacity to deliver CBZ. The explanation for OGD's approach, as provided in Mohammad Hossain's 3/4/97 memorandum to me concerning the topic, is as follows. OGD is persuaded by literature reports that CBZE is not formed through a presystemic clearance mechanism (i.e., AUCs for CBZ following oral and parenteral administration of equimolar doses are the same). Thus, any difference in systemic CBZE concentrations in the presence of bioequivalent concentrations of CBZ following the oral administration of two CBZ oral products cannot attributable, in OGD's

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[1] Whether or not this statement is a fair one depends upon the frame of reference. The two species could be equipotent vis a vis their antiepileptic activity, but not in regard to their potential to cause untoward effects. While important to the final approval decision, the difference in capacity to cause adverse events at equivalent levels of exposure is irrelevant in making a determination as to whether the data show the new product to be effective in use.

[2] This argument by no means covers all possible situations. For example, if, arguendo, CBZ and CBZE were cleared at different rates, the rate at which systemic AED activity would be lost following discontinuation of treatment might differ as a function of the proportion of each species present. It seems, however, at least within the accuracy we have to measure them, that the half-lives of CBZ and CBZE are very similar, 35 to 40 hours following a single dose. Comparisons after repeated dosing are less meaningful because CBZ induces its own metabolism and between subject differences confound the evaluation.

view, to a difference in formulation behavior, but are best explained by intra or inter subject variability[3]. Their argument has considerable logical force, but turns on the implicit assumption that CBZ released in the GI tract by the new formulation is no more subject to presystemic clearance than the innovator standard. While this seems a reasonably safe assumption, it is not a logical nor biological necessity[4].

In any case, when the current application was received, staff in the Division of Pharmaceutical Evaluation I (HFD-860) to whom it was assigned, recognized, correctly, that the strategies employed by ODE 1 and OGD to assess bioequivalence differed fundamentally.

Current Submission.

Evidence of Effectiveness in use:

Once the basis for OGD's strategy for assessing bioequivalence was articulated, DNDP agreed that Carbatrol's effectiveness for use could be established if, under the conditions of recommended use, it could be shown to deliver the same quantity of CBZ (as judged by the limits of the 90% CI on the ratio of AUCs for the 2 products, i.e., 0.8 to 1.25) as equimolar doses of the reference product, provided it did so with equal or

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[3] The fact that CBZ induces its own metabolism is further reason to accept greater variability in CBZE levels because the latter are likely to reflect intrinsic differences within subjects over time in their capacity to convert CBZ to CBZE, and, therefore, are a poor choice for an indicator of each product's capacity to provide equivalent amounts of CBZ to the absorptive surface of the bowel, and, in the absence of presystemic clearance, to the systemic circulation.

[4] Conceivably, an extended or delayed release formulation might cause delivery of a drug substance to more distal portions of the bowel than the innovator reference formulation ordinarily does. If that more distal section had a capacity to metabolize CBZ that was not present in more proximal bowel, the OGD's assumption would be invalidated. An absolute bio study of the new product could easily resolve any residual doubt about this matter. In the present case, however, equal molar doses of the drug products being compared are equally bioavailable in regard to CBZ levels and there would be no way to explain this, given equal or lower levels of CBZE for the extended release product, if it were subject to first pass metabolism and the comparator standard release was not.

less plasma CBZ fluctuation (Cmax - Cmin/Cavg).

The sponsor has provided a report of a PK study that documents the standard has been met, thereby establishing that Carbatrol will be effective in use as recommended for the same claimed uses as the innovator, Tegretol.

Study 101.103, a classic 2 period counter-balanced cross over design, evaluated 24 epileptic subjects dosed for 14 days (the length of a period) with either Carbatrol given bid or Tegretol qid. The doses examined included 800, 1200 and 1600 mg/day; the analyses showed that whether considered in terms of free or total CBZ levels, the ratio rule was met over the course of a 24 hour day.

Additional PK studies were conducted, but these served only to provide estimates of Carbatrol's performance; none compared it to the innovator.

The NDA also includes the results of a clinical trial that serves as an independent source of evidence of Carbatrol's effectiveness in use. **STUDY 101.104** is a multiclinic (all in Poland), randomized, active control, investigation, that compared Carbatrol (800, 1200 and 1600 mg/day) with valproate (500-1000 mg/day), each given on a bid regimen. The study was conducted in patients receiving CBZ as monotherapy or in combination with no more than one other AED. After a 30 day baseline period, patients were randomized to their assigned treatment groups and converted, over a period of 3 to 8 weeks to their final intended dose level (time to final dose varied because dose was escalated accordingly to fixed schedule). The randomized comparison phase of the trial was 12 weeks in duration, 3 to 8 weeks of which were used for titration. Outcome was assessed in terms of the proportion of patients in treatment meeting outcome criteria. The results were statistically significant, favoring Carbatrol over valproate, not only in regard to the primary analysis, but in terms of time to outcome using a log-rank analysis.

Given the 505[b][2] status of the application, however, the findings of **STUDY 101.104** are irrelevant to the Division's assessment of Carbatrol's efficacy in use which turns exclusively on its functional 'bioequivalence' to the innovator product as a source of carbamazepine.

Safety:

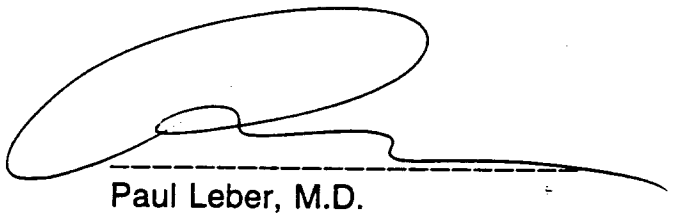
Dr. McCormick, the primary clinical neurology reviewer assigned to the application notes that actual reports of clinical experience with Carbatrol are limited. Given the 505[b][2] nature of the application this is expected. In fact, from the perspective of a generic approval, the number is quite large. In any event, there are but 350 or so "distinct" individuals who have been exposed to Carbatrol. Among these, only 120 or so were exposed for 24 weeks or longer at a dose of 400 mg or greater. The experience is unremarkable in light of the known risks of carbamazepine.

Conclusion:

Based upon the demonstration of its bioequivalence to Tegretol Tablets in a clinical PK study and upon the evidence justifying the agency's approval of the NDA for the innovator AED, Tegretol, the Carbatrol NDA may be approved under the requirements of section 505[b][2] of the FD&C Act.

Action to be taken:

Issuance of an approvable action letter.



Paul Leber, M.D.
March 19, 1997

cc:
Orig NDA 20-712
HFD-101
Temple
HFD-120
Katz
McCormick
Ware