CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20738

BIOEQUIVALENCE REVIEW(S)

D. Willard

AUG 22 1997

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NDA 20-738
Priority: 1 S
Teveten® (Eprosartan mesylate)
Tablets 300 and 400 mg)

SUBMISSION DATES: OCT. 11, 1996
OCT. 31, 1996
FEB. 5, 1997
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JULY 1, 1997
JULY 11, 1997
JULY 31, 1997.

SMITHKLINE BEECHAM

REVIEWER: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: Original NME

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SYNOPSIS:

The sponsor has studied the pharmacokinetics (single and multiple dose), metabolism and excretion of eprosartan, a new angiotensin II receptor antagonist, and has investigated the dose proportionality of eprosartan to include the dosing range covered in the proposed package insert. Absolute bioavailability is about 14% and eprosartan plasma concentrations increase with dose in less than proportional manner. Eprosartan does not undergo oxidative metabolism by P450 enzymes and acyl glucuronidation is the only metabolic pathway. Acceptable studies have been performed to study renal and liver impairment as well as age and gender effects. Drug interaction between eprosartan and digoxin, glyburide, ranitidine, ketoconazole, fluconazole and warfarin were studied. Co-administration of eprosartan with high fat meal results in increased plasma concentrations. The clinical trial formulations are not bioequivalent to the to-be-marketed formulations. An *in vitro* dissolution method has been provided but the recommended dissolution specification has been changed from Q= at 45 minutes to Q= at 30 minutes. This should be an interim specification prior to setting a final specification as recommended on page 14.

RECOMMENDATION:

The Division of Pharmaceutical Evaluation I has reviewed the sponsor's NDA 20-738 and has some concerns related to this drug product and recommends that the sponsor should respond to the comments below (page 14). The comments on page 13 should be forwarded to the medical officer.

TABLE OF CONTENTS:

BACKGROUND: Eprosartan is a synthetic compound with structure shown in Figure 1. Eprosartan blocks all physiologically relevant actions of angiotensin II by binding to the AT_1

pharmacodynamics studies and 2 *in vitro* studies in support of the NDA and all the studies were reviewed. The recommended dosing is 400 to 800 mg once daily.

Eprosartan is an acidic polar compound with a solubility of >100 mg/ml in ethanol and >20 mg/ml in water at pH 7.5. The solubility is pH dependent and lowest between pH 3 to 5 (Figure 2). The average partition coefficient in octanol-water (phosphate buffer, pH 7.4; initial aqueous phase concentration 0.01mg/ml) system is 0.047. An aqueous solution of eprosartan with excess drug substance has a pH of 2 after 30 minutes. The apparent pKa values of eprosartan mesylate obtained by titration with both hydrochloric acid and sodium hydroxide in 2:1 methanol:water were pK_{a1}=4.11, pK_{a2}=5.68 and pK_{a3}=6.89.

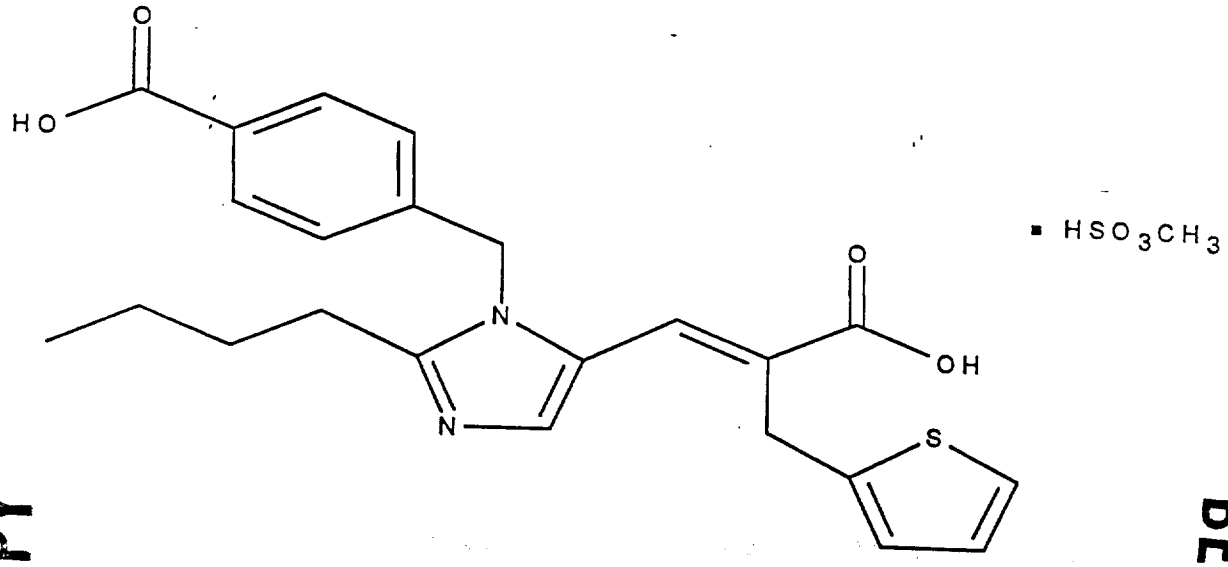

FIGURE 1. EPROSARTAN MESYLATE

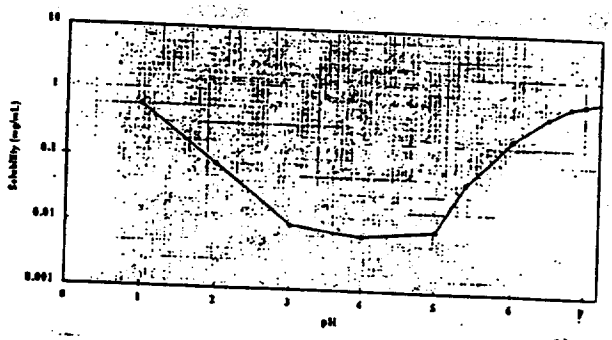

Figure 2

Solubility of Eprosartan Drug Substance

SUMMARY OF BIOAVAILABILITY / PHARMACOKINETICS/PHARMACODYNAMICS

1. BIOAVAILABILITY/BIOEQUIVALENCE:

A. Absolute Bioavailability: With reference to a 20 mg IV dose, the absolute bioavailabilty of Eprosartan given as 3x100 mg non-market (clinically tested) tablet averaged 14.1% (CV 41.1%) (Study 108566/005). The low systemic availability is probably due to poor oral absorption.

B. Bioequivalence: Bioequivalence was evaluated on log-transformed parameters and 90% confidence intervals were reported. Study 108566/034 was a replicate bioequivalence study that compared the 100 mg clinical trials tablet formulation to the commercial tablet formulation. The two one-sided test procedure on the AUC (0.84 - 0.98) and Cmax (0.78 - 0.95) for eprosartan showed that the two formulations are bioinequivalent. Study 108566/035 compared the 100 mg clinical trials tablet formulation and the commercial formulation to the 400 mg commercial tablet formulation. The 90% CI from the two one-sided test procedure on the AUC (1.09 - 1.24) and Cmax (1.19 - 1.42) for eprosartan showed that the 100 mg clinical formulation and the 400 mg commercial formulation are bioinequivalent and the two one-sided test procedure on the AUC (0.78 - 0.88) and Cmax (0.75 - 0.89) for eprosartan showed that the commercial formulation and the 400 mg commercial formulation are bioinequivalent. Study 108566/089 compared the 100 mg clinical trials tablet formulation to the 300 mg commercial tablet formulation. The two one-sided test procedure on the AUC (1.02 - 1.29) and Cmax (1.11 - 1.55) for eprosartan showed that the two formulations are bioinequivalent. Study 108566/018 compared the different formulations of eprosartan tablets (50 and 100 mg) used for clinical trials and demonstrated similar bioavailability between the formulations but bioequivalence was not demonstrated because of lack of power due to small sample size. Study 108566/092 compared the 100 mg and 200 mg clinical trials tablet formulations (100 mg +200 mg) and the 300 mg commercial formulations but failed to demonstrate bioequivalence between these formulations. Although the formulations are exactly compositionally proportional it is difficult to understand why they are absorbed to different extent (see comments on page 14).

C. Food effect: The effect of food on the absorption of eprosartan administered as a single 800 mg dose (2x400 mg commercial tablet formulation) was evaluated (Study 108566/086). After coadministration of a standard high fat meal (caloric content = 1020 calories) the Tmax increased from 1.5 hours to 3.2 hours, AUC increased by about 20% for eprosartan but the Cmax remained unchanged for eprosartan. The other two food effect studies (Study 108566/005 and Study 108566/007) did not use the commercial tablet formulations of eprosartan. However, Study 108566/007 that used a direct compression investigational formulation showed significant increase in AUC (80%) and Cmax (54%) but no effect on the terminal half-life of eprosartan.

II. PHARMACOKINETICS:

Pharmacokinetics of eprosartan were evaluated in several studies in healthy volunteers as well as in the target population of patients with hypertension. Single IV doses covered a range from 0.1 to 20 mg (30 minutes infusion). Single oral doses covered a range from 1 to 800 mg and multiple oral doses ranged from 50 to 1200 mg once daily for up to 1 week. Eprosartan is rapidly absorbed after oral administration with T_{max} ranging from 1-3 hours. After single (oral or IV) or multiple (oral) dose administration, C_{max} and AUC increased (Tables 1, 2 & 3) in a slightly less than dose proportional manner (Study 108566/008, Study 108566/009, Study 108566/048). Following IV administration of 20 mg dose (Study 108566/005), eprosartan concentrations declined bi-exponentially with a terminal half-life ($t_{1/2}$) of about 2 hours, systemic clearance (CL_s) of about 130 ml/minute and the volume of distribution (V_{ss}) of about 13 liters (indicating that eprosartan is not widely distributed because of its polar nature and extensive protein binding).

Table 1. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Healthy Volunteer (Study 108566/008)

PARAMETER	DOSE (MG)			
	100	200	400	800
Cmax (ng/ml)	439 (234)	702 (255)	1273 (577)	1857 (736)
Cmax/Dose (ng/ml/mg)	4.39 (2.34)	3.51 (1.27)	3.18 (1.44)	2.32 (0.92)
$AUC_{(0-t)}$ (ng*h/ml)	1400 (637)	2620 (1046)	4887 (2525)	7855 (2782)
$AUC_{(0-t)}$/Dose (ng*h/ml/mg)	14.0 (6.37)	13.1 (5.23)	12.22 (6.31)	9.82 (3.48)
Tmax (h)	2.85 (0.75)	2.92 (0.69)	3.15 (0.85)	2.88 (0.79)

Both CL_s and V_{ss} were independent of dose (3 - 20 mg dose range) suggesting that the non-linear pharmacokinetics of eprosartan following oral administration may be a consequence of saturable process during the absorption phase (Study 108566/004). The terminal elimination half-life ($t_{1/2}$) following single or multiple oral doses (Tables 2 & 3) ranged from 4-12.2 hours (longer $t_{1/2}$ following oral administration may be related to the longer length of time eprosartan plasma concentrations remain above the lower limit of quantitation and/or absorption-rate limited terminal phase ("flip-flop" pharmacokinetics).

Table 2. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Hypertensive Patients (Study 108566/009)

PARAMETER	50 MG		100 MG		350 MG		150 MG#	
	SD	MD	SD	MD	SD	MD	SD	MD
Cmax (ng/ml)	968 (584)	673 (675)	1406 (526)	1480 (867)	2276 (752)	1818 (763)	1647 (666)	1635 (710)
$AUC_{(0-t)}$ (ng*h/ml)	3359 (2421)	2770 (2783)	5287 (2643)	5768 (2792)	10133 (5253)	8067 (2936)	6249 (3192)	6340[a] (2818)
$AUC_{(0-inf)}$ (ng*h/ml)	3442 (2425)	2923 (2766)	5477 (2657)	6284 (3015)	10486 (5418)	8184 (3169)	6422 (3171)	ND
T_{max} (h)	1.75 (0.92)	1.84 (0.83)	1.69 (0.65)	1.38 (0.42)	1.91 (0.98)	1.97 (1.07)	1.22 (0.41)	1.81 (1.19)
$T_{1/2}$ (h)	4.09 (2.78)	5.74 (3.51)	7.54 (5.04)	9.60 (3.1)	6.77 (3.22)	7.76 (1.40)	7.92 (3.09)	ND
Accumulation Ratio	0.95 (0.68)		1.16 (0.61)		0.88 (0.38)		1.06 (0.30)	

#150 MG Every 12 hours
[a]AUC(0-12)
ND= Not Determined
SD = Single Dose
MD = Multiple Dose

Table 3. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Hypertensive Patients (Study 108566/048)

PARAMETER	600 MG		800 MG		1200 MG	
	SD	MD	SD	MD	SD	MD
Cmax (ng/ml)	1622 (802)	1608 (726)	2081 (937)	2103 (1502)	2785 (1012)	2961 (1432)
$AUC_{(0-t)}$ (ng*h/ml)	7829 (4477)	9731 (4381)	9639 (5476)	9521 (4975)	14642 (6838)	19125 (8632)
$AUC_{(0-inf)}$ (ng*h/ml)	7895 (4507)	10786 (4963)	10520 (5777)	10443 (4818)	16310 (8141)	22423 (10749)
T_{max} (h)	2.5 (1.9)	2.6 (1.8)	2.9 (0.6)	1.9 (1.1)	2.1 (1.7)	2.7 (1.6)
$T_{1/2}$ (h)	11.5 (7.0)	9.0 (3.1)	7.9 (5.7)	8.6 (4.2)	10.4 (6.6)	12.2 (6.6)
Accumulation Ratio	1.18 (0.45)		0.95 (0.52)		1.28 (0.69)	

SD = Single Dose
MD = Multiple Dose

After multiple daily doses, steady state conditions are reached after 3-4 days and $t_{1/2}$ was similar to that obtained after single dose administration (Study 108566/048, Study 108566/009). The accumulation factor after multiple doses (50 to 1200 mg) for eprosartan ranged from 0.88 to 1.28 (Tables 2 & 3), however, a lack of accumulation is concluded over the therapeutic range.

III. METABOLISM:

Following both intravenous and oral of administration of ^{14}C-eprosartan, the major route of excretion was via the feces (61% and 90% of the dose respectively) while urinary excretion accounted for 37% and 7% giving total recoveries of radioactivity of 98% of dose by both routes (Study 108566/020). Eprosartan was the only drug-related compound found in the plasma and in the feces. Approximately 20% of the radioactivity excreted in the urine was an acyl glucuronide of eprosartan, with the remaining 80% being unchanged eprosartan. Acyl glucuronidation was therefore the only metabolic pathway found.

The results obtained from the in vitro human microsomal metabolic studies (Protocol D94063/108566) showed that eprosartan did not cause significant inhibition of CYP1A, CYP2A6, CYP2C9/8, CYP2C19, CP2E and CYP3A at concentrations up to 100 μM and there is no indication that oxidative metabolism of eprosartan would produce a metabolite with significant potential to inhibit cytochrome P450 enzymes.

VI. SPECIAL POPULATIONS:

A. Renal Impairment: Renally insufficient patients with creatinine clearances ranging from > 5 ml/min and healthy volunteers with creatinine clearances >80 ml/min were administered 200 mg oral dose of eprosartan twice daily for seven days (Study 108566/021). The data obtained from the study show that: (I) total and unbound plasma concentrations of eprosartan increased with decreasing renal function (total Cmax and AUC increased by about 50% while unbound Cmax and AUC increased 3-fold in patients with severe renal impairment when compared to healthy volunteers); (ii) renal clearance of eprosartan decreased with decreasing renal function (CLr in patients with severe renal impairment is about 5% of healthy volunteers and amount excreted in urine is about 10% of heathy volunteers); (iii) $t_{1/2}$ increased 2-fold in patients with severe renal impairment when compared to healthy volunteers (Table 4). Active secretion contributes to the overall renal clearance.

Table 4. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Subjects with Renal Impairment and Healthy Volunteers

PARAMETER	NORMAL[a]	MILD[b]	MODERATE[c]	SEVERE[d]
Cmax (ng/ml)	590 (318)	536 (217)	795 (388)	888 (202)
$AUC_{(0\text{-}12)}$ (ng*h/ml)	2961 (1558)	2239 (8674)	3711 (1772)	4597 (1423)
Tmax (h)	3.71 (1.25)	3.88 (0.35)	4.00 (1.10)	3.00 (3.00)
$t_{1/2}$ (h)	2.81 (0.49)	2.81 (0.49)	3.76 (2.04)	6.19 (1.58)
%fu (*ex vivo*)	1.40 (0.22)	1.60 (0.12)	1.60 (0.19)	2.70 (0.51)
Free $AUC_{(0\text{-}12)}$ (ng*h/ml)	40.0 (18.5)	35.4 (13.2)	61.2 (35.3)	124.0 (50.0)
Free Cmax (ng/ml)	8.2 (4.5)	8.4 (3.2)	13.2 (7.7)	23.3 (1.4)
CLr (ml/min)	39.2 (27.1)	45.6 (7.3)	23.1 (17.4)	2.2 (0.6)
AEU (% Dose)	2.78 (1.56)	3.0 (1.14)	2.18 (1.41)	0.28 (0.05)

[a]Group A: Normal renal function (Clcr > 80 ml/min), n=7
[b]Group B: Mild renal function (Clcr > 60-80 ml/min), n=8
[c]Group C: Moderate renal function (Clcr > 39-59 ml/min), n=11
[d]Group D: Severe renal function (Clcr > 5-29 ml/min), n=3

The results of the study in hemodialysis patients compared to healthy volunteers (Study 108566/099) showed that: (I) AUC increased more than 2-fold and Cmax increased by 22% in hemodialysis patients when compared to healthy volunteers; (ii) the %fraction unbound

increased by 74% in hemodialysis patients when compared to healthy volunteers; (iii) unbound AUC increased more than 4-fold and unbound Cmax increased more than 2-fold in hemodialysis patients when compared to healthy volunteers; (iv) compared to non-dialysis day, AUC and Cmax increased by about 35% and $T_{1/2}$ increased 2-fold on dialysis day; (v) compared to pre-hemodialysis sample, the observed %fraction unbound was lower (about 40% decrease) when assessed immediately post-hemodialysis (7 hours post-dose); (vi) CL_{hd} of eprosartan determined by dialysate measurement was 11.22 ml/min; (vi) the pharmacokinetics of eprosartan in hemodialysis patients were highly variable compared to healthy volunteers.

B. Hepatic Impairment: Study 108566/022 compared the pharmacokinetics of eprosartan in normal subjects and patients with impaired liver function following single oral dose of 100 mg eprosartan. Comparison of the data from the subjects with hepatic impairment to those from healthy male subjects showed that: (I) total Cmax and AUC are increased by 14% and 62% respectively in hepatic subjects; (ii) free Cmax and AUC are increased by 25% and 84% respectively in hepatic subjects, (iii) $t_{1/2}$ increased by about 18% in hepatic subjects. Observations I-iii could be due to increased bioavailability or decreased clearance; (iv) the variabilities in the Cmax and AUC are higher in hepatic subjects (Table 5).

Table 5. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Subjects with Hepatic Impairment and Healthy Volunteers

PARAMETER	HEPATIC SUBJECTS	NORMAL SUBJECTS
Cmax (ng/ml)	486 (243)	428 (128)
$AUC_{(0\text{-inf})}$ (ng*h/ml)	2610 (1624)	1616 (379)
Tmax (h)	5.0 (1.51)	4.24 (1.17)
$T_{1/2}$ (h)	2.45 (0.66)	2.08 (0.92)
fu (%)	1.93 (0.33)	1.77 (0.29)
Free $AUC_{(0\text{-inf})}$ (ng*h/ml)	52.6 (43.2)	28.5 (7.23)
Free Cmax (ng/ml)	9.51 (5.93)	7.62 (2.57)

C. Elderly and Gender: Elderly subjects (8 males; age 68-78 years) and young subjects (8 males and 8 females; age 20-39 years) were administered a single dose of 200 mg eprosartan tablet (Study 108566/025). The results obtained from the study showed that: (I) elderly males had plasma levels of eprosartan that were approximately 2-fold higher than young males in terms of free and total $AUC_{0\text{-inf}}$ and Cmax; (ii) The Tmax and $t_{1/2}$ of eprosartan were approximately 2-fold higher in the elderly males compared to young males. These observations

(I & ii) could be due to increased absorption or decreased elimination of eprosartan in the elderly when compared to the young males; (iii) The pharmacokinetics of eprosartan are similar in young males and young females; (iv) There was no age or gender effect on protein binding of eprosartan
(Table 6).

Table 6. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Healthy Volunteers

PARAMETER	YOUNG MALES	YOUNG FEMALES	ELDERLY MALES
Cmax (ng/ml)	489 (347)	599 (509)	914 (353)
$AUC_{(0\text{-}inf)}$ (ng*h/ml)	2171 (1544)	2322 (1806)	4572 (1653)
Tmax (h)	2.75 (0.46)	3.52 (0.76)	4.89 (1.25)
$T_{1/2}$ (h)	2.81 (0.49)	3.76 (2.04)	6.19 (1.58)
fu (%)	2.11 (0.31)	2.15 (0.22)	2.17 (0.22)
Free $AUC_{(0\text{-}inf)}$ (ng*h/ml)	44.7 (30.5)	49.7 (40.5)	98.5 (34.6)
Free Cmax (ng/ml)	10.2 (6.7)	12.9 (11.2)	19.8 (7.9)

V. DRUG INTERACTIONS:

A. Digoxin: Study 108566/023 examined the effects of steady state eprosartan (200 mg twice daily for 7 days) on single dose of digoxin capsule (0.6 mg Lanoxicaps on Day 4). The data obtained from the study showed that co-administration of digoxin with eprosartan did not affect the AUC and the Cmax of digoxin but resulted in an increase in the terminal half life of digoxin by about 7 hours (from 39.8 hours to 46.9 hours).

B. Warfarin: In Study 108566/027, the effect of eprosartan on the anticoagulant activity of warfarin at steady state was evaluated. The results obtained from the study showed that co-administration of warfarin with eprosartan was statistically equivalent to coadministration of warfarin with placebo on the anticoagulant activity of warfarin (as measured by the international normalized ratio). There is therefore no apparent pharmacodynamic interaction between eprosartan and warfarin with regard to anticoagulant effect of warfarin but there is no data available to rule out a pharmacokinetic interaction.

C. Glyburide: In Study 108566/028 the effect of concomitant administration of eprosartan and

glyburide on the 24-hour plasma glucose profiles in diabetic patients was studied. The results obtained from the study showed that eprosartan taken concomitantly with glyburide for a period of one week had no effect on the mean 24-hour glucose concentrations in diabetic patients stabilized on glyburide therapy but there is no data available to rule out a pharmacokinetic interaction.

D. Ranitidine: The effect of multiple oral doses of ranitidine on the pharmacokinetics of a single oral dose of eprosartan was investigated in Study 108566/029.The results obtained from the study show that co-administration of 400 mg eprosartan with 150 mg ranitidine leads to a decrease of 11% in Cmax, 7% in AUC and about 13% in CLr and amount of eprosartan excreted in urine indicating that increased gastric pH due to ranitidine administration does not significantly affect the rate and extent of absorption of eprosartan.

E. Fluconazole: Study 108566/094 examined the effects of steady state fluconazole on the pharmacokinetics of repeat oral doses of eprosartan and urine uric acid excretion. The results obtained from the study showed that: (I) Fluconazole administration did not alter the steady-state pharmacokinetics of eprosartan (because eprosartan is not metabolized by CYP2C9), and (ii) Eprosartan had similar effects as placebo on urine uric acid excretion when administered as single dose alone or repeated doses administered with or without fluconazole.

F. Ketoconazole: Study 108566/095 examined the effects of steady state ketoconazole on the pharmacokinetics of repeat oral doses of eprosartan and urine uric acid excretion. The results obtained from the study showed that:(I) Co-administration with ketoconazole did not affect the steady state pharmacokinetics of eprosartan thus confirming the CYP3A is not involved in the metabolism of eprosartan, and (ii) Eprosartan had similar effects as placebo on urine uric acid excretion when administered as single dose alone or repeated doses administered with or without ketoconazole.

VI. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP: In Study 108566/006 the following objectives were investigated: (1) assessment of the onset of inhibitory effect of eprosartan on angiotensin-II-induced decreases in effective renal plasma flow (ERPF); (2) assessment of the onset of inhibitory effect of eprosartan on angiotensin-II-induced decreases in ERPF at 24 hours after dosing; (3) assessment of the lack of agonist activity of eprosartan as determined by the absence of an eprosartan-induced decrease in ERPF; (4) assessment of the dose-response profile of single oral doses of eprosartan an eprosartan pharmacokinetics and on inhibition of angiotensin-II-induced decreases in effective renal plasma ERPF; (5) investigation of the relationship between plasma concentrations of eprosartan and inhibition of angiotensin-II-induced decreases in ERPF. The results obtained from the study show that the concentration-effect relationship was not well characterized due to insufficient number of data points resulting from limited number of subjects, short duration of angiotensin II infusions, and small number of plasma concentration sampling points. Eprosartan inhibited the decrease in ERPF (measured as PAH clearance) induced by exogenous angiotensin II in a dose-related fashion. The effect of eprosartan was maximum at one to two

hours after dosing, was maintained for at least 15 hours but was absent at 24 hours after dosing.
The relationship between plasma concentrations of eprosartan and the primary efficacy variables in 6 clinical trials (Studies 010, 011, 013, 017, 045 and 049) was examined graphically. There were no obvious relationships between eprosartan concentrations in responders compared to non-responders.

VII. POPULATION PHARMACOKINETICS: The population pharmacokinetics of eprosartan in hypertensive patients were evaluated in five studies following once daily (Study 045) and twice daily (Studies 010, 011, 013, and 017) administration of eprosartan. A one-compartment model with first order absorption and first order elimination best described the data. The population pharmacokinetics of eprosartan were not influenced by weight, race, gender or severity of hypertension at baseline. The population mean oral clearance (CL/F) was about 50 L/h (similar to value obtained in healthy males) and was shown to be a linear function of age with CL/F decreasing 0.62 L/h for every year increase. The population mean estimate for the steady-state volume of distribution (Vss/F) was about 300 L which was 4-fold greater than the value in healthy volunteers. This could be a result of an inability to obtain an accurate estimate of the absorption rate constant (Ka) due to the study design and therefore the need to use a fixed values of Ka for the analysis.

VIII. FORMULATION: The three tablet formulations to be marketed 300 and 400 mg) are compositionally proportional. Their compositions are shown in Table 1 (Attached).

IX. DISSOLUTION: The proposed dissolution method of

XI. PLASMA PROTEIN BINDING: Plasma protein binding of eprosartan was extensive but varied between species (% free fraction in rat, dog and human were 1.9, 11.1, and 1.6% respectively at 10 μg(acid)/ml). The free fraction in all species remained approximately linear up to 10 μg(acid)/ml but increased in a non-linear fraction above at concentrations above 100 μg(acid)/ml.

XII. BLOOD/PLASMA PARTITIONING: The blood/plasma ratio for eprosartan remained constant for all three species and was approximately 0.54 in rat and dog blood (0.01 - 1000 μg(acid)/ml) and approximately 0.62 in human blood (0.01 - 100 μg(acid)/ml) thus suggesting little association with blood cells.

XIII. PEDIATRIC POPULATION: The pharmacokinetics of eprosartan has not been

described in the pediatric population.

XIV. LABELING: The clinical pharmacology section of the labeling is deficient and the firm has been advised to modify it accordingly (see comments below).

XV. INFLUENCE OF RACE: The population pharmacokinetics of eprosartan were not influenced by race (see population pharmacokinetics above).

GENERAL COMMENTS TO THE MEDICAL OFFICER:

FORMULATIONS AND BIOINEQUIVALENCE

The sponsor has not demonstrated bioequivalence between the clinical trial tablet formulations and the to-be-marketed tablet formulations. This was surprising since the number of subjects in the studies is high and the formulations are compositionally proportional. Although this lack of equivalence may appear less critical for a drug that will be individually titrated and a wide dose range is considered safe, it is more of an issue if, for example, 2x200 mg tablets is switched with 1x400 mg tablet. The firm has been requested to explain the discrepancy in the formulations/in vivo performance. It is very likely that there are some process differences between the formulations (for example, particle size, compression force).

DOSAGE ADJUSTMENT IN SPECIAL POPULATIONS (ELDERLY AND SEVERE RENAL IMPAIRMENT)

The plasma levels of eprosartan in elderly males is approximately double the levels in young males (although population pharmacokinetics analysis did not show age to be an important co-variate) while the plasma levels in severely renally impaired patients there is a 3-fold increase and in hemodialysis patients a 4-fold increase (in AUC) when compared to healthy volunteers. The pharmacokinetics of eprosartan in hemodialysis patients were highly variable compared to healthy volunteers. There is no established plasma concentration-effect relationship for eprosartan. It is therefore difficult to recommend a dosage adjustment based on the available pharmacokinetic data. However, it could be recommended that these population of patients should be started on lower doses and titrated up as needed based on response.

LABELING - FOOD EFFECT

Because of the pronounced food effect observed from the direct compression tablets used for Phase I/II studies, all the efficacy trials and the bioequivalence trials were done under fed conditions. There was no food effect on the commercial formulations (20% *increase in AUC*). Since the clinical trials were done with food, should the label be restrictive with respect to administration with food?

COMMENTS TO BE SENT TO THE FIRM:

FORMULATIONS: Although the formulations are exactly compositionally proportional it is difficult to understand why they are absorbed to different extent. Is there a particle size or other formulation factors different between the clinical formulations and the commercial formulations? Please, provide in vitro dissolution data for these lots in three different media (see below) and different RPMs (50 and 75).

FOOD EFFECT STUDY; The components of the
tablets were similar, however, there was a large difference in the magnitude and direction of food effect. The sponsor should explain this.

DISSOLUTION METHOD: The solubility of eprosartan drug substance is

LABELING COMMENTS:

The following subsections of the Clinical Pharmacology section of the labeling should be edited as shown below:

General
The statement on food effect should read *"Administration of eprosartan with a high fat meal causes an increase in AUC (20%) and delays absorption".*

Hepatic Insufficiency
The first statement should read *"Eposartan AUC (but Cmax) increased, on average, approximately 60% in a study of hepatically impaired men compared to healthy men who each received a single 100 mg oral dose of eprosartan".*

8/21/97
Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by A. Parekh, Ph.D. Aneeta Parekh 8/22/97
Biopharm Day - 7/24/97: Lesko, Malinowski, Chen, Lazor, Mehta, Bailey, Parekh, Burnette, Uppor, Ette, U, Hammond, Gordon.

cc: NDA 20-738, HFD-110, HFD-860 (Fadiran), CDR (Attn: Barbara Murphy), Chron, Drug, Review, HFD-340 (Vish).

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Table 1.

QUANTITATIVE COMPOSITION

Strength	Specification	300 mg	400 mg
Ingredients		Quantity (mg)/ tablet	
Eprosartan mesylate[1]	see Item 3.A. (3.A.6)	367.92	490.55
Lactose, Monohydrate	NF		
Microcrystalline Cellulose[2]	NF		
Pregelatinized Starch	NF		
Purified Water[3]	USP		
Microcrystalline Cellulose	NF		
Croscarmellose Sodium	NF		
Magnesium Stearate	NF		

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APPENDIX

METABOLIC PROFILING

STUDY 108566/ 020 VOLUME: 1.059 PAGES: 1 - 301

INVESTIGATOR AND LOCATION: J. UPWARD, M.D.
SMITHKLINE BEECHAM PHARMACEUTICALS
CLINICAL PHARMACOLOGY UNIT, UK.

STUDY DATE: April 12 - May 11, 1994.

OBJECTIVES: (1) To investigate the disposition and routes of elimination of eprosatan following single intravenous and oral administration to human subjects, (2) To quantify and structurally characterize the major compound-related components in human plasma and excreta (urine and feces), and (3) To compare concentrations of total radiolabel and of eprosartan in human plasma following single intravenous and oral administration, to assess the presence of circulating metabolites.

FORMULATIONS: Eprosartan batch M94040 and ^{14}C-eprosartan batch M94041.

STUDY DESIGN:
A randomized, open, two-period cross-over study in 3 healthy volunteers with a washout period of 28 days. ^{14}C-eprosartan was administered in the first and second periods either as a single 100 mg oral dose (68.5 - 69.4 μCi) or as a single 30 minute intravenous infusion of 20 mg dose (69.2 - 70.3 μCi). Blood samples (10 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 32, and 48 hours after oral dose; and at 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 32, and 48 hours after the start of the infusion. Three additional 20 ml samples were taken during the first 6 hours postdose for metabolite assessment. Urine samples were collected predose (-24-0 hour) and at 0-6, 6-12, 12-24, and each subsequent 24 hour up to 5 days after each dose. Feces were collected over an approximately 24 hour period prior to dosing and over approximately 24 hour periods up to a maximum of 8 days after each dose.

ASSAYS:

RESULTS: Tables 1- 7 summarise the data obtained from the study.

Table 1

Mean [SD] pharmacokinetic parameter values for eprosartan and for total radioactivity:

	Intravenous		Oral	
Parameter	Eprosartan (20 mg)	Radiolabel (20 mg)	Eprosartan (100 mg)	Radiolabel (100 mg)
Cmax[a] (ng/mL)	2020 [319]	2190 [257]	671 [271]	784 [321]
Tmax[b] (h)	0.50 (0.50 - 0.52)	0.50 (0.5 - 0.5)	1.25 (1.00 - 1.50)	1.25 (1.0 - 1.5)
AUC(0-inf)[a] (ng.h/mL)	2230 [421]	2470 [403]	2030 [1120]	2680 [1970]
T1/2 (h)	2.59 [0.64]	2.53 [0.47]	4.05 [0.77]	4.59 [2.42]
F (%)	-	-	14.7 [8.19]	-

[a] Units for radioactivity ng equivalents eprosartan/mL [b] Median (range) Tmax

Table 2

Plasma clearance (CL) and steady state volume of distribution (Vss) for eprosartan following a single intravenous infusion (20 mg) over 0.5 hour of [^{14}C]eprosartan to healthy male subjects

Subject	CL (L/h)	Vss (L)
1		
2		
3		
4		
No.	3	3
Mean	9.2	17.1
Median	8.3	14.7
SD	2.3	6.9
Min.		
Max.		

ND - no dose administered

Table 3

Excretion of radioactivity (expressed as percent of dose) following a single intravenous infusion of 20 mg of [^{14}C]eprosartan to three male subjects

Sample	Time (hours)	Subject† 1	2	4	Mean	+/- SD.
Urine	0-6					
	6-12					
	12-24					
	24-48					
	48-72					
	72-96					
	96-120					
Total in urine	0-120	36.34	33.59	41.14	37.02	3.82
Faeces	0-24					
	24-48					
	48-72					
	72-96					
	96-120					
	120-144					
	144-168					
	168-192					
Total in faeces	0-192	61.80	65.32	57.17	61.44	4.09
Total recovery	0-192	98.14	98.91	98.31	98.46	0.41

<LLQ less than the lower limit of quantification

† Subject 3 was withdrawn from the study prior to the intravenous dose

* Subject 1, 0-24 h faecal sample was very small and was combined with the 24-48 h collection to provide a pooled 0-48 h sample

NS no sample collected

Table 4

Excretion of radioactivity (expressed as percent of dose) following a single oral dose of 100 mg of [^{14}C]eprosartan to four male subjects

Sample	Time (hours)	Subject 1	2	3	4	Mean	+/- SD
Urine	0-6						
	6-12						
	12-24						
	24-48						
	48-72						
	72-96						
	96-120						
Total in urine	0-120	5.86	6.73	12.12	4.14	7.21	3.44
Faeces	0-24						
	24-48						
	48-72						
	72-96						
	96-120						
	120-144						
	144-168						
	168-192						
Total in faeces	0-192	91.79	90.47	85.80	93.52	90.40	3.31
Total recovery	0-192	97.65	97.20	97.92	97.66	97.61	0.30

<LLQ less than the lower limit of quantification

* Subject 1, 0-24 h faecal sample was very small. Combined with the 24-48h collection to provide a pooled 0-48 h sample

NS no sample collected

Table 5

Radiometabolite Quantification of Pooled 0-12 Hour Urine from Human Subjects Following Single Intravenous (20 mg) Administration of [^{14}C]Eprosartan expressed as percent of total urinary radioactivity and as *(percent of total administered dose)*

Metabolite	Subject 1	Subject 2	Subject 3	Subject 4	Mean
HU1 (25.8) *					18.9 *(6.8)*
Eprosartan (26.5)*					79.7 *(28.8)*
Total	99.6 *(35.4)*	98.2 *(32.0)*	ND	98.0 *(39.4)*	98.6 *(35.6)*
Total % of administered dose in 0-12 h urine	*(35.6)*	*(32.7)*	*ND*	*(40.3)*	*(36.2)*
Extraction efficiency (%)	100.3	104.2	ND	101.8	102.1
Column recovery (%)	98.3	109.6	ND	84.3	97.4

Table 6

Radiometabolite Quantification of Pooled 0-12 Hour Urine from Human Subjects Following Single Oral (100 mg) Administration of [^{14}C]Eprosartan expressed as percent of total urinary radioactivity and as *(percent of total administered dose)*

Metabolite	Subject 1	Subject 2	Subject 3	Subject 4	Mean
HU1 (25.8) *					18.7 *(1.2)*
Eprosartan (26.5)*					80.5 *(5.1)*
Total	98.3 *(5.1)*	99.8 *(5.6)*	98.8 *(10.5)*	99.9 *(3.7)*	99.2 *(6.2)*
Total % of administered dose in 0-12 h urine	*(5.2)*	*(5.6)*	*(10.6)*	*(3.7)*	*(6.3)*
Extraction efficiency (%)	96.9	100.3	104.3	96.3	99.5
Column recovery (%)	103.0	97.8	105.0	104.6	102.6

Table 7

Minimum absorption of drug-related material
calculated from the urinary excretion of radioactivity

	Subject 1	Subject 2	Subject 4	Mean
Percent of dose in urine after oral dose				
Percent of dose in urine after iv dose				
Minimum absorption of drug-related material				

Subject 3 was not dosed intravenously

CONCLUSIONS: The results obtained from the study show that:

1. Following intravenous administration, the concentrations of eprosartan declined bi-exponentially with a terminal $T_{1/2}$ of 2.5 hours, the systemic clearance is low (9.2 l/h) and the average V_{ss} of of 17.1 L indicated that the drug (due to its polar nature and extensive protein binding) is not widely distributed (Tables 1 & 2). Given the low clearance, it is likely that low absorption rather than extensive first pass metabolism accounts for the low systemic availability (F=15% at 100 mg oral dose).

2. Following oral administration, the peak plasma concentration of eprosartan occurred between 1-1.5 hours and declined bi-exponentially with a terminal $T_{1/2}$ of about 4 hours.

3. Following both intravenous and oral administration, the major route of excretion was via the feces (61% and 90% of the dose respectively) while urinary excretion accounted for 37% and 7% giving total recoveries of radioactivity of 98% of dose by both routes (Tables 3 & 4). The minimum absorption of the drug following oral administration is about 15% (Table 7).

4. Eprosartan was the only drug-related compound found in the plasma and in the feces. Approximately 20% of the radioactivity excreted in the urine was an acyl glucuronide of eprosartan, with the remaining 80% being unchanged eprosartan (Tables 5 & 6). Acyl glucuronidation was therefore the only metabolic pathway found.

SINGLE DOSE PHARMACOKINETICS

STUDY 108566/ 003 VOLUME: 1.051 PAGES: 1 - 381

INVESTIGATOR AND LOCATION: BERNARD ILSON, M.D.
SMITHKLINE BEECHAM CLIN. RES. UNIT
PHILADELPHIA, USA.

STUDY DATE: June 3 to October 5, 1992.

OBJECTIVES: The primary objective was to evaluate the single dose safety and tolerability of oral eprosartan (SK&F 108566) over the dosage range of 1 to 500 mg. The seconadry objective was to provide preliminary pharmacokinetic data for oral eprosartan in humans.

FORMULATIONS:
Eprosartan oral solution (5 mg/ml) batch # U-92010
Eprosartan 10 mg tablet batch # U-92054
Eprosartan 50 mg tablet batch # U-92055

STUDY DESIGN:
A randomized, single blind, placebo controlled, oral dose-rising study in 18 healthy volunteers. Each subject participated in one to four sessions separated by at least one week.At each study session, subjects received (30 minutes infusion) randomly allocated placebo or one of the following oral doses of eprosartan solution: 1, 3, 10, 50, 100, or 200 mg; or 30, 50, 100, 200 and 350 mg eprosartan tablet. Blood samples (5 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours following administration of study medication. Plasma samples were stored at -20°C until assayed for eprosartan.

DATA ANALYSIS: AUC, Cmax, Tmax, and $t_{1/2}$ were calculated.

RESULTS: Tables 1 and 2 summarise the pharmacokinetic data obtained from the study while Figure 1 shows the plasma concentration-time profiles for subjects who received 200 mg oral solution and Figure 2 shows the plasma concentration-time profiles for subjects who received 350 mg oral tablet.

Table 1. Mean (SD) Parameter Values for Eprosartan Following Administration of Oral Solution to Healthy Volunteers

PARAMETER	DOSE (MG)						
	1 (n=6)	3 (n=4)	10 (n=5)	30 (n=4)	50 (n=4)	100 (n=7)	200 (n=6)
Cmax (ng/ml)	29 (6)	45 (12)	100 (37)	396 (258)	579 (204)	979 (459)	3040 (1111)
$AUC_{(0-t)}$ (ng*h/ml)	66 (26)	94 (22)	254 (135)	1092 (368)	1399 (657)	2502 (1258)	7021 (3253)
$AUC_{(0-inf)}$ (ng*h/ml)	NC	NC	NC	1164 (411)	1511 (754)	2634 (1317)	7174 (3272)
$T_{1/2}$ (h)	NC	NC	NC	3.32 (1.0)	3.1 (1.3)	3.8 (2.1)	4.9 (2.6)
T_{max} (h)	1.4 (0.4)	1.6 (1.0)	1.4 (0.4)	1.3 (0.5)	1.3 (0.3)	1.0 (0.3)	1.0 (0)

NC = Not Calculated; insufficient number of measurable plasma concentrations to estimate this parameter.

Table 2. Mean (SD) Parameter Values for Eprosartan Following a Single Oral Dose of the Tablet Formulation to Healthy Volunteers

PARAMETER	DOSE (MG)				
	30 (n=2)	50 (n=4)	100 (n=6)	200 (n=6)	350 (n=3)
Cmax (ng/ml)	437 (86)	458 (288)	1007 (466)	1118 (525)	1317 (454)
$AUC_{(0-t)}$ (ng*h/ml)	1230 (164)	1000 (443)	2354 (1246)	3950 (2295)	5880 (1620)
$AUC_{(0-inf)}$ (ng*h/ml)	1308 (146)	1048 (471)	2493 (1313)	4087 (2301)	5986 (1589)
$T_{1/2}$ (h)	3.3 (0)	2.6 (0.7)	3.8 (1.9)	4.5 (2.5)	5.5 (1.3)
T_{max} (h)	1.5 (0.7)	1.3 (0.5)	1.1 (0.5)	1.3 (0.8)	2.2 (1.6)

Figure 3

PLASMA CONCENTRATIONS OF SK&F 108566 FOLLOWING A 200 MG ORAL DOSE OF THE SOLUTION FORMULATION TO HEALTHY VOLUNTEERS

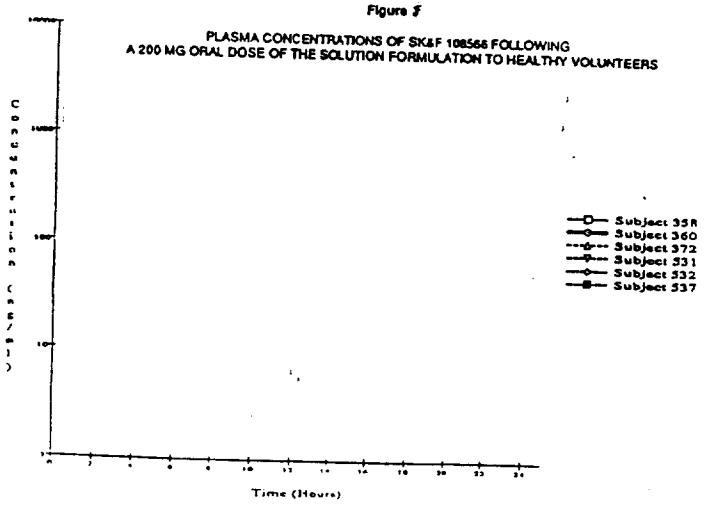
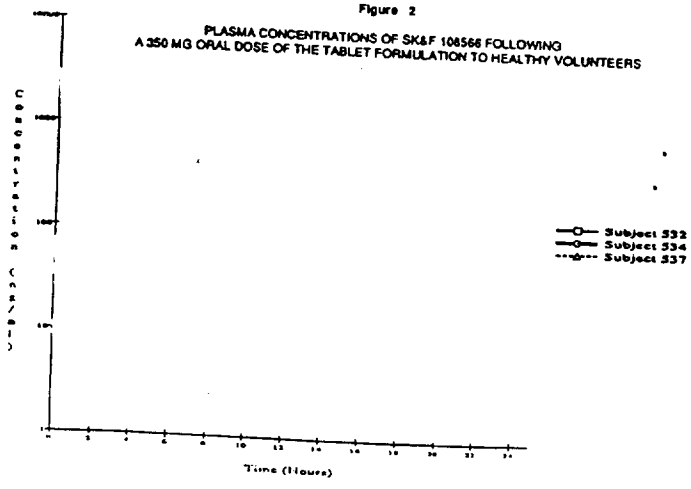


Figure 2

PLASMA CONCENTRATIONS OF SK&F 108566 FOLLOWING A 350 MG ORAL DOSE OF THE TABLET FORMULATION TO HEALTHY VOLUNTEERS



CONCLUSIONS: The results obtained from the study show that:

(1) Following administration of 1 to 200 mg oral solution of eprosartan (Table 1):

(i) Eprosartan was rapidly absorbed with Tmax ranging from 1.0 to 1.6 hours.

(ii) C_{max} increased in an approximately dose-proportional manner while AUC increased with dose but not in a proportional manner.

(iiii) Terminal $T_{1/2}$ ranged from 3.3 to 4.9 hours for the 30 to 200 mg dose range.

(2) Following administration of 30 to 350 mg oral dose of the tablet formulation of eprosartan (Table 2):

(i) Eprosartan was rapidly absorbed with Tmax ranging from 1.1 to 2.2 hours.

(ii) AUC increased with dose but not in a proportional manner while Cmax increased with dose up to 100 mg but there was no appreciable increase with dose thereafter.

(iiii) Terminal $T_{1/2}$ ranged from 2.6 to 5.5 hour.

(3). The relative bioavailability (tablet/solution) based on $AUC_{(0\text{-inf})}$ for the 50, 100 and 200 mg doses are 69%, 95% and 57% respectively (Tables 1 &2).

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SINGLE DOSE PHARMACOKINETICS

STUDY 108566/ 004 VOLUME: 1.052 PAGES: 1 - 126

INVESTIGATOR AND LOCATION: BERNARD ILSON, M.D.
SMITHKLINE BEECHAM CLIN. RES. UNIT
PHILADELPHIA, USA.

STUDY DATE: June 17 to August 14, 1992.

OBJECTIVES: The primary objective was to evaluate the single dose safety and tolerability of intravenous eprosartan (SK&F 108566) over the dosage range of 0.1 to 50 mg. The seconadry objective was to provide preliminary pharmacokinetic data for intravenous eprosartan in humans.

FORMULATIONS: Eprosartan intravenous injection (5 mg/ml in 10 ml ampoules) batch U-92010.

STUDY DESIGN:
A randomized, single blind, placebo controlled, intravenous dose-rising study in 12 healthy volunteers. Each subject participated in one to four sessions separated by at least one week.At each study session, subjects received (30 minutes infusion) randomly allocated placebo (0.9% sodium chloride injection) or one of the following intravenous doses of eprosartan: 0.1, 0.3, 1, 3, 5, 10, and 20 mg (maximum dose was limited to 20 mg). Blood samples (5 ml) were collected at 0 (predose), 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours following the start of the infusion of study medication. Plasma samples were stored at -20°C until assayed for eprosartan.

DATA ANALYSIS: AUC, Cmax, Tmax, $t_{1/2}$, Vdss, and CL, were calculated.

RESULTS: Table 1 summarises the pharmacokinetic data obtained from the study while Figure 1 shows the plasma concentration-time profiles for subjects who received the highest dose (20 mg).

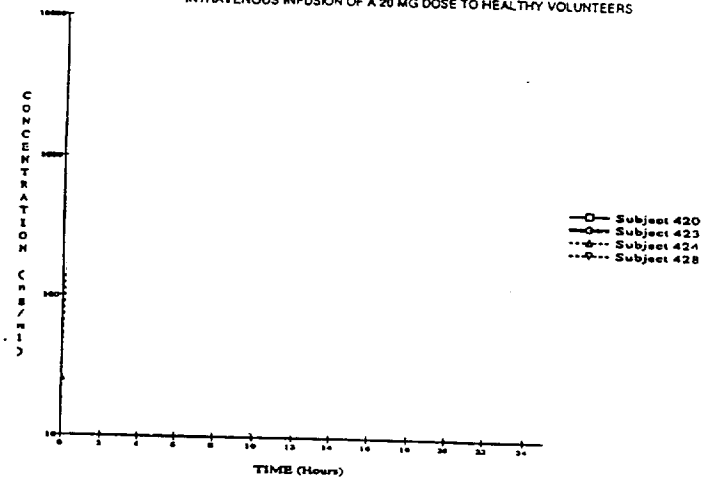
Table 1. Mean (SD) Parameter Values for Eprosartan Following a 30 Minute Infusion to Healthy Volunteers

PARAMETER	DOSE (MG) / N=4 SUBJECTS						
	0.1	0.3	1	3	5	10	20
Cmax (ng/ml)	NC	39 (10)	119 (35)	332 (21)	556 (159)	1313 (345)	2287 (734)
$AUC_{(0-t)}$ (ng*h/ml)	NC	NC	110 (47)	459 (216)	595 (224)	1573 (538)	2249 (895)
$AUC_{(0-inf)}$ (ng*h/ml)	NC	NC	131 (46)	499 (238)	629 (218)	1602 (531)	2491 (901)
$T_{1/2}$ (h)	NC	NC	1.2 (0.5)	2.2 (1.9)	1.8 (0.6)	2.1 (0.4)	2.2 (0.3)
CL (ml/min)	NC	NC	NC	114 (40)	147 (58)	112 (33)	150 (61)
V_{ss} (L)	NC	NC	NC	12.5 (1.2)	14 (4.2)	12 (4.2)	15.3 (5.6)

NC = Not Calculated; insufficient number of measurable plasma concentrations to estimate this parameter.

Figure 1

PLASMA CONCENTRATIONS OF SK&F 108566 FOLLOWING A 30-MINUTE INTRAVENOUS INFUSION OF A 20 MG DOSE TO HEALTHY VOLUNTEERS



CONCLUSIONS: The results obtained from the study show that following intravenous administration of 1 to 20 mg dose range of eprosartan (Table 1):

(i) AUC and C_{max} increased in an approximately dose-proportional manner.

(ii) Terminal $T_{1/2}$ ranged from 1.2 to 2.2 hours.

(iii) Plasma clearance ranged from 114 to 150 ml/min while volume of distribution at steady state ranged from 12.5 to 15.3 liters for the 3 to 20 mg dose range.

DOSE PROPORTIONALITY STUDY

STUDY 108566/ 008 VOLUME: 1.055 PAGES: 178 - 391

INVESTIGATOR AND LOCATION: BERNARD ILSON, M.D.
SMITHKLINE BEECHAM CLIN. RES. UNIT
PHILADELPHIA, USA.

STUDY DATE: January 19 to March 28, 1995.

OBJECTIVES: (1) To assess the dose proportionality and tolerability of the final commercial formulation of eprosartan in single oral doses of 100, 200, 400 and 800 mg, (2) To assess the safety and tolerability of single oral doses of the final commercial formulation of eprosartan.

FORMULATIONS:
Eprosartan 100 mg tablet, Lot number U-94191 (Formula AF)
Eprosartan 200 mg tablet, Lot number U-94190 (Formula AF)

STUDY DESIGN:
An open-label, randomized, four-period, period balanced for dose and first-order carryover, crossover study in 23 healthy male volunteers and a washout period of at least 3 days.Each subject received 100 mg, 200 mg, 400 mg (2x200 mg) and 800 mg (4x200 mg) single oral doses of eprosartan following a standard breakfast. Blood samples (5 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours following administration of study medication. Plasma samples were stored at -20°C until assayed for eprosartan.

DATA ANALYSIS: AUC, Cmax, Tmax were calculated.

RESULTS: Table 1 summarises the pharmacokinetic data obtained from the study while Figures 1-4 show the plasma concentration-time profiles for different doses of eprosartan.

Table 1. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Healthy Volunteer

PARAMETER	DOSE (MG)			
	100	200	400	800
Cmax (ng/ml)	439 (234)	702 (255)	1273 (577)	1857 (736)
Cmax/Dose (ng/ml/mg)	4.39 (2.34)	3.51 (1.27)	3.18 (1.44)	2.32 (0.92)
$AUC_{(0-t)}$ (ng*h/ml)	1400 (637)	2620 (1046)	4887 (2525)	7855 (2782)
$AUC_{(0-t)}$/Dose (ng*h/ml/mg)	14.0 (6.37)	13.1 (5.23)	12.22 (6.31)	9.82 (3.48)
Tmax (h)	2.85 (0.75)	2.92 (0.69)	3.15 (0.85)	2.88 (0.79)

Figure 1
Plasma SK&F 108566 Concentrations Following Single Oral 100 mg Dose Administration to Healthy Male Subjects

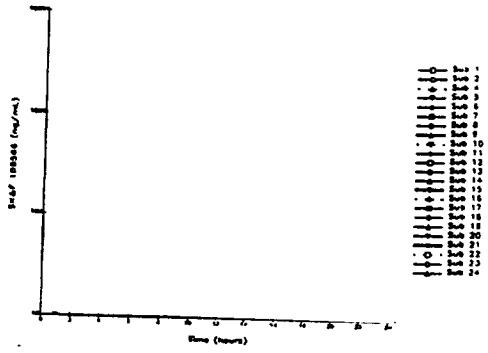


Figure 2
Plasma SK&F 108566 Concentrations Following Single Oral 200 mg Dose Administration to Healthy Male Subjects

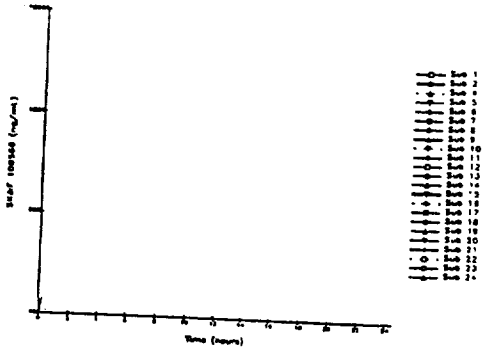


Figure 3
Plasma SK&F 108566 Concentrations Following Single Oral 400 mg Dose Administration to Healthy Male Subjects

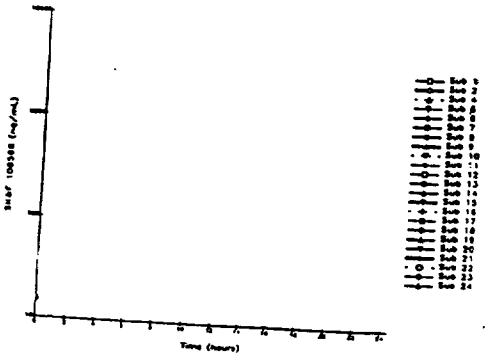
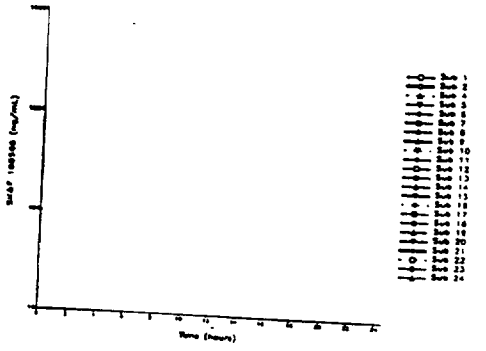


Figure 4
Plasma SK&F 108566 Concentrations Following Single Oral 800 mg Dose Administration to Healthy Male Subjects



CONCLUSION: The results obtained from the study show that the pharmacokinetics of the final formulation of eprosartan tablets in healthy subjects is non-linear in the 100 to 800 mg dose range.

SINGLE / MULTIPLE DOSE PHARMACOKINETICS STUDY

STUDY 108566/ 009 VOLUMES: 1.056 - 1.057

INVESTIGATOR AND LOCATION:

STUDY DATE: October 19, 1992 - March 8, 1993.

OBJECTIVE: (1) To evaluate the safety and tolerability of eprosartan administered orally in repeated single daily doses for one week in patients with mild to moderate essential hypertension; (2) To obtain pharmacokinetic data on single and repeated dose administration of eprosartan in patients with mild to moderate essential hypertension; and (3) To evaluate the short term (one week) effect of eprosartan on blood pressure and pulse rate in patients with mild to moderate essential hypertension.

FORMULATIONS:
Eprosartan 50 mg tablets Lot No. U-92055 and matching placebo tablets Lot No. U-92053.

STUDY DESIGN:
A randomized, double-blind, placebo-controlled, repeated oral dose, dose-rising, two period, period-balanced crossover study in 32 mild to moderate hypertensive patients with a washout period of at least 6 days. Following a washout period of at least two weeks, four active dose levels of eprosartan (50, 100, and 350 mg/day and 150 every 12 hours) were studied in four groups (n=8) of patients. During each of the two study periods, patients received seven days of therapy with placebo or one of the active dose levels of eprosartan. Blood samples (5 ml) were collected at 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18 and 24 hours following the first (Day 1) and the last (Day 7) dose. Plasma samples were stored at -20°C until assayed for eprosartan.

DATA ANALYSIS: AUC, Cmax, Tmax, Accumulation Ratio and $t_{1/2}$ were calculated.

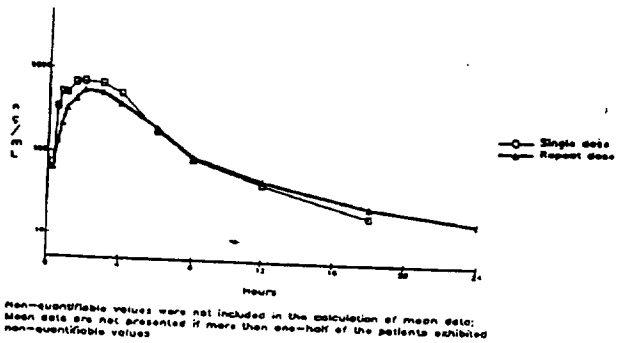
RESULTS: Tables 1 summarises the pharmacokinetic data obtained from the study while Figures 1-4 show the mean plasma concentration-time profiles following the administration of 50, 100 and 350 mg per day and 150 mg every 12 hours of eprosartan to the patients.

Table 1. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Hypertensive Patients

PARAMETER	50 MG		100 MG		350 MG		150 MG′	
	SD	MD	SD	MD	SD	MD	SD	MD
Cmax (ng/ml)	968 (584)	673 (675)	1406 (526)	1480 (867)	2276 (752)	1818 (763)	1647 (666)	1635 (710)
$AUC_{(0-t)}$ (ng*h/ml)	3359 (2421)	2770 (2783)	5287 (2643)	5768 (2792)	10133 (5253)	8067 (29365)	6249 (3192)	6340* (2818)
$AUC_{(0-\infty)}$ (ng*h/ml)	3442 (2425)	2923 (2766)	5477 (2657)	6284 (3015)	10486 (5418)	8184 (31698)	6422 (3171)	ND
T_{max} (h)	1.75 (0.92)	1.84 (0.83)	1.69 (0.65)	1.38 (0.42)	1.91 (0.98)	1.97 (1.07)	1.22 (0.41)	1.81 (1.19)
$T_{1/2}$ (h)	4.09 (2.78)	5.74 (3.51)	7.54 (5.04)	9.60 (3.1)	6.77 (3.22)	7.76 (1.40)	7.92 (3.09)	ND
Accumulation Ratio	0.95 (0.68)		1.16 (0.61)		0.88 (0.38)		1.06 (0.30)	

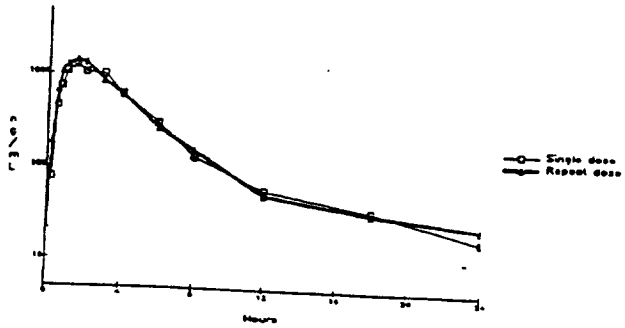
′150 MG Every 12 hours
*AUC(0-12)
ND= Not Determined
SD = Single Dose
MD = Multiple Dose

Figure
MEAN PLASMA CONCENTRATION VS. TIME PROFILES FOR SK&F 108566 AFTER SINGLE AND REPEAT DOSE ADMINISTRATION OF 50 mg DAILY



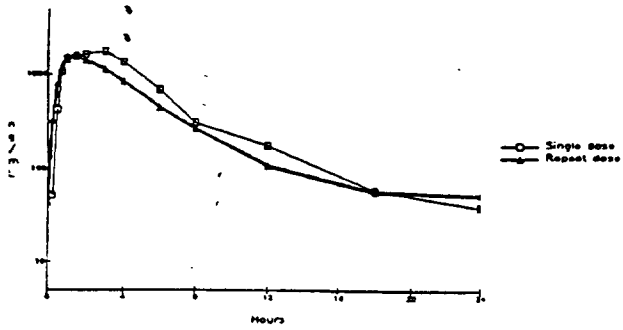
Non-quantifiable values were not included in the calculation of mean data; Mean data are not presented if more than one-half of the patients exhibited non-quantifiable values

Figure
MEAN PLASMA CONCENTRATION VS. TIME PROFILES FOR SK&F 108566 AFTER SINGLE AND REPEAT DOSE ADMINISTRATION OF 100 mg DAILY



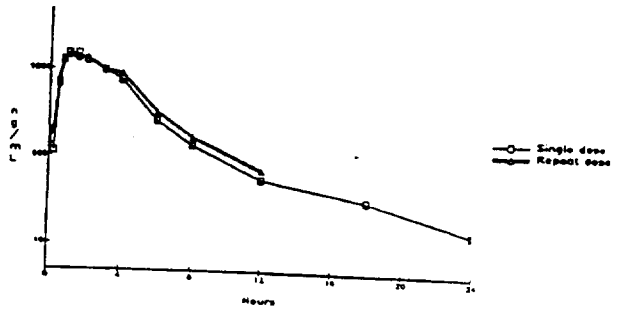
Non-quantifiable values were not included in the calculation of mean data

Figure
MEAN PLASMA CONCENTRATION VS. TIME PROFILES FOR SK&F 108566 AFTER SINGLE AND REPEAT DOSE ADMINISTRATION OF 350 mg DAILY



Non-quantifiable values were not included in the calculation of mean data

Figure
MEAN PLASMA CONCENTRATION VS. TIME PROFILES FOR SK&F 108566 AFTER SINGLE AND REPEAT DOSE ADMINISTRATION OF 150 EVERY TWELVE HOURS



Non-quantifiable values were not included in the calculation of mean data; Blood samples were obtained to 12 hours post-dose for repeat dosing

CONCLUSIONS: The results obtained from the study show that :
(1) Mean Cmax and AUC values increased but in a less than dose proportional manner over the 50 to 350 mg dose range after single and multiple dose administration
(2) Mean T1/2 ranged from 4.1 to 9.6 hours
(3) Mean Tmax ranged from 1.4 to 2.0 hours
(4) Mean accumulation ratio ranged from 0.88 to 1.16 over the dose range.

SINGLE / MULTIPLE DOSE PHARMACOKINETICS STUDY

STUDY 108566/ 048 VOLUMES: 1.068 - 1.069

INVESTIGATOR AND LOCATION:

STUDY DATE: June 6 to September 27, 1994.

OBJECTIVE: (1) To evaluate the safety and tolerability of eprosartan administered orally in repeated single daily doses for one week in patients with mild to moderate essential hypertension; (2) To obtain pharmacokinetic data on single and repeated dose administration of eprosartan in patients with mild to moderate essential hypertension; (3) To evaluate the short term (one week) effect of eprosartan on blood pressure and pulse rate in patients with mild to moderate essential hypertension; and (4) To describe the effect of eprosartan on urine uric acid excretion.

FORMULATIONS:
Eprosartan 100 mg coated tablets Batch # U-93235 and matching placebo tablets Batch # U-94031.

STUDY DESIGN:
A randomized, double-blind, placebo-controlled, repeated oral dose, dose-rising, two period, period-balanced crossover study in 24 mild to moderate hypertensive patients with a washout period of at least 6 days. Following a washout period of up to six weeks, three active dose levels of eprosartan (600, 800, and 1200 mg/day) were studied in three groups (n=8) of patients. During each of the two study periods, patients received seven days of therapy with placebo or one of the active dose levels of eprosartan. Blood samples (5 ml) were collected at 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18 and 24 hours following the first (Day 1) and the last (Day 7) dose. Plasma samples were stored at -20°C until assayed for eprosartan.

DATA ANALYSIS: AUC, Cmax, Tmax, Accumulation Ratio and $t_{1/2}$ were calculated.

RESULTS: Tables 1 summarises the pharmacokinetic data obtained from the study while Figures 1-3 show the mean plasma concentration-time profiles following the administration of 600, 800 and 1200 mg eprosartan to the patients.

Table 1. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Hypertensive Patients

PARAMETER	600 MG		800 MG		1200 MG	
	SD	MD	SD	MD	SD	MD
Cmax (ng/ml)	1622 (802)	1608 (726)	2081 (937)	2103 (1502)	2785 (1012)	2961 (1432)
$AUC_{(0-t)}$ (ng*h/ml)	7829 (4477)	9731 (4381)	9639 (5476)	9521 (4975)	14642 (6838)	19125 (8632)
$AUC_{(0-inf)}$ (ng*h/ml)	7895 (4507)	10786 (4963)	10520 (5777)	10443 (4818)	16310 (8141)	22423 (10749)
T_{max} (h)	2.5 (1.9)	2.6 (1.8)	2.9 (0.6)	1.9 (1.1)	2.1 (1.7)	2.7 (1.6)
$T_{1/2}$ (h)	11.5 (7.0)	9.0 (3.1)	7.9 (5.7)	8.6 (4.2)	10.4 (6.6)	12.2 (6.6)
Accumulation Ratio	1.18 (0.45)		0.95 (0.52)		1.28 (0.69)	

SD = Single Dose
MD = Multiple Dose

Figure 1 Mean Plasma Concentration-Time Profiles for SK&F 108566 Following Single and Multiple Dose Administration of 600 Mg Daily to Patients with Hypertension

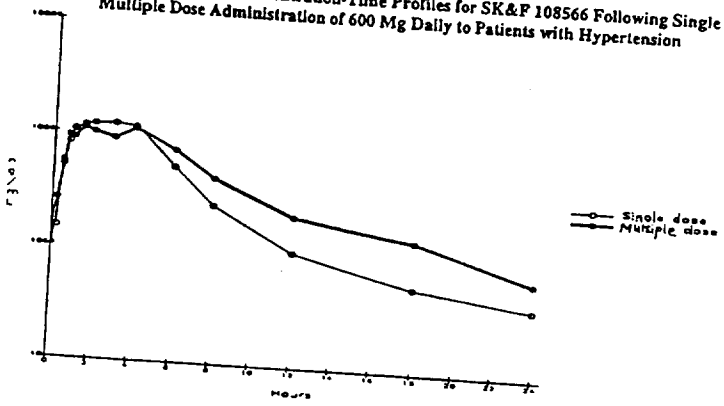


Figure 2 Mean Plasma Concentration-Time Profiles for SK&F 108566 Following Single and Multiple Dose Administration of 800 Mg Daily to Patients with Hypertension

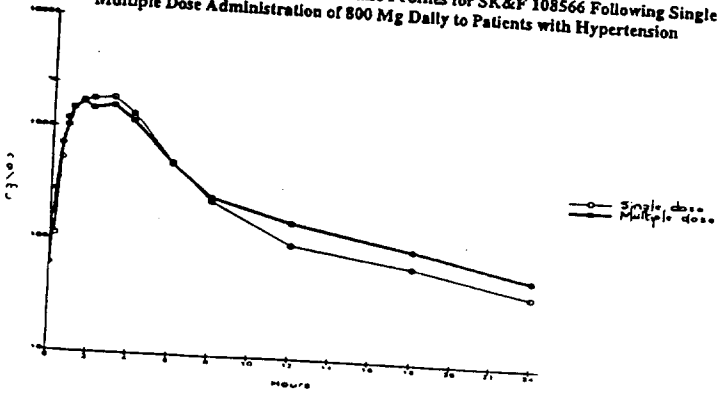
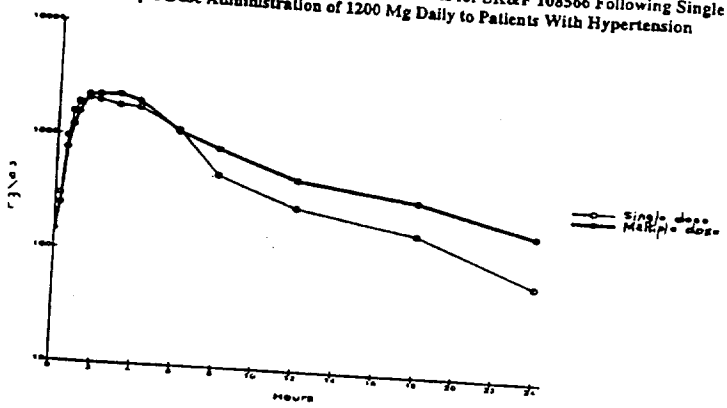


Figure 3 Mean Plasma Concentration-Time Profiles for SK&F 108566 Following Single and Multiple Dose Administration of 1200 Mg Daily to Patients With Hypertension



CONCLUSIONS: The results obtained from the study show that :
(1) Mean Cmax and AUC values increased in an approximately dose proportional manner over the 600 to 1200 mg dose range after single and multiple dose administration (except multiple dose of 800 mg)
(2) Mean T1/2 ranged from 8 to 12 hours
(3) Mean Tmax ranged from 1.9 to 2.9 hours
(4) Mean accumulation ratio ranged from 0.85 to 1.28 over the dose range.

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BIOAVAILABILITY / BIOEQUIVALENCE STUDY

STUDY 108566/ 005 **VOLUME:** 1.052 **PAGES:** 127 - 367

INVESTIGATOR AND LOCATION:

STUDY DATE: March 8 to May 3, 1995.

OBJECTIVES: (1) To estimate the difference between the pharmacokinetics of single oral doses of the final commercial formulation for eprosartan following a standard high fat meal and under fasting conditions in healthy male volunteers, (2) To estimate the absolute bioavailability of the final commercial formulation for eprosartan following administration of an immediate release tablet compared to an intravenous infusion, (3) To evaluate the safety and tolerability of the intravenous and oral eprosartan.

FORMULATIONS:
Eprosartan 100 mg tablet, Lot # U-94191
Eprosartan injection, 10 ml ampule (5 mg/ml), Lot # U-92078

STUDY DESIGN:
A randomized, open label, three period, period balanced, crossover study in 18 healthy male volunteers with washout period of 3 days. Each subject received the three treatments in randomized fashion: Treatment A - 300 mg (3 x 100) eprosartan orally under fasting condition, Treatment B - 300 mg (3 x 100) eprosartan orally following a standard high fat meal and Treatment C - 20 mg eprosartan intravenously under fasting condition (administered as a 30 minutes infusion in 50 ml 0.9% sodium chloride). Blood samples (5 ml) were collected following oral dosing at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours following administration of study medication, following intravenous dosing at 0 (predose), 0.25, 0.5 (immediately after termination of infusion), 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours following the start of the infusion. Plasma samples were stored at -20°C until assayed for eprosartan.
The meal consisted of 2 eggs cooked in butter, 2 strips of bacon, 2 pieces of toast, 2 teaspoons (10 g) of butter, 4 ounces (113 g) of hash brown potatoes, and 8 ounces (240 ml) of whole milk (equivalent to **1020 calories** consisting of 58 g carbohydrate, 33 g protein and 58-75 g fat).

study.

DATA ANALYSIS: AUC, Cmax, Tmax, CL, VD_{ss} and $t_{1/2}$ were calculated.

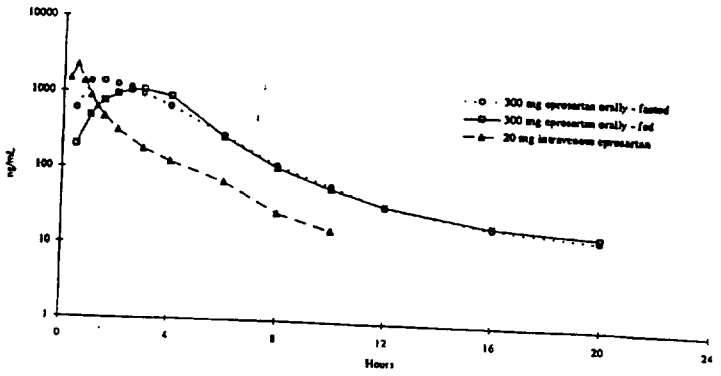
RESULTS: Tables 1 summarises the pharmacokinetic data obtained from the study while Figure 1 shows the mean plasma concentration-time profiles following the three treatments

Table 1. Mean (SD) Parameter Values for Eprosartan Following Oral and Intravenous Administration to Healthy Volunteers

PARAMETER	TREATMENT A (FASTED)	TREATMENT B (FED)	TREATMENT C (IV)
Cmax (ng/ml)	1612 (720)	1205 (484)	2246 (255)
$AUC_{(0-t)}$ (ng*h/ml)	5657 (2694)	4807 (1907)	2631 (582)
$AUC_{(0-inf)}$ (ng*h/ml)	5750 (2716)	4950 (1884)	2671 (576)
$T_{1/2}$ (h)	4.52 (3.05)	7.25 (4.61)	2.07 (0.63)
T_{max} (h)	1.62 (0.63)	2.82 (0.61)	0.50
CL (ml/min)	ND	ND	131.8 (36.2)
VD_{ss} (l)	ND	ND	12.6 (2.6)

ND = Not Determined after oral administration

Figure 1. Mean Plasma Concentration-Time Profiles of Eprosartan



CONCLUSIONS: The results obtained from the study show that (Table 1):
(1) Administration of 300 mg eprosartan with with a high fat meal (1020 calories) results in:

(i) a decrease of 16% in the $AUC_{0\text{-}inf}$
(ii) an decrease of 25% in the C_{max}
(iii) a delay of 1.2 hours in the Tmax
(iv) an increase in the terminal half life from 4.52 hours to 7.25 hours.

(2) The absolute bioavailability of 300 mg eprosartan tablet compared to 20 mg IV dose is about 14%

(3) Following intravenous administration of 20 mg dose, the concentrations of eprosartan declined bi-exponentially with a terminal $T_{1/2}$ of about 2 hours, the systemic clearance is low (131.8ml/min) and the average V_{ss} of 12.6 L indicated that the drug (due to its polar nature and extensive protein binding) is not widely distributed. Given the low clearance, it is likely that low absorption rather than extensive first pass metabolism accounts for the low systemic availability.

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BIOAVAILABILITY / BIOEQUIVALENCE STUDY

STUDY 108566/ 018 **VOLUME:** 1.058 **PAGES:** 1-197

INVESTIGATOR AND LOCATION: BERNARD ILSON, M.D.
SMITHKLINE BEECHAM CLIN. RES. UNIT
PHILADELPHIA, USA.

STUDY DATE: October 19 to December 17, 1993.

OBJECTIVE: To compare the systemic bioavailability of the original tablet formulation of eprosartan and a newly developed immediate release tablet intended for use in clinical trials.

FORMULATIONS:
(1) Eprosartan 50 mg tablet, Lot # U-93180 (New wet granulation formulation)
(2) Eprosartan 100 mg tablet, Lot # U-93174 (New wet granulation formulation)
(3) Eprosartan 50 mg tablet, Lot # U-93008 (Original direct compression formulation)

STUDY DESIGN:
A randomized, open label, three period, period balanced, crossover study in 24 healthy male volunteers with washout period of 1 week. Following a standard breakfast, each subject received the three treatments in randomized fashion: Treatment A - 100 mg (2 x 50) eprosartan tablet formulation 1 above, Treatment B - 100 mg (1 x 100) eprosartan tablet formulation 2 above and Treatment C - 100 mg (1 x 100) eprosartan tablet formulation 3 above. Blood samples (5 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, and 24 hours following administration of study medication. Plasma samples were stored at -20°C until assayed for eprosartan.

DATA ANALYSIS: AUC, Cmax, Tmax, and $t_{1/2}$ were calculated.

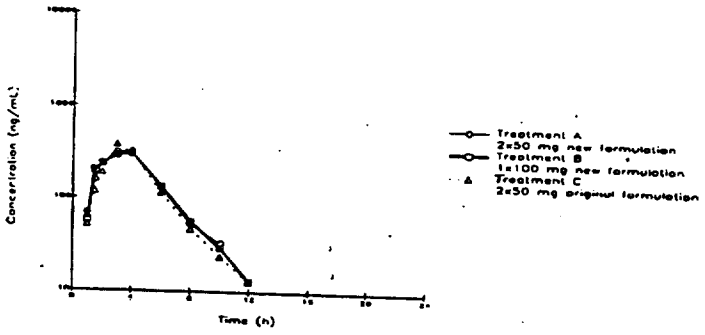
RESULTS: Tables 1 summarises the pharmacokinetic data obtained from the study while Figure 1 shows the mean plasma concentration-time profiles following the three treatments

Table 1. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Healthy Volunteers

PARAMETER	TREATMENT A	TREATMENT B	TREATMENT C	95% CI	
				A:C	B:C
Cmax (ng/ml)	420 (177)	384 (1514)	436 (228)	80 - 1 34	73 - 122
$AUC_{(0-t)}$ (ng*h/ml)	1454 (623)	1451 (566)	1417 (548)	86 - 127	84 - 126
$AUC_{(0-inf)}$ (ng*h/ml)	1464 (609)	1504 (588)	1538 (523)	-	-
$T_{1/2}$ (h)	1.94 (0.89)	2.14 (0.87)	2.29 (1.293)	-	-
T_{max} (h)	3.17 (0.87)	3.22 (0.961)	3.27 (0.63)	-	-

TREATMENT A = New formulation (2 x 50 mg)
TREATMENT B = New formulation (1 x 100 mg)
TREATMENT C = Original formulation (2 x 50 mg)

Figure 1. Mean Plasma Concentration-Time Profiles of Eprosartan



CONCLUSIONS: The results obtained from the study showed that the bioavailability of the new wet granulation tablet formulations of eprosartan (50 and 100 mg) used in Phase III studies was similar to the original direct compression tablet formulation of eprosartan (50 mg) used in Phase I/II studies. However, bioequivalence between these formulations was not established because of lack of power in the study due to the small sample size.

BIOAVAILABILITY / BIOEQUIVALENCE STUDY

STUDY 108566/ 034 VOLUME: 1.066 PAGES: 1 - 276

INVESTIGATOR AND LOCATION: BERNARD ILSON, M.D.
SMITHKLINE BEECHAM CLIN. RES. UNIT
PHILADELPHIA, USA.

STUDY DATE: October 3 to December 22 1994.

OBJECTIVES: (1) To compare the bioequivalence of the new tablet formulation, intended for commercial release, with the old clinical trials tablet formulation of SK&F 108566.
(2) To assess the safety and tolerability of SK&F 108566 in healthy male volunteers.

FORMULATIONS:
Eprosartan 100 mg tablet, Lot # U-94068, Formula AB (Clinical Trial Formulation)
Eprosartan 200 mg tablet, Lot # U-94175, Formula AG (New Commercial Formulation)

STUDY DESIGN:
A randomized, open label, four period, period balanced, crossover study in 32 healthy male volunteers with washout period of 3 days. During each treatment, subjects received either 2 x 100 mg eprosartan (Reference, Formula AB) or 1 x 200 mg eprosartan (Test, Formula AG) orally every 12 hours for 7 doses. Each subject received each regimen during two separate treatment periods, for a total of four study treatment periods administered in one of four sequences (RTTR, TTRR, RRTT, TRRT). Blood samples (5 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours following administration of study medication. Plasma samples were stored at -20°C until assayed for eprosartan.

DATA ANALYSIS: AUC, Cmax, and Tmax were calculated.

RESULTS: Tables 1 summarises the pharmacokinetic data obtained from the study while Figure 1 shows trough plasma concentrations and Figure 2 shows the mean plasma concentration-time profiles.

Table 1. Mean (SD) Pharmacokinetic Parameter Values for Eprosartan Following Oral Administration to Healthy Volunteers

PARAMETER	REFERENCE FORMULATION#	TEST FORMULATION*	90% CI
Cmax (ng/ml)	859 (352)	737 (274)	78 - 95
$AUC_{(0-t)}$ (ng*h/ml)	2981 (1339)	2655 (981)	84 - 98
Tmax (h)	2.63 (0.51)	2.48 (0.62)	-

#Mean of replicate administrations of Reference Formulation (2 x 100 mg)
*Mean of replicate administrations of Test Formulation (1 x 200 mg)

Fig. 1. Trough Plasma Concentrations for SK&F 108566 Following Administration of SK&F 108566 Every 12 Hours For 7 Doses to Healthy Male Volunteers

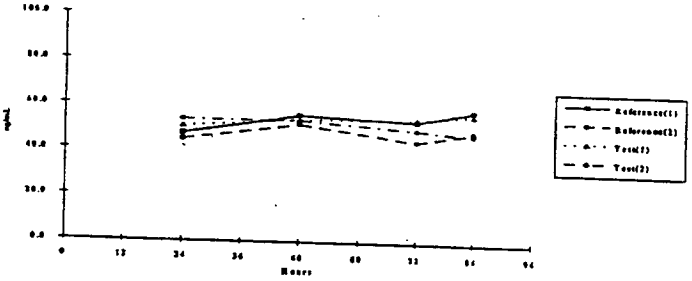
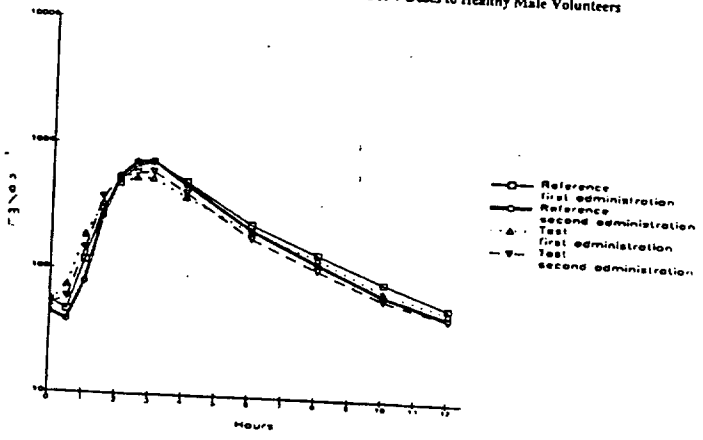


Fig. 2. Mean plasma concentration-time profiles for SK&F 108566 Following Administration of SK&F 108566 Every 12 Hours For 7 Doses to Healthy Male Volunteers



CONCLUSIONS: The results obtained from the study show that the 100 mg clinical trial tablet formulation of eprosartan is not bioequivalent to the 200 mg commercial tablet formulation.

Statistical Report: TEVENTEN™ (Eprosartan) Tablets; Office of Clinical Pharmacology and Biopharmaceutics NDA 20-738, SmithKline Beecham Pharmaceuticals.

OCPB reviewer: Emmanuel Fadiran
Study: 108566/034
Volume: 1.066

In this study 30 subjects were given two formulations of Eprosartan, 2 x 100mg tablets (Reference) and 1 x 200mg tablet (Test), in a randomized, four period, four sequence cross-over study. The outcome of interest is Cmax, which failed in the sponsor's analysis of bioequivalence.

Study Design and Model

The four sequences were RTTR, TRRT, RRTT, and TTRR.
The endpoint analyzed was log of Cmax of Eprosartan (logcmax).

The Model:

Let y_{ijkl} be a measurement of log(Cmax) for subject j in sequence i in period k, at which time this subject received treatment l. We allowed subject and subject-by-treatment interaction to be random effects and sequence, period, and treatment to be fixed. We used the following statistical model;

$$y_{ijkl} = \mu + \alpha_i + s_j + \gamma_k + \tau_l + (s\tau)_{jl} + \epsilon_{ijkl}$$

$$s_j \sim \text{iid}(0,\sigma_s^2)$$
$$(s\tau)_{jl} \sim \text{iid}(0,\sigma_{st}^2)$$
$$\epsilon_{ijkl} \sim \text{iid}(0,\sigma^2)$$

μ = mean response
α_i = sequence effect
s_j = subject effect
γ_k = period effect
τ_l = treatment effect
$(s\tau)_{jl}$ = subject-by-treatment effect

SAS Code:

We used the following SAS code to generate a mixed model analysis:

```
proc mixed;
class subj trt per seq;
model logcmax=trt per seq /solution;
random trt / subject=subj type=un;
lsmeans trt / cl pdiff alpha=.1;
run;
```

We also ran a General Linear Model statement in SAS. The following code will give similar output to that submitted by the sponsor.

```
proc glm;
class subj trt per seq;
model logcmax=trt per seq subj(seq) trt*subj(seq);
random subj(seq) trt*subj(seq);
lsmeans trt/ e=trt*subj(seq) cl pdiff alpha=.1;
run;
```

The analyses differ in the method of estimation; Proc GLM uses a least squares estimation method while Proc Mixed uses a likelihood-based estimation method.

Definition of Bioequivalence

Bioequivalence of the compounds is concluded if each of the confidence intervals for the ratios (T/R) for each of the endpoints lies entirely in the interval (0.8,1.25).

Results of Analysis

The parameters and 90% confidence intervals for Cmax, back transformed, are given in the table that follows. DIFF is the estimated difference between test and reference in log scale. This was calculated as (test - reference). SE is the standard error of the estimated difference. DDF are the degrees of freedom used to construct the confidence interval. Alpha, set at 0.10 corresponds to a two-one-sided procedure at a 0.05 level of significance. ELOWER is the lower bound of the estimated ratio of effects, EHIGHER is the upper bound.

Table: Bioequivalence Ratios for 1 x 200mg tablet (test) versus 2 x 100mg tablets (reference) for Cmax.

	DIFF	SE	DDF	ALPHA	ELOWER	EDIFF	EUPPER
Proc Mixed	-0.149	0.058	29	0.10	0.78	0.86	0.95
Proc GLM	-0.148	0.056	29	0.10	0.78	0.86	0.95
Sponsor's Results	-0.148	0.057	29	0.10	0.78	0.86	0.95

The confidence interval of T/R for Cmax is not contained within the interval (0.80,1.25). Cmax for the 2x100mg tablets is larger than Cmax for the 1x200mg tablet. These results were consistent with the results from the sponsor.

Conclusion

The confidence limits do not change from those of the sponsor in either of our analyses, thus the lower limit cannot be viewed as an artifact. However, the value 0.78 is close to the nominal lower bound (0.80).

Karen M. Higgins, Sc.D.
Staff Fellow, QMR
February 11, 1997

Alfred H. Balch, Ph.D.
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Fedruary 11, 1997

Concur: Stella G. Machado

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HFD-705	Stella G. Machado
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BIOAVAILABILITY / BIOEQUIVALENCE STUDY

STUDY 108566/ 035 **VOLUME:** 1.067 **PAGES:** 1- 380

INVESTIGATOR AND LOCATION: BERNARD ILSON, M.D.
SMITHKLINE BEECHAM CLIN. RES. UNIT
PHILADELPHIA, USA.

STUDY DATE: August 17 to October 18, 1995.

OBJECTIVE: To determine the bioequivalence of the new 400 mg tablet formulation, intended for commercial release, with the old clinical trials tablet formulations of eprosartan and to assess the safety and tolerability of eprosartan in healthy male volunteers.

FORMULATIONS:
(1) Eprosartan 400 mg tablet, Formula AJ, Lot # U-95111 (Manufactured at Crawley)
(2) Eprosartan 100 mg tablet, Formula AB, Lot # U-93235 (Old formulation)
(3) Eprosartan 200 mg tablet, Formula AG, Lot # U-94190 (new formulation)

STUDY DESIGN:
A randomized, open label, three period, crossover study in 61 healthy male volunteers with washout period of 1 week. Following a standard breakfast, each subject received the three treatments in randomized fashion: Treatment A - 400 mg (1 x 400) eprosartan tablet formulation 1 above, Treatment B - 400 mg (4 x 100) eprosartan tablet formulation 2 above and Treatment C - 400 mg (2 x 200) eprosartan tablet formulation 3 above. Blood samples (5 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours following administration of study medication. Plasma samples were stored at -20°C until assayed for eprosartan.

DATA ANALYSIS: AUC, Cmax, Tmax, and $t_{1/2}$ were calculated.

RESULTS: Tables 1 summarises the pharmacokinetic data obtained from the study while Figure 1 shows the mean plasma concentration-time profiles following the three treatments

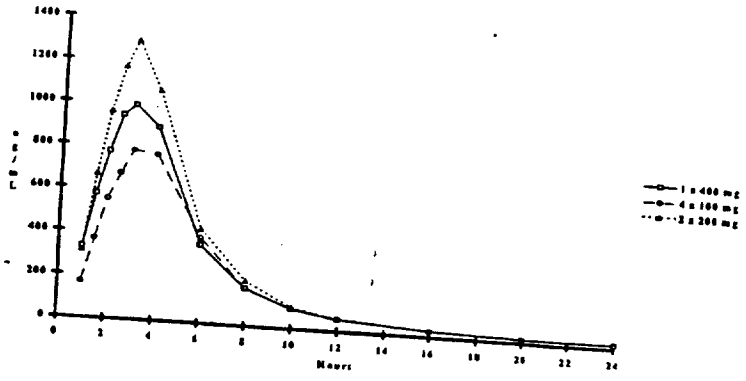
Table 1. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Healthy Volunteers

PARAMETER	TREATMENT A	TREATMENT B	TREATMENT C	90% CI		
				A:B	A:C	C:B
Cmax (ng/ml)	1200 (566)	932 (445)	1455 (581)	119-142	75-89	146-174
$AUC_{(0-t)}$ (ng*h/ml)	4872 (2224)	4170 (1759)	5829 (2331)	109-124	78-88	132-150
T_{max} (h)	2.78 (0.97)	3.29 (0.91)	2.86 (0.75)	-	-	-

TREATMENT A = 1 x 400 mg tablet (Formula AJ)
TREATMENT B = 4 x 100 mg tablet (Formula AB)
TREATMENT C = 2 x 200 mg tablet (Formula AG)

NOTE: $AUC_{(0-inf)}$ was not reported.

Figure 1. Mean Plasma Concentration-Time Profiles of Eprosartan



CONCLUSIONS: The results obtained from the study show that: (i) the 100 mg (tablet formula AB) and the 200 mg (tablet formula AG) clinical trials formulations of eprosartan were not bioequivalent to the 400 mg commercial tablet formulation (tablet formula AJ); (ii) the 200 mg clinical trials/commercial formulation (tablet formula AG) was not bioequivalent to the 100 mg (tablet formula AB) clinical trials formulations of eprosartan.

BIOAVAILABILITY / BIOEQUIVALENCE STUDY

STUDY 108566/ 089 VOLUME: 1.071 PAGES: 1- 313

INVESTIGATOR AND LOCATION:

STUDY DATE: January 17 to February 12, 1996.

OBJECTIVE: (1) To assess the bioequivalence of the new eprosartan 300 mg tablet formulation, intended for commercial release, with the old eprosartan clinical trials tablet formulations, and (2) To assess the safety and tolerability of eprosartan in healthy male volunteers.

FORMULATIONS:
(1) Eprosartan 300 mg tablet, Formula AH, Lot # U-95110 (commercial formulation)
(2) Eprosartan 100 mg tablet, Formula AB, Lot # U-94068 (clinical trials formulation)

STUDY DESIGN:
A randomized, open label, two period, crossover study in 48 healthy male volunteers with washout period of 7 days. Following a standard breakfast, each subject received the two treatments in randomized fashion: Treatment A - 300 mg (1 x 300) eprosartan tablet formulation 1 above and Treatment B - 300 mg (3 x 100) eprosartan tablet formulation 2 above. Blood samples (5 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours following administration of study medication. Plasma samples were stored at -20°C until assayed for eprosartan.

DATA ANALYSIS: AUC, Cmax, Tmax, and $t_{1/2}$ were calculated.

RESULTS: Tables 1 summarises the pharmacokinetic data obtained from the study while Figure 1 shows the mean plasma concentration-time profiles following the two treatments

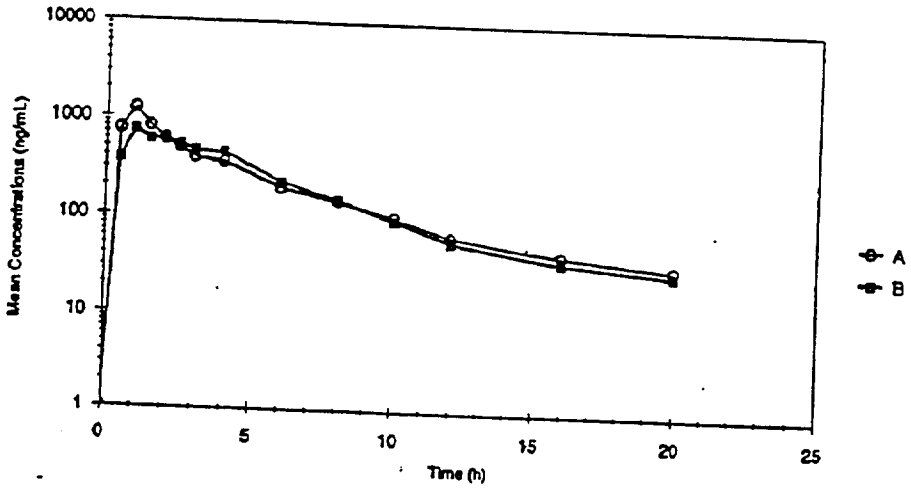
Table 1. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Healthy Volunteers

PARAMETER	TREATMENT A	TREATMENT B	90% CI
Cmax (ng/ml)	1280 (927)	926 (676)	111 - 155
$AUC_{(0-t)}$ (ng*h/ml)	4118 (2247)	3788 (3750)	102 - 129
T_{max} (h)	1.29 (1.22)	1.55 (0.97)	-

TREATMENT A = 1 x 300 mg tablet (Formula AH)
TREATMENT B = 3 x 100 mg tablet (Formula AB)

NOTE: $AUC_{(0-inf)}$ was not reported.

Figure 1. Mean Plasma Concentration-Time Profiles of Eprosartan



CONCLUSIONS: The results obtained from the study show that the 100 mg (tablet formula AB) clinical trials formulation of eprosartan was not bioequivalent to the 300 mg commercial tablet formulation (tablet formula AH).

BIOAVAILABILITY / BIOEQUIVALENCE STUDY

STUDY 108566/ 092 VOLUME: 1.072 PAGES: 1- 322

INVESTIGATOR AND LOCATION:

STUDY DATE: February 1 to 21, 1996.

OBJECTIVE: (1) To assess the bioequivalence of the new eprosartan 300 mg tablet formulation, intended for commercial release, with the clinical trials tablet formulations, and (2) To assess the safety and tolerability of eprosartan in healthy male volunteers.

FORMULATIONS:
(1) Eprosartan 300 mg tablet, Formula AH, Lot # U-95110 (commercial formulation)
(2) Eprosartan 100 mg tablet, Formula AF, Lot # U-94191 (clinical trials formulation)
(3) Eprosartan 200 mg tablet, Formula AG, Lot # U-94190 (clinical trials formulation)

STUDY DESIGN:
A randomized, open label, two period, crossover study in 48 healthy male volunteers with washout period of 7 days. Following a standard breakfast, each subject received the two treatments in randomized fashion: Treatment A - 300 mg (1 x 300) eprosartan tablet formulation 1 above and Treatment B - 300 mg (1 x 100 + 1 x 200 mg) eprosartan tablet formulations 2 and 3 above. Blood samples (5 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours following administration of study medication. Plasma samples were stored at -20°C until assayed for eprosartan.

DATA ANALYSIS: AUC, Cmax, Tmax, and $t_{1/2}$ were calculated.

RESULTS: Tables 1 summarises the pharmacokinetic data obtained from the study while Figure 1 shows the mean plasma concentration-time profiles following the two treatments

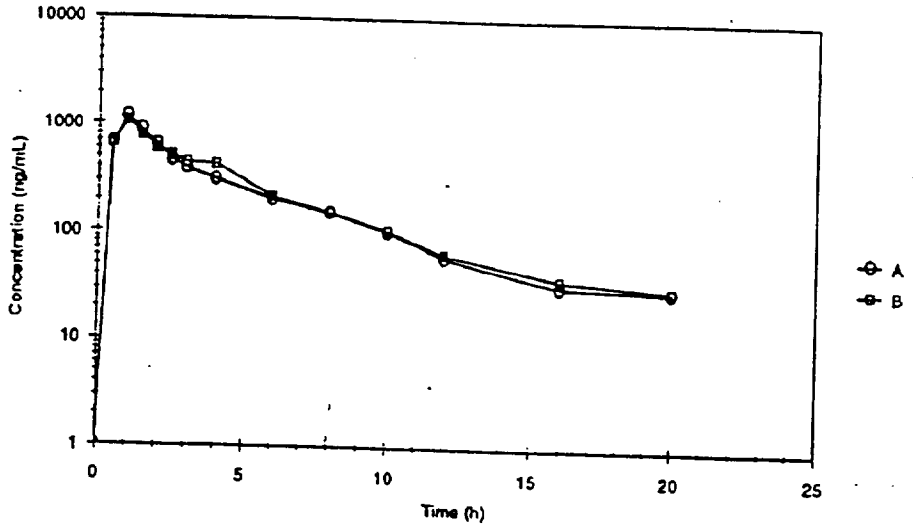
Table 1. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Healthy Volunteers

PARAMETER	TREATMENT A	TREATMENT B	90% CI
Cmax (ng/ml)	1279 (734)	1226 (972)	86 - 127
$AUC_{(0-t)}$ (ng*h/ml)	4000 (3387)	4199 (6270)	84 - 128
T_{max} (h)	1.25 (0.84)	1.48 (1.31)	-

TREATMENT A = 1 x 300 mg tablet (Formula AH)
TREATMENT B = 1 x 100 mg tablet (Formula AF) + 1 x 200 mg tablet (Formula AG)

NOTE: $AUC_{(0-inf)}$ was not reported.

Figure 1. Mean Plasma Concentration-Time Profiles of Eprosartan



CONCLUSIONS: The results obtained from the study show that the 100 mg (tablet formula AF) and the 200 mg (tablet formula AG) clinical trials formulation of eprosartan were not bioequivalent to the 300 mg commercial tablet formulation (tablet formula AH).

FOOD EFFECT STUDY
STUDY 108566/ 007 VOLUME: 1.055 PAGES: 1 - 175

INVESTIGATOR AND LOCATION: BERNARD ILSON, M.D.
SMITHKLINE BEECHAM CLIN. RES. UNIT
PHILADELPHIA, USA.

STUDY DATE: December 16, 1992 to February 1, 1993.

OBJECTIVES: (1) To estimate the difference between the pharmacokinetics and tolerability of single oral doses of eprosartan following a standard high fat meal and under fasting conditions in healthy male volunteers, (2) To describe the effect of eprosartan uric acid excretion.

FORMULATIONS:
Eprosartan 50 mg tablet, Lot # U-92055

STUDY DESIGN:
A randomized, open label, single dose, two-period, period balanced, crossover study in 12 healthy male volunteers with washout period of 7 days. Each subject received the two treatments in randomized fashion: Treatment A - 350 mg (7 x 50 mg tablet) eprosartan orally under fasting condition, Treatment B - 350 mg (7 x 50 mg tablet) eprosartan orally following a standard high fat meal. Blood samples (5 ml) were collected following oral dosing at 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 18, and 24 hours following administration of study medication. Plasma samples were stored at -20°C until assayed for eprosartan.
The meal consisted of 2 eggs cooked in butter, 2 strips of bacon, 2 pieces of toast, 2 pats of butter, 4 ounces (113 g) of hash brown potatoes, and 8 ounces (240 ml) of whole milk (equivalent to 1020 calories consisting of 58 g carbohydrate, 33 g protein and 58-75 g fat).

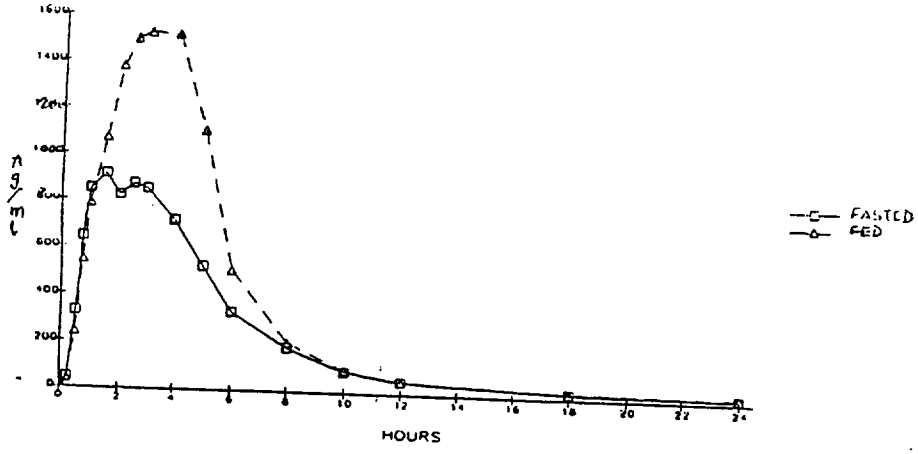
DATA ANALYSIS: AUC, Cmax, Tmax, and $t_{1/2}$ were calculated.

RESULTS: Tables 1 summarises the pharmacokinetic data obtained from the study while Figure 1 shows the mean plasma concentration-time profiles following the two treatments.

Table 1. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Healthy Volunteers

PARAMETER	TREATMENT A (FASTED)	TREATMENT B (FED)
Cmax (ng/ml)	1247 (411)	2259 (792)
$AUC_{(0-t)}$ (ng*h/ml)	5041 (1600)	7836 (2459)
$AUC_{(0-inf)}$ (ng*h/ml)	5207 (1547)	8004 (2574)
$T_{1/2}$ (h)	6.60 (4.39)	6.42 (3.22)
T_{max} (h)	2.04 (0.99)	2.75 (1.00)

Figure 1. Mean Plasma Concentration-Time Profiles of Eprosartan



CONCLUSIONS: The results obtained from the study show that administration of 350 mg eprosatan with with a high fat meal (1020 calories) results in:

(i) an increase of 54% in the AUC_{0-inf}
(ii) an increase of 80% in the C_{max}
(iii) a delay of 0.7 hours in the Tmax
(iv) no effect on the terminal half life eprosartan.

FOOD EFFECT STUDY
STUDY 108566/ 086 VOLUME: 1.070 PAGES: 1 - 184

INVESTIGATOR AND LOCATION:

STUDY DATE: November 28 to December 29, 1995.

OBJECTIVES: (1) To estimate the difference between the pharmacokinetics of a single oral doses of 800 mg (2 x 400 mg tablets) of eprosartan under fasting conditions and following a standard high fat meal in healthy male volunteers, (2) To evaluate the safety and tolerability of oral eprosartan.

FORMULATIONS:
Eprosartan 400 mg tablet, Lot # U-95111 (final commercial formulation).

STUDY DESIGN:
A randomized, open label, single dose, two-period, period balanced, crossover study in 20 healthy male volunteers with washout period of 7 days. Each subject received the two treatments in randomized fashion: Treatment A - 800 mg (2 x 400 mg tablet) eprosartan orally under fasting condition, Treatment B - 800 mg (2 x 400 mg tablet) eprosartan orally following a standard high fat meal. Blood samples (5 ml) were collected following oral dosing at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, and 30 hours following administration of study medication. Plasma samples were stored at -20°C until assayed for eprosartan.
The meal consisted of 2 eggs cooked in butter, 2 strips of bacon, 2 pieces of toast, 2 teapoons (10 g) of butter, 4 ounces (113 g) of hash brown potatoes, and 8 ounces (240 ml) of whole milk (equivalent to 1020 calories consisting of 58 g carbohydrate, 33 g protein and 58-75 g fat).

DATA ANALYSIS: AUC, Cmax, and Tmax were calculated.

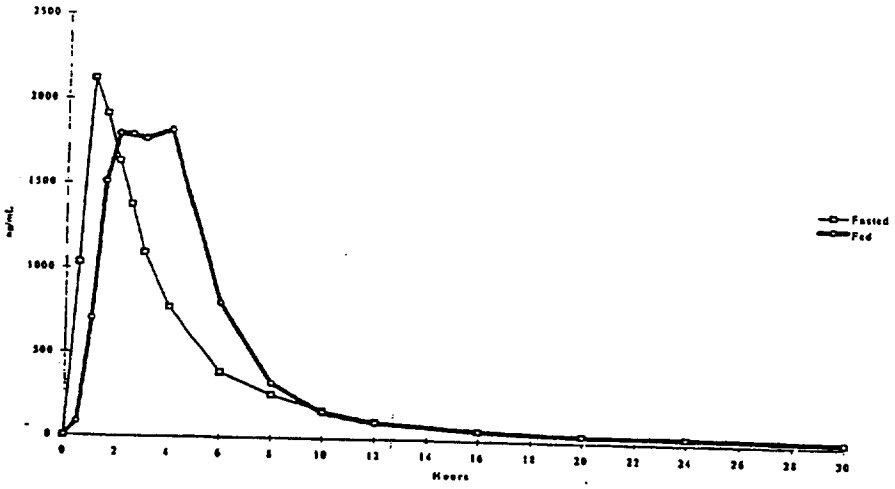
RESULTS: Tables 1 summarises the pharmacokinetic data obtained from the study while Figure 1 shows the mean plasma concentration-time profiles following the two treatments.

Table 1. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Healthy Volunteers

PARAMETER	TREATMENT A (FASTED)	TREATMENT B (FED)	95% CI
Cmax (ng/ml)	2508 (841)	2312 (745)	101 - 141
$AUC_{(0-t)}$ (ng*h/ml)	8456 (3068)	10102 (3591)	77 - 112
T_{max} (h)	1.45 (0.58)	3.15 (0.96)	100 - 250

$AUC_{(0-inf)}$ was not reported.

Figure 1. Mean Plasma Concentration-Time Profiles of Eprosartan Following administration of a Single 800 mg dose of Eprosartan Under Fed and Fasting Conditions to Healthy Volunteers



CONCLUSIONS: The results obtained from the study show that administration of 800 mg eprosatan with with a high fat meal (1020 calories) results in:

(i) an increase of about 20% in the AUC_{0-t}
(ii) no effect on the in the C_{max}
(iii) a delay of 1.7 hours in the Tmax

RENAL IMPAIRMENT STUDY

STUDY 108566/ 021 VOLUMES: 1.060-1.061

INVESTIGATOR AND LOCATION:

STUDY DATE: October 31, 1994 to January 9, 1996.

OBJECTIVES: (1) To compare the pharmacokinetics of multiple oral doses of eprosartan in subjects who have normal renal function to subjects who have renal insufficiency; (2) to describe the plasma protein binding of eprosartan in subjects who have normal renal function and in subjects who have renal insufficiency; (3) to describe the safety profile of single and multiple oral doses of eprosartan in subjects with normal and impaired renal function.

FORMULATIONS:
Eprosartan 100 mg tablet, Lot numbers U-93235 and U-94068.

STUDY DESIGN:
An open label, parallel group, multiple dose study in 29 subjects (7 normal and 22 patients with varying degrees of insufficiency). Each subject received 200 mg (2x100 mg) oral dose of eprosartan every 12 hours with food for seven days. Blood samples (5 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, and 48 hours following administration of study medication on Day 7 and predose on Days 2, 4 and 6. In addition, blood samples (7 ml) were obtained prior to dosing and at 1, 6, and 12 hours after dosing for the determination of *in vitro* (predose sample) and *ex vivo* (post-dose samples) plasma protein binding of eprosartan. Urine was coolected predose and over 0-12 hours and 21-24 hours following dose on Day 7. Plasma and urine samples were stored at -20°C until assayed for eprosartan.

ASSAYS:

DATA ANALYSIS: AUC, Cmax, Tmax, %fu, AEU (amount excreted in urine expressed as % dose) and $t_{1/2}$ were calculated.

RESULTS: Tables 1 summarises the pharmacokinetic data obtained from the study while Figures 1- 4 show the plasma concentration-time profiles following the administration of eprosartan to the four groups of subjects..

Table 1. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Subjects with Renal Impairment and Healthy Volunteers

PARAMETER	NORMAL[a]	MILD[b]	MODERATE[c]	SEVERE[d]
Cmax (ng/ml)	590 (318)	536 (217)	795 (388)	888 (202)
$AUC_{(0-12)}$ (ng*h/ml)	2961 (1558)	2239 (8674)	3711 (1772)	4597 (1423)
Tmax (h)	3.71 (1.25)	3.88 (0.35)	4.00 (1.10)	3.00 (3.00)
$T_{1/2}$ (h)	2.81 (0.49)	2.81 (0.49)	3.76 (2.04)	6.19 (1.58)
%fu (*ex vivo*)	1.40 (0.22)	1.60 (0.12)	1.60 (0.19)	2.70 (0.51)
Free $AUC_{(0-12)}$ (ng*h/ml)	40.0 (18.5)	35.4 (13.2)	61.2 (35.3)	124.0 (50.0)
Free Cmax (ng/ml)	8.2 (4.5)	8.4 (3.2)	13.2 (7.7)	23.3 (1.4)
CLr (ml/min)	39.2 (27.1)	45.6 (7.3)	23.1 (17.4)	2.2 (0.6)
AEU (% Dose)	2.78 (1.56)	3.0 (1.14)	2.18 (1.41)	0.28 (0.05)

[a]Group A: Normal renal function (Clcr > 80 ml/min), n=7
[b]Group B: Mild renal function (Clcr > 60-80 ml/min), n=8
[c]Group C: Moderate renal function (Clcr > 39-59 ml/min), n=11
[d]Group D: Severe renal function (Clcr > 5-29 ml/min), n=3

Figure 1
Eprosartan Plasma Concentrations Following Repeated Oral 200 mg BID Dose Administration to Normal Subjects

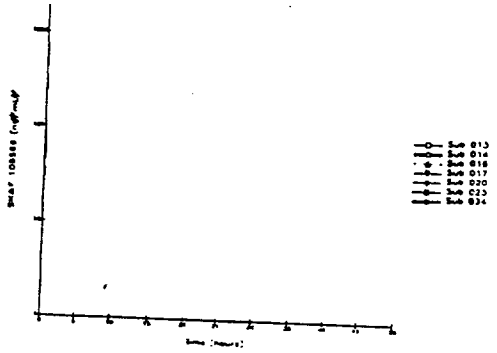


Figure 2
Eprosartan Plasma Concentrations Following Repeated Oral 200 mg BID Dose Administration to Patients with Mild Renal Impairment

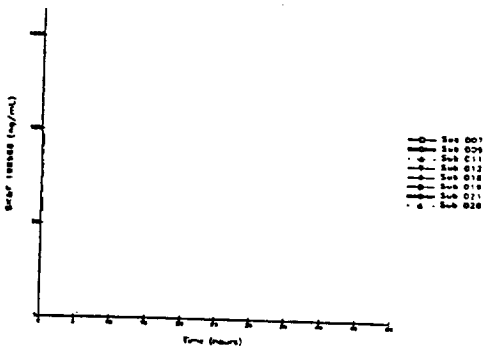


Figure 3
Eprosartan Plasma Concentrations Following Repeated Oral 200 mg BID Dose Administration to Patients with Moderate Renal Impairment

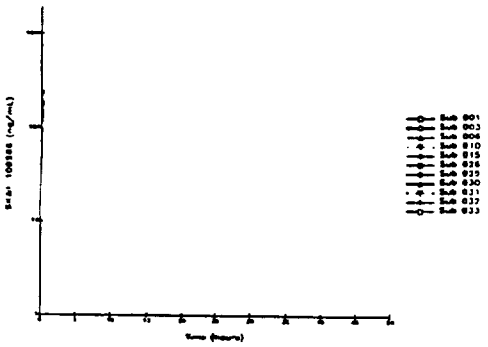
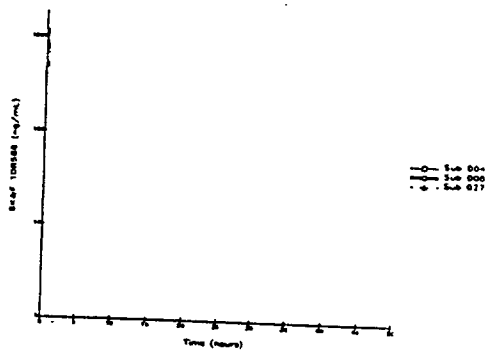


Figure 4
Eprosartan Plasma Concentrations Following Repeated Oral 200 mg BID Dose Administration to Patients with Severe Renal Impairment



CONCLUSIONS: The data obtained from the study show that: (I) total and unbound plasma concentrations of eprosartan increased with decreasing renal function (total Cmax and AUC increased by about 50% while unbound Cmax and AUC increased 3-fold in patients with severe renal impairment when compared to healthy volunteers); (ii) renal clearance of eprosartan decreased with decreasing renal function (CLr in patients with severe renal impairment is about 5% of healthy volunteers and amount excreted in urine is about 10% of heathy volunteers); (iii) T1/2 increased 2-fold in patients with severe renal impairment when compared to healthy volunteers.

HEPATIC IMPAIRMENT STUDY

STUDY 108566/ 022 VOLUME: 1.062

INVESTIGATOR AND LOCATION:

STUDY DATE: July 18, 1994 to January 9, 1995

OBJECTIVES: (1) To compare the pharmacokinetics of a single 100 mg oral dose of eprosartan in male subjects who have normal hepatic function and male subjects who have chronic hepatic insufficiency; (2) to describe the plasma protein binding of eprosartan in male subjects who have normal hepatic function and male subjects who have chronic hepatic insufficiency; (3) to describre the safety profile of eprosartan in subjects with normal and subjects with impaired hepatic function.

FORMULATIONS:
Eprosartan 100 mg tablet, Lot # U-93234

STUDY DESIGN:
An open label, parallel group, single dose study in 16 male subjects (8 normal, 8 with chronic hepatic insufficiency). Each subject received a single 100 mg oral dose of eprosartan following a standard breakfast. Blood samples (5 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, and 24 hours following administration of study medication. In addition, blood samples (7 ml) were obtained prior to dosing and at 1, 6, and 12 hours after dosing for the determination of *in vitro* (predose sample)) and *ex vivo* (post-dose samples) plasma protein binding of eprosartan. Plasma samples were stored at -20°C until assayed for eprosartan.

DATA ANALYSIS: AUC, Cmax, Tmax, and $t_{1/2}$ were calculated.

RESULTS: Tables 1 summarises the pharmacokinetic data obtained from the study while Figures 1 and 2 show the mean plasma concentration-time profiles following the administration of eprosartan to the two groups of subjects..

Table 1. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Subjects with Hepatic Impairment and Healthy Volunteers

PARAMETER	HEPATIC SUBJECTS	NORMAL SUBJECTS
Cmax (ng/ml)	486 (243)	428 (128)
$AUC_{(0\text{-}inf)}$ (ng*h/ml)	2610 (1624)	1616 (379)
Tmax (h)	5.0 (1.51)	4.24 (1.17)
$T_{1/2}$ (h)	2.45 (0.66)	2.08 (0.92)
fu (%)	1.93 (0.33)	1.77 (0.29)
Free $AUC_{(0\text{-}inf)}$ (ng*h/ml)	52.6 (43.2)	28.5 (7.23)
Free Cmax (ng/ml)	9.51 (5.93)	7.62 (2.57)

Figure 1
Plasma SK&F 108566 Concentrations Following Single Oral 100 mg Dose Administration to Subjects with Hepatic Impairment

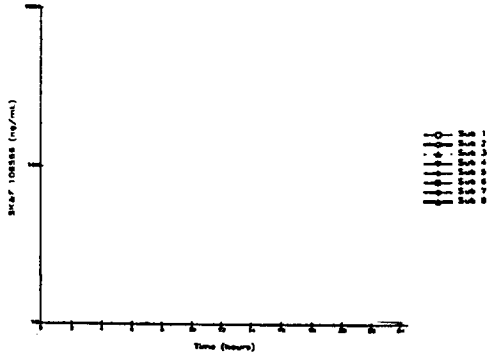
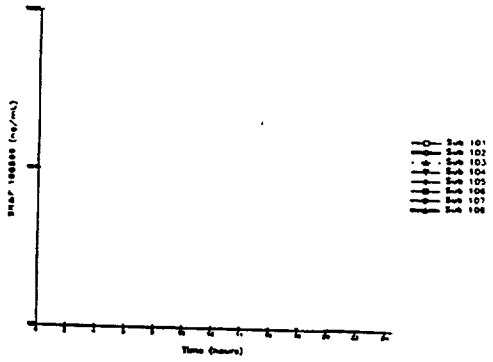


Figure 2
Plasma SK&F 108566 Concentrations Following Single Oral 100 mg Dose Administration to Healthy Subjects



CONCLUSIONS: Comparison of the data from the subjects with hepatic impairment to those from healthy male subjects show that: (i) total Cmax and AUC are increased by 14% and 62% respectively in hepatic subjects; (ii) free Cmax and AUC are increased by 25% and 84% respectively in hepatic subjects, (iii) T1/2 increased by about 18% in hepatic subjects. Observations i-iii could be due to increased bioavailability or decreased clearance; (iv) the variablities in the Cmax and AUC are higher in hepatic subjects.

AGE / GENDER EFFECT STUDY

STUDY 108566/ 025 VOLUME: 1.064 PAGES: 1 - 210

INVESTIGATOR AND LOCATION: BERNARD ILSON, M.D.
SMITHKLINE BEECHAM CLIN. RES. UNIT
PHILADELPHIA, USA.

STUDY DATE: March 24 to August 9, 1994

OBJECTIVES: (1) To compare the pharmacokinetics of a single 200 mg oral dose of eprosartan between young men and elderly men and between young men and premenopausal women; (2) to investigate the plasma protein binding of eprosartan in young male, young female, and elderly male subjects.

FORMULATIONS:
Eprosartan 100 mg tablet, Lot # U-93234

STUDY DESIGN:
An open label, parallel group, single dose study in 24 subjects (8 young male, 8 elderly male and 8 young female). Each subject received a single 200 mg (2x100 mg) oral dose of eprosartan following a standard breakfast. Blood samples (5 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, and 24 hours following administration of study medication. In addition, blood samples (7 ml) were obtained prior to dosing and at 1, 6, and 12 hours after dosing for the determination of *in vitro* (predose sample)) and *ex vivo* (post-dose samples) plasma protein binding of eprosartan. Plasma samples were stored at -20°C until assayed for eprosartan.

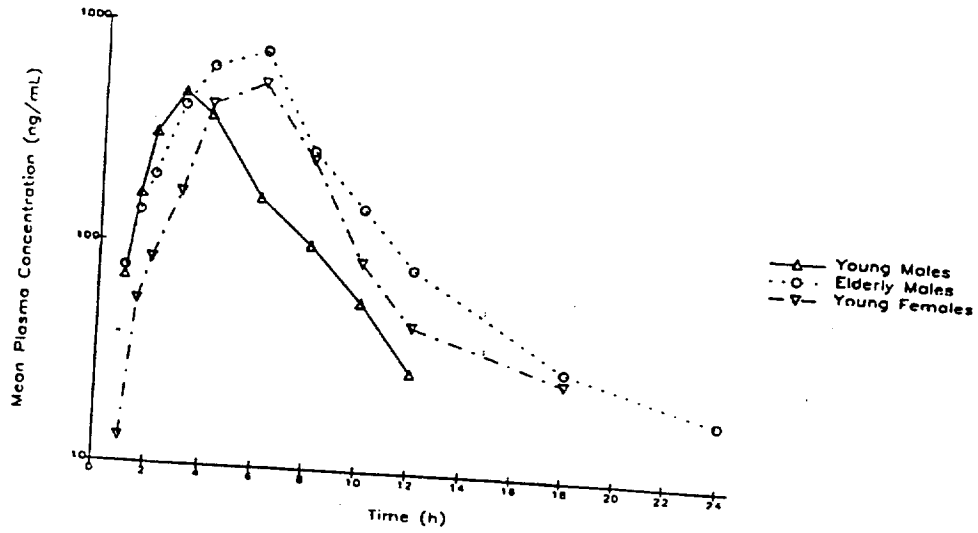
DATA ANALYSIS: AUC, Cmax, Tmax, and $t_{1/2}$ were calculated.

RESULTS: Tables 1 summarises the pharmacokinetic data obtained from the study while Figure 1 shows the mean plasma concentration-time profiles following the administration of eprosartan to the three groups of subjects..

Table 1. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Healthy Volunteers

PARAMETER	YOUNG MALES	YOUNG FEMALES	ELDERLY MALES
Cmax (ng/ml)	489 (347)	599 (509)	914 (353)
$AUC_{(0\text{-}inf)}$ (ng*h/ml)	2171 (1544)	2322 (1806)	4572 (1653)
Tmax (h)	2.75 (0.46)	3.52 (0.76)	4.89 (1.25)
$T_{1/2}$ (h)	2.81 (0.49)	3.76 (2.04)	6.19 (1.58)
fu (%)	2.11 (0.31)	2.15 (0.22)	2.17 (0.22)
Free $AUC_{(0\text{-}inf)}$ (ng*h/ml)	44.7 (30.5)	49.7 (40.5)	98.5 (34.6)
Free Cmax (ng/ml)	10.2 (6.7)	12.9 (11.2)	19.8 (7.9)

Figure 1. Mean Plasma Concentration-Time Profiles of Eprosartan



CONCLUSIONS: The results obtained from the study show that following administration of a single 200 mg oral dose of eprosartan

(i) elderly males had plasma levels of eprosartan that were approximately 2-fold higher than young males in terms of free and total $AUC_{0\text{-}inf}$ and Cmax.

(ii) The Tmax and T1/2 of eprosartan were approximately 2-fold higher in the elderly

males compared to young males
These obsevations (i & ii) could be due to increased absorption or decreased elimination of eprosartan in the elderly when compared to the young males.
(iii) The pharmacokinetics of eprosartan are similar in young males and young females.
(iv) No effect of age or gender on protein binding of eprosartan

EPROSARTAN / DIGOXIN INTERACTION STUDY

STUDY 108566/ 023 VOLUME: 1.063

INVESTIGATOR AND LOCATION:

STUDY DATE: January 15 to August 4, 1994.

OBJECTIVES: (1) To compare the pharmacokinetics of single oral doses of digoxin (0.6 mg) given alone or when coadministered with orally administered eprosartan which has been dosed to steady-state, (2) To assess the safety and tolerability of concomitant oral administration of digoxin and eprosartan.

FORMULATIONS:
Eprosartan 100 mg tablet, Lot # U-93235
Digoxin 0.2 mg (Lanoxicaps®) capsules, Lot # X94064

STUDY DESIGN:
A randomized, open label, two period, period balanced, crossover study in 12 healthy male volunteers with washout period of 14 days. Each subject received the two treatments in randomized fashion: Treatment A - 0.6 mg (3 x 0.2 mg) oral dose of digoxin capsules and Treatment B - 200 mg (2 x 100 mg) eprosartan orally every 12 hours for 7 days with a single 0.6 mg oral dose of digoxin given on day 4. Blood samples (5 ml) were collected following oral dosing at 0 (predose), 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, 84 and 96 hours following administration of digoxin. Plasma samples were stored at -20°C until assayed for digoxin.

DATA ANALYSIS: AUC, Cmax, Tmax, and $t_{1/2}$ of digoxin were calculated.

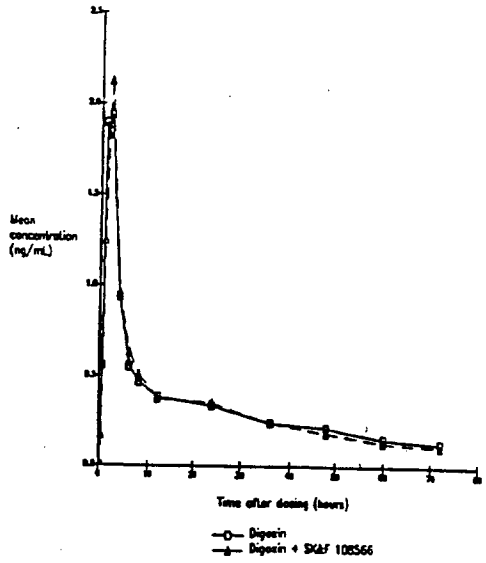
RESULTS: Tables 1 summarises the digoxin pharmacokinetic data obtained from the study while Figure 1 shows the mean plasma concentration-time profiles following the two treatments.

Table 1. Mean (SD) Parameter Values for Digoxin Following Oral Administration to Healthy Volunteers in the Presence and Absence of Eprosartan

PARAMETER	TREATMENT A	TREATMENT B
Cmax (ng/ml)	2.53 (0.76)	2.57 (0.81)
$AUC_{(0-t)}$ (ng*h/ml)	24.3 (5.9)	24.2 (5.9)
$AUC_{(0-inf)}$ (ng*h/ml)	32.6 (8.50)	33.2 (7.2)
$T_{1/2}$ (h)	39.8 (7.2)	46.9 (15.7)
T_{max} (h)	1.5 (0.5)	1.7 (0.8)

Figure 1

Mean plasma concentration (ng/mL) for digoxin following oral administration of 0.6 mg digoxin alone or administered with 200 mg (bid) SK&F 108566 at steady-state to healthy male volunteers (n=12)



CONCLUSIONS: The data obtained from the study show that (Table 1) co-administration of digoxin with eprosartan does not affect the AUC and the Cmax of digoxin but results in an increase in the terminal half life of digoxin by about 7 hours (from 39.8 hours to 46.9 hours).

EPROSARTAN / WARFARIN INTERACTION STUDY

STUDY 108566/ 027 VOLUME: 1.064 PAGES: 211 - 460

INVESTIGATOR AND LOCATION:

STUDY DATE: October 3 to November 22, 1994.

OBJECTIVES: (1) To evaluate the effect of eprosartan on the anticogulant activity of warfarin at steady state, (2) To assess the safety and tolerability of concomitant oral administration of eprosartan and warfarin, and (3) if an effect on anticoagulant activity were shown, then the effect of eprosartan on the pharmacokinetics of the S- and R-enantiomers of warfarin would be investigated..

FORMULATIONS:
Eprosartan 100 mg tablet, Lot # U-94068
Matching placebo tablet, Lot # U-94111
Coumadin® (Warfarin) 1 mg tablet, Batch No. HC052A
Coumadin® (Warfarin) 2 mg tablet, Batch No. EHC073A
Coumadin® (Warfarin) 2.5 mg tablet, Batch No. EHD097A
Coumadin® (Warfarin) 5 mg tablet, Batch No. HC110A
AquaMephyton® (Vitamin K) 10 mg/ml injection, Batch No. 0480A

STUDY DESIGN:
A randomized, double-blind (eprosartan dosing phase only), placebo controlled, parallel group study in 20 healthy subjects (10 per group) of the pharmacodynamics with/without pharmacokinetics of warfarin in the presence or absence of eprosartan. During the 14 day run in period each subject received daily doses of warfarin titrated to achieve an international normalized (INR) ratio of 1.3 to 1.6 . Subjects that met the entry criteria were randomized to either (1) 300 mg eprosartan (3x100 mg) twice a day plus warfarin dose which was established during the run in period or (2) matched placebo tablets (three) twice a day plus warfarin dose which was established during the run in period for 7 days. Blood samples (7 ml) were collected on days 14 and 21following warfarin dosing at 0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18 and 24 hours following administration of warfarin and predose on days 12, 13, 19 and 20. Plasma samples were stored at -20°C until assayed for warfarin. INR was determined for all subjects on day 22 of the study. All subjects received a single subcutaneous injection of vitamin K, 10 mg, at the end of their participation in the study.

ASSAY: The samples were not assayed and pharmacokinetic analyses were not performed because warfarin administered with eprosartan was statistically equivalent to warfarin administered with placebo.

DATA ANALYSIS: The mean INR on day 22 for warfarin administered with eprosartan and warfarin administered with placebo were subjected to an analysis of covariance (ANCOVA) with terms for treatment (eprosartan or placebo), the baseline INR (calculated as the average of the INR on days 12, 13, and 14) as the covariate and the intraction term between treatment and baseline INR included in the model. The associated 90% confidence interval was calculated.

RESULTS: Tables 1 summarises INR data obtained from the study.

Table 1. Mean (SD) INR Values for Warfarin Following Oral Administration to Healthy Volunteers in the Presence and Absence of Eprosartan

PARAMETER	WARFARIN + EPROSARTAN	WARFARIN + PLACEBO
Baseline INR	1.48 (0.08)	1.41 (0.20)
INR on day 22	1.44 (0.26)	1.31 (0.18)
Adjusted INR on day 22	1.42	1.35
Mean difference	0.068	
90% CI	-0.11 - 0.25	

CONCLUSIONS: The data obtained from the study showed that (Table 1) as measured by the INR, co-administration of warfarin with eprosartan was statistically equivalent to coadministration of warfarin with placebo on the anticoagulant activity of warfarin. There is therefore no apparent pharmacodynamic interaction between eprosartan and warfarin with regard to anticoagulant effect of warfarin but there is no data available to rule out a pharmacokinetic interaction.

EPROSARTAN / GLYBURIDE INTERACTION STUDY

STUDY 108566/ 028 VOLUME: 1.065 PAGES: 1- 271

INVESTIGATOR AND LOCATION:

STUDY DATE: March 9 to September 7, 1995.

OBJECTIVES: (1) To establish that concomitant administration of eprosartan and glyburide had no effect on the 24-hour plasma glucose profiles in diabetic patients relative to glyburide plus placebo; (2) To assess the safety and tolerability of concomitant oral administration of multiple oral doses of glyburide and eprosartan (200 mg twice a day) to diabetic patients; and (3) if an effect on the 24-hour plasma glucose profile was shown, then the effect of eprosartan on the steady state pharmacokinetics of glyburide was to be investigated..

FORMULATIONS:
Eprosartan 100 mg tablet, Lot # U-94068
Matching placebo tablet, Lot # U-94111
Micronase® (Glyburide) 1.25 mg tablet, Batch No. 640JF
Micronase® (Glyburide) 2.5 mg tablet, Batch No. 884JC
Micronase® (Glyburide) 5.0 mg tablet, Batch No. 667JC

STUDY DESIGN:
A randomized, double-blind (eprosartan dosing phase only), placebo controlled, two-period, period-balanced, crossover study in 12 patients with non-insulin-dependent diabetics mellitus (NIDDM) and a washout period of 14 days. Patients receiving a stable dose of glyburide (3.75-10 mg/day) for at least 30 days prior to the first dose of study medication were randomized to receive 200 mg eprosartan (2x100 mg) or placebo twice a day concomitantly with glyburide once daily according to their pre-determined regimen (3.75-10 mg/day) for 7 days. Blood samples (3 ml) for the measurement of plasma glucose levels were collected on days 0 and 7 of each regimen following glyburide dosing at 0 (predose), 1, 2.5, 4, 5, 6, 7.5, 9, 12, 13, 14.5, 16 and 24 hours.

ASSAY: The pharmacokinetic analyses were not performed because glyburide administered with eprosartan was statistically equivalent to glyburide administered with placebo as measured by the 24-hour plasma glucose profiles.

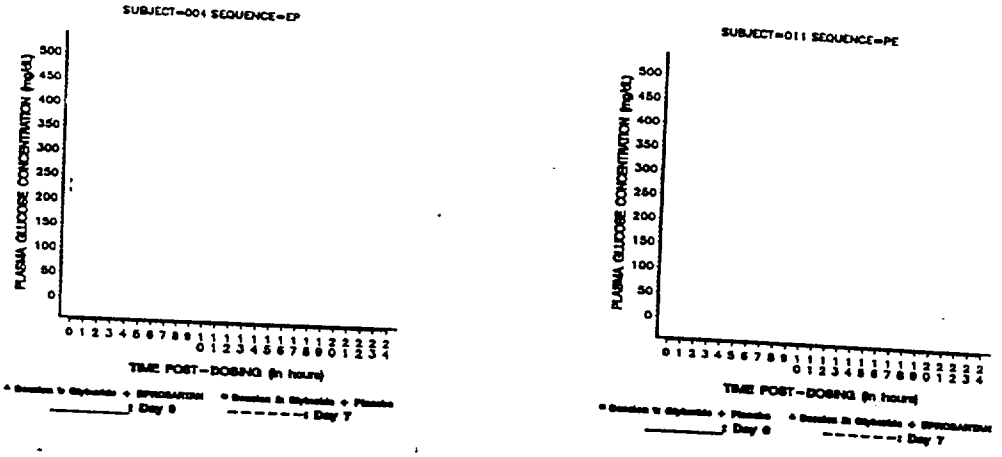
DATA ANALYSIS: The mean plasma glucose concnetrations on days 0 and 7 for glyburide administered with eprosartan and warfarin administered with placebo were subjected to an analysis of variance (ANOVA) using an equivalence approach. Equivalence was shown if the 90% confidence interval for the treatment difference 'glyburide-eprosartan' versus 'glyburide-placebo' was completely contained within the 30% equivalence range on Day 7.

RESULTS: Tables 1 summarises the data obtained from the study while Figure 1 shows typical individual 24-hour glucose profiles.

Table 1. Mean (SD) Plasma Glucose Concentrations Following Oral Administration og Glyburide to Patients in the Presence and Absence of Eprosartan

STUDY DAY	GLYBURIDE + EPROSARTAN	GLYBURIDE + PLACEBO	90% CI
Day 0	199 (63.7)	206 (67.1)	83 - 110
Day 7	203 (65.16)	212 (52.0)	90 - 101

FIG. 1: TYPICAL INDIVIDUAL PLASMA GLUCOSE CONCENTRATION-TIME PLOTS



CONCLUSIONS: The data obtained from the study showed that (Table 1) eprosartan taken concomitantly with glyburide for a period of one week had no effect on the mean 24-hour glucose concentrations in diabetic patients stabilized on glyburide therapy but there is no data available to rule out a pharmacokinetic interaction.

EPROSARTAN / RANITIDINE INTERACTION STUDY

STUDY 108566/ 029 VOLUME: 1.065 PAGES: 272 - 455

INVESTIGATOR AND LOCATION: BERNARD ILSON, M.D.
SMITHKLINE BEECHAM CLIN. RES. UNIT
PHILADELPHIA, USA.

STUDY DATE: June 20 to September 5, 1995.

OBJECTIVES: (1) To estimate the effect of multiple doses of ranitidine on the pharmacokinetics of a single oral dose of eprosartan; (2) To evaluate the safety and tolerability of concomitant administration of ranitidine and eprosartan.

FORMULATIONS:
Eprosartan 100 mg tablet, Lot number U-95018
Zantac® (Ranitidine) 150 mg tablet, Lot No. 5ZPT044

STUDY DESIGN:
An open-label, randomized, two-period, period balanced crossover study in 17 healthy male volunteers and a washout period of at least 7 days. Each subject received the following treatments: Treatment A - a single oral dose of 400 mg eprosartan and Treatment B - 150 mg ranitidine orally twice daily for 3 days followed by a single oral concomitant dose of 400 mg eprosartan and 150 mg ranitidine on Day 4. Blood samples (5 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, and 24 hours following administration eprosartan. Urine samples were collected over the 0-12 and 12-24 hour time intervals following administration of eprosartan. Plasma and urine samples were stored at -20°C until assayed for eprosartan.

ASSAYS:

DATA ANALYSIS: AUC, Cmax, Tmax, Ae (amount excreted in urine expressed as % dose) and CLr were calculated.

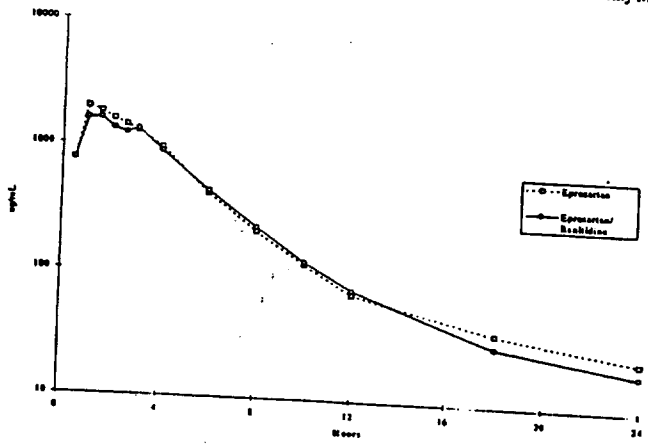
RESULTS: Table 1 summarises the pharmacokinetic data obtained from the study while Figure 1 show the mean plasma concentration-time profiles following the two treatments

Table 1. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Healthy Volunteers in the Presence and Absence of Ranitidine

PARAMETER	EPROSATAN	EPROSARTAN + RANITIDINE
Cmax (ng/ml)	2260 (1465)	2019 (1173)
$AUC_{(0-t)}$ (ng*h/ml)	8042 (4128)	7504 (4635)
Tmax (h)	1.60 (0.71)	1.83 (1.29)
Ae (mg)	12.86 (5.74)	11.19 (6.39)
CLr (ml/min)	31.2 (17.4)	27.3 (10.5)

Figure 1

Mean Plasma Concentration-Time Profiles of Eprosartan Following a Single Dose of 400 mg Eprosartan Alone and a Single Dose of 400 mg Eprosartan with Multiple Oral Doses of 150 mg Ranitidine in Healthy Male Volunteers



CONCLUSION: The results obtained from the study show that co-administration of 400 mg eprosartan with 150 mg ranitidine leads to a decrease of 11% in Cmax, 7% in AUC and about 13% in CLr and amount of eprosartan excreted in urine indicating that increased gastric pH due to ranitidine administration does not significantly affect the rate and extent of absorption of eprosartan.

EPROSARTAN / FLUCONAZOLE INTERACTION STUDY

STUDY 108566/ 094 VOLUMES: 1.073 - 1.074

INVESTIGATOR AND LOCATION:

STUDY DATE: February 19 to April 6, 1996.

OBJECTIVES: To estimate the effect of steady state fluconazole on the pharmacokinetics of repeat oral doses of eprosartan, losartan and E-3174 (the active metabolite for losartan) and to evaluate the effect of single and repeat oral doses of eprosartan and losartan, with and without fluconazole, on urine uric acid excretion.

FORMULATIONS:
Eprosartan 300 mg tablet, Lot Number U-95110
Placebo tablet, Lot Number. U-95146
Cozaar® (Losartan) 50 mg tablet, Lot No. JJ289A
Diflucan® (Fluconazole) 200 mg tablet, Lot No. 54PO11A

STUDY DESIGN:
An open-label, placebo-controlled, paralell group study in 44 healthy male volunteers (14 for eprosartan group, 16 for losartan group and 14 for placebo). Each subject received one of the following treatments: Treatment A - 300 mg eprosartan twice daily from Days 1 to 20 and 200 mg fluconazole daily from Days 11 to 20, and Treatment B - 100 mg (2x50 mg) losartan daily from Days 1 to 20 and 200 mg fluconazole daily from Days 11 to 20, Treatment C one placebo tablet daily from Days 1 to 20 and 200 mg fluconazole daily from Days 11 to 20. Urine samples were collected ad libitum on Days 0, 1, 10 and 20. On Day 0, blood samples (5 ml) were obtained at the following times in relationship to first morning urine void: -1, 0, 1, 2, 3, 4, 5, 6, 12 and 23 hours. On Days 1, 10 and 20 blood samples were obtained at the following times in relationship to the the morning dose: -1, 0, 1, 2, 3, 4, 5, 6, 12 and 24 hours postdose. Blood samples (5 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, and 24 hours following administration eprosartan on Days 10 and 20 and predose on Days 8, 9, 18 and 19. Blood samples (5 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, and 24 hours following administration losartan on Days 10 and 20 and predose on Days 8, 9, 18 and 19. Plasma and urine samples were stored at -20°C until assayed for eprosartan.

ASSAYS:

DATA ANALYSIS: AUC, Cmax, Tmax and UUA/UCr (urine uric acid to urine creatinine ratio) were calculated.

RESULTS: The results obtained from the study are summarised in Tables 1-3 and Figures 1-3.

Table 1. Mean (SD) Pharmacokinetic Parameters for Eprosartan, Losartan and E-3174 Following Oral Administration of Eprosartan or Losartan to Healthy Volunteers in the Presence and Absence of Fluconazole

Eprosartan Parameters	Eprosartan Alone (Day 10)	Eprosartan with Fluconazole (Day 20)	Ratio (95% CI)
AUC(0-t) (ng·h/mL)	4331 (1967)	4505 (2096)	1.04 (0.87, 1.25)
Cmax (ng/mL)	1254 (547)	1133 (464)	0.89 (0.67, 1.19)
Tmax* (h)	1.74 (1.00-4.00)	1.50 (0.50-4.00)	0.00 (-0.52, 0.50)**
Losartan Parameters	**Losartan Alone (Day 10)**	**Losartan with Fluconazole (Day 20)**	**Ratio (95% CI)**
AUC(0-t) (ng·h/mL)	483 (114)	818 (261)	1.66 (1.44, 1.92)
Cmax (ng/mL)	246 (125)	323 (157)	1.30 (0.92, 1.84)
Tmax* (h)	1.50 (0.50-4.00)	1.50 (0.50-2.50)	-0.13 (-0.75, 0.50)**
E-3174 Parameters	**Losartan Alone (Day 10)**	**Losartan with Fluconazole (Day 20)**	**Ratio (95% CI)**
AUC(0-t) (ng·h/mL)	2857 (770)	1676 (620)	0.57 (0.52, 0.62)
Cmax (ng/mL)	425 (122)	195 (85.5)	0.44 (0.39, 0.49)
Tmax* (h)	3.00 (2.00-6.00)	3.50 (2.50-6.03)	0.25 (-0.74, 0.99)**

* Data presented as median (range).

** Data presented as the estimated median difference (Day 20-Day 10) and 95% CI.

Table
Mean Observed Maximum UUA/UCr (SD)

Regimen*	Day 0	Day 1	Day 10	Day 20
A	0.486 (0.080)	0.544 (0.097)	0.493 (0.086)	0.430 (0.096)
B	0.470 (0.089)	0.761 (0.199)	0.587 (0.139)	0.555 (0.200)
C	0.463 (0.094)	0.468 (0.065)	0.455 (0.091)	0.419 (0.064)

Source: Tables 11.10 through 11.12 (n=13-16)

*Regimen A: eprosartan 300 mg oral twice daily x 20 days; on Day 11, subjects began fluconazole 200 mg oral once daily from Day 11 up to and including Day 20

Regimen B: losartan 100 mg oral once daily x 20 days; on Day 11, subjects began fluconazole 200 mg oral once daily from Day 11 up to and including Day 20

Regimen C: placebo one tablet once daily x 20 days; on Day 11, subjects began fluconazole 200 mg oral once daily from Day 11 up to and including Day 20

Table
Mean (SD) for Total Daily Excretion of Urine Uric Acid (mg) and Urine Creatinine (mg)

Regimen	Day 0	Day 1	Day 10	Day 20
Urine Uric Acid (mg)				
A	625.2 (151.0)	689.6 (144.5)	663.7 (173.7)	626.0 (161.3)
B	672.6 (134.6)	734.4 (220.7)	662.7 (236.5)	686.8 (229.2)
C	610.2 (208.7)	702.5 (198.2)	620.9 (161.1)	644.7 (146.2)
Urine Creatinine (mg)				
A	1748.3 (400.5)	1862.5 (392.3)	1798.2 (545.0)	1945.8 (446.1)
B	1887.5 (353.9)	1784.9 (405.7)	1771.2 (500.1)	1921.5 (572.3)
C	1818.3 (424.1)	1959.1 (465.3)	1733.6 (454.4)	1841.0 (472.5)

Figure 1

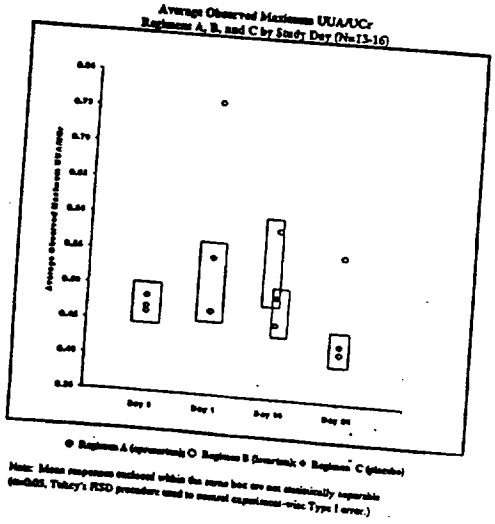


Figure 2

Mean Steady-State Eprosartan Plasma Concentration Time Profiles Following Twice Daily Oral Administration of 300 mg of Eprosartan (Day 10) and Twice Daily Oral Administration of Eprosartan with Once Daily Oral Administration of 200 mg of Fluconazole (Day 20) in Healthy Subjects

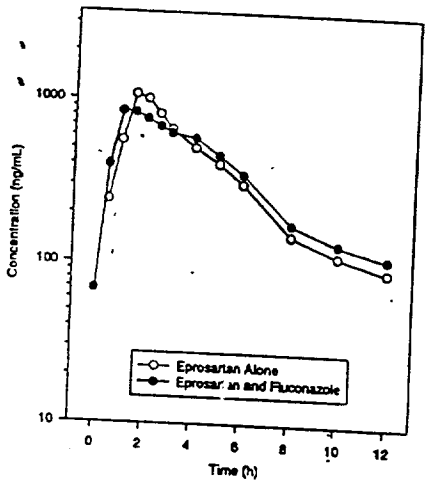
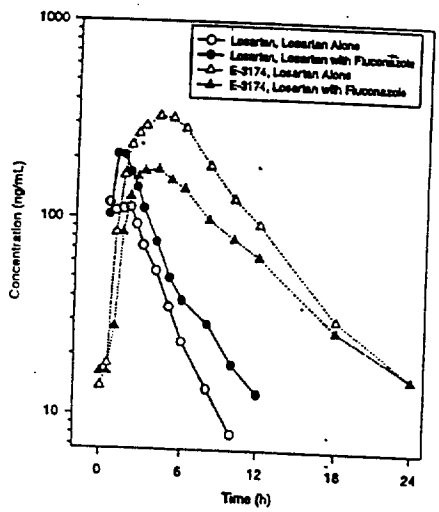


Figure 3

Mean Steady-State Losartan and E-3174 Plasma Concentration Time Profiles Following Twice Daily Oral Administration of 100 mg of Losartan (Day 10) and Twice Daily Oral Administration of Eprosartan with Once Daily Oral Administration of 200 mg of Fluconazole (Day 20) in Healthy Subjects



CONCLUSION: The results obtained from the study showed that :

(i) Single dose of losartan alone or repeated doses of losartan co-administered with fluconazole significantly increased urine uric acid excretion, as measured by the urine uric acid to urine creatine ratio, compared to either eprosartan or placebo.

(ii) Eprosartan had similar effects as placebo on urine uric acid excretion when administered as single dose alone or repeated doses administered with or without fluconazole.

(iii) Co-administration of fluconazole with losartan leads to increased plasma levels of losartan (about 70% increase in AUC and 30% increase in Cmax) and decreased plasma levels of E-3174 (about 42% decrease in AUC and 54% decrease in Cmax) presumably due to inhibition of CYP2C9.

(iv) Fluconazole administration did not alter the steady-state pharmacokinetics of eprosartan.

EPROSARTAN / KETOCONAZOLE INTERACTION STUDY

STUDY 108566/ 095 VOLUMES: 1.075 - 1.076

INVESTIGATOR AND LOCATION:

STUDY DATE: February 13 to March 18, 1996.

OBJECTIVES: To estimate the effect of steady state ketoconazole on the pharmacokinetics of repeat oral doses of eprosartan, losartan and E-3174 (the active metabolite for losartan) and to evaluate the effect of single and repeat oral doses of eprosartan and losartan, with and without ketoconazole, on urine uric acid excretion.

FORMULATIONS:
Eprosartan 300 mg tablet, Lot Number U-95110
Placebo tablet, Lot Number. U-95146
Cozaar® (Losartan) 50 mg tablet, Lot No. JJ289A
Nizoral® (Ketoconazole) 200 mg tablet, Lot No. 95K364A.

STUDY DESIGN:
An open-label, placebo-controlled, paralell group study in 44 healthy male volunteers (134 for eprosartan group, 14 for losartan group and 15 for placebo). Each subject received one of the following treatments: Treatment A - 300 mg eprosartan twice daily from Days 1 to 10 and 200 mg ketoconazole daily from Days 6 to 10, and Treatment B - 100 mg (2x50 mg) losartan daily from Days 1 to 10 and 200 mg ketoconazole daily from Days 6 to 10, Treatment C one placebo tablet daily from Days 1 to 10 and 200 mg ketoconazole daily from Days 6 to 10. Urine samples were collected ad libitum on Days 0, 1, 5 and 10. On Day 0, blood samples (5 ml) were obtained at the following times in relationship to first morning urine void: -1, 0, 1, 2, 3, 4, 5, 6, 12 and 23 hours. On Days 1, 5 and 10 blood samples were obtained at the following times in relationship to the the morning dose: -1, 0, 1, 2, 3, 4, 5, 6, 12 and 24 hours postdose. Blood samples (5 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, and 24 hours following administration eprosartan on Days 5 and 10 and predose on Days 3, 4, 8 and 9. Blood samples (5 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, and 24 hours following administration losartan on Days 5 and 10 and predose on Days 3, 4, 8 and 9. Plasma and urine samples were stored at -20°C until assayed for eprosartan.

ASSAYS

DATA ANALYSIS: AUC, Cmax, Tmax and UUA/UCr (urine uric acid to urine creatinine ratio) were calculated.

RESULTS: The results obtained from the study are summarised in Tables 1-5 and Figures 1-4.

Table 1

Mean (SD) Eprosartan Pharmacokinetic Parameters (n=13) Following Repeat Administration of Eprosartan Alone and with Ketoconazole

Parameter (units)	Eprosartan Alone	Eprosartan + Ketoconazole
AUC(0-t) (ng.h/mL)	4470 (1686)	4406 (1852)
Cmax (ng/mL)	1193 (285)	1028 (537)
Tmax (h)*	1.50 (1.00-4.00)	1.50 (1.00-5.00)

*median (range)

Table 2

Mean (SD) Losartan Pharmacokinetic Parameters (n=14) Following Repeat Administration of Losartan Alone and with Ketoconazole

Parameter (units)	Losartan Alone	Losartan + Ketoconazole
AUC(0-t) (ng.h/mL)	633 (255)	627 (241)
Cmax (ng/mL)	337 (167)	300 (143)
Tmax (h)*	1.50 (0.50-4.00)	2.00 (1.00-3.00)

*median (range)

Table 3

Mean (SD) E-3174 Pharmacokinetic Parameters (n=14) Following Repeat Administration of Losartan Alone and with Ketoconazole

Parameter (units)	Losartan Alone	Losartan + Ketoconazole
AUC(0-t) (ng.h/mL)	2817 (939)	2986 (949)
Cmax (ng/mL)	431 (187)	478 (205)
Tmax (h)*	3.00 (2.00-8.00)	4.00 (2.00-6.00)

*median (range)

Table 4
Mean Observed Maximum UUA/UCr (SD)

Regimen*	Day 0	Day 1	Day 5	Day 10
A	0.437 (0.070)	0.503 (0.125)	0.449 (0.084)	0.461 (0.095)
B	0.474 (0.093)	0.760 (0.147)	0.623 (0.188)	0.627 (0.238)
C	0.401 (0.089)	0.427 (0.041)	0.442 (0.068)	0.435 (0.105)

Source: Tables 11.10 through 11.12 (n=13-16).

*Regimen A: eprosartan 300 mg oral twice daily x 10 days; on Day 6, subjects began ketoconazole 200 mg oral once daily from Day 6 up to and including Day 10

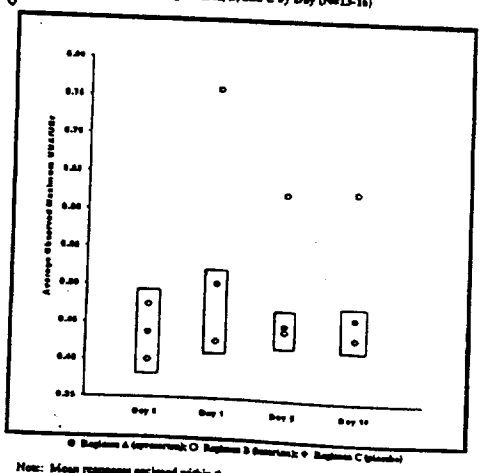
Regimen B: losartan 100 mg oral once daily x 10 days; on Day 6, subjects began ketoconazole 200 mg oral once daily from Day 6 up to and including Day 10

Regimen C: placebo one tablet once daily x 10 days; on Day 6, subjects began ketoconazole 200 mg oral once daily from Day 6 up to and including Day 10

Table 5
Mean (SD) for Total Daily Excretion of Urine Uric Acid (mg) and Urine Creatinine (mg)

Regimen*	Day 0	Day 1	Day 5	Day 10
Urine Uric Acid (mg)				
A	542.8 (107.6)	674.3 (208.9)	699.0 (234.0)	694.3 (239.6)
B	565.7 (163.6)	716.2 (212.6)	686.0 (184.5)	646.0 (248.2)
C	545.5 (146.6)	621.6 (162.5)	689.0 (186.3)	601.4 (192.1)
Urine Creatinine (mg)				
A	1698.0 (371.6)	1812.2 (476.0)	1947.0 (421.8)	1973.7 (463.6)
B	1757.3 (366.9)	1691.2 (462.2)	1833.7 (424.9)	1760.0 (587.7)
C	1746.8 (306.1)	1777.5 (402.2)	1949.6 (450.8)	1851.8 (606.6)

Figure 1.



Note: Mean responses enclosed within the same box are not statistically separable (α=0.05, Tukey's HSD procedure used to control experiment-wise Type I error.)

Figure 2

Mean Eprosartan Concentration-Time Profiles Following Administration of Eprosartan Alone and with Concomitant Ketoconazole

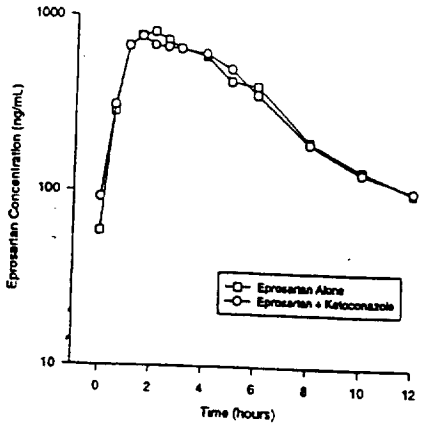


Figure 3

Mean E-3174 Concentration-Time Profiles Following Administration of Losartan Alone and with Concomitant Ketoconazole

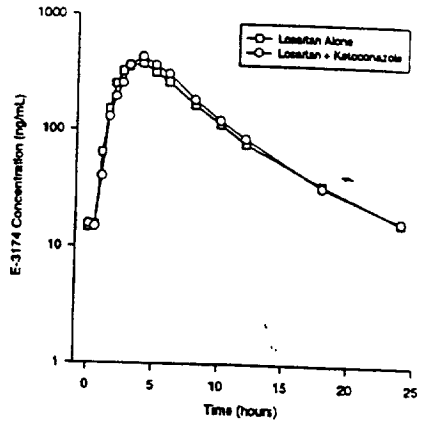
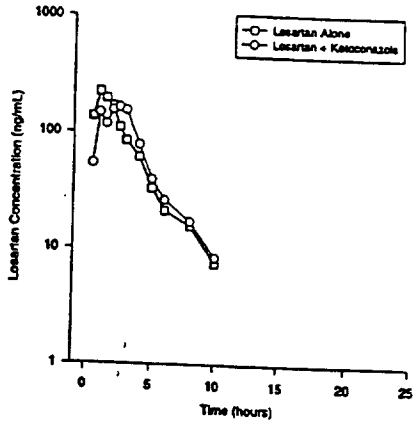


Figure 4

Mean Losartan Concentration-Time Profiles Following Administration of Losartan Alone and with Concomitant Ketoconazole



CONCLUSION: The results obtained from the study showed that :

(i) Single dose of losartan alone or repeated doses of losartan co-administered with ketoconazole appears to significantly increase urine uric acid excretion, as measured by the urine uric acid to urine creatine ratio, compared to either eprosartan or placebo.

(ii) Eprosartan had similar effects as placebo on urine uric acid excretion when administered as single dose alone or repeated doses administered with or without ketoconazole.

(iii) Co-administration with ketoconazole did not affect the steady state pharmacokinetics of eprosartan thus confirming the CYP3A is not involved in the metabolism of eprosartan.

(iv) Co-administration of losartan with ketoconazole did not affect the steady state pharmacokinetics of losartan and E-3174 thus suggesting that CYP3A does not play a major role in the first pass or systemic conversion of losartan to E-3174.

PHARMACOKINETICS / PHARCODYNAMICS STUDY

STUDY 108566/006 VOLUMES: 1.053-1.054

INVESTIGATOR AND LOCATION: BERNARD ILSON, M.D.
SMITHKLINE BEECHAM CLIN. RES. UNIT
PHILADELPHIA, USA.

STUDY DATE: August 21 to December 22, 1992.

OBJECTIVES: (1) To assess the onset of inhibitory effect of eprosartan on angiotensin-II-induced decreases in effective renal plasma flow (ERPF) (Part 1); (2) To assess the onset of inhibitory effect of eprosartan on angiotensin-II-induced decreases in ERPF at 24 hours after dosing (Part 1); (3) To establish the lack of agonist activity of eprosartan as determined by the absence of an eprosartan-induced decrease in ERPF (Part 1); (4) To assess the dose-reponse profile of single oral doses of eprosartan an eprosartan pharmacokinetics and on inhibition of angiotensin-II-induced decreases in effective renal plasma ERPF (Part 2); (5) To describe the relationship between plasma concentrations of eprosartan and inhibition of angiotensin-II-induced decreases in ERPF (Part 2); (6) To assess the onset of inhibitory effect of selected doses of eprosartan on angiotensin-II-induced decreases in ERPF).

FORMULATIONS:
Eprosartan 10 mg tablet, Lot # U-92054
Eprosartan 50 mg tablet, Lot # U-92055
Matching placebo tablet, Lot # U-92053

STUDY DESIGN:
Double-blind, randomized, single-dose, placebo-controlled, four-period crossover study conducted in three parts (Parts 1, 2, and 3) with washout period of seven days between the study sessions. Aminohippurate sodium (PAH) was administered over six hour interval and angiotensin II was administered over a four hour interval. During two study sessions of Part 1 PAH alone (without angiotensin II administration) was administered to assess the angiotensin II agonist effect of eprosartan compared to placebo. During the remainder of Part 1 and during Parts 2 and 3, PAH and angiotensin II were administered to assess the the changes in effective renal plasma flow (PAH clearance), blood pressure and pulse rate, and serum aldosterone concentrations at 0 to 3 hours and 24 to 27 hours after dosing (Part 1, Sessions 1 to 4), at 0 to 3 hours after dosing (Part 2 of the study), and at 12 to 15 hours (Part 1, Session 5 and Part 3 of the study) following administration of eprosartan or placebo. All subjects were maintained on high-salt diet throughout the study. Table 1 below summarises the treatment regiments. Blood samples were obtained for PAH, cortisol and aldosterone (5 ml) were obtained during Part 1(sessions 1 to 4) as follows: -1, 0 (predose), 1, 2, 3, 4, 23, 25, 26, 27, and 28 hours post dose (eprosartan or placebo); during Part 2 at -1, 0 (predose), 1, 2, and 3 hours post dose; and during Part 1 (session 5) and Part 3 at 10.75, 11, 12, 14, 15, and 16 hours following the evening dose of study medication. Blood samples (5 ml) for pharmacokinetic analysis were obtained in Part 2 at 0 (predose), 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 15, and 24 hours following administration of study medication and in Part 3

at 0 (predose), 0.5, 1, 1.5, 2, 3, 6, 10, 12, 15, and 20 hours following administration of study medication. Plasma samples were stored at -20°C until assayed for PAH, aldosterone, cortisol or eprosartan.

TREATMENT REGIMENS

			PAH		Angiotensin-II	
Part	Session	Study Medication$^{\phi}$	Start* (hrs)	Stop* (hrs)	Start* (hrs)	Stop* (hrs)
1	1 - 4§	A, B	-2 22	4 28	-1 23	3 27
		C, D	-2 22	4 28	Not given	
	5	E	10	16	11	15
2	1 - 4§	A, B, C, D, E, F, G	-2	4	-1	3
3	1 - 4§	A, B, C, D	10	16	11	15

* Infusion start and stop times relative to time of dosing with study medication

ϕ Study Medication: Part 1 - SK&F 108566 350 mg = A, C, E; Placebo = B, D
Part 2 - SK&F 108566: A= 10 mg, B= 30 mg, C= 50 mg, D= 70 mg, E= 100 mg, F= 200 mg; G = Placebo
Part 3 - SK&F 108566: A=50 mg, B=100 mg, C=350 mg; D = Placebo

§ Sequence of administration of study medication was double blind and randomized. Subjects received seven tablets, comprised of active drug and/or placebo, for each dose of study medication.

ASSAYS:

DATA ANALYSIS:
ERPF was estimated by calculation of the serum clearance of PAH (CL_{PAH}) using the following formula:

$$CL_{PAH}\ (ml/min) = \frac{\text{PAH Maintenance Dose (mg/min)}}{S_{PAH}\ (mg/ml)} = \frac{I_{PAH}\ (mg/ml) \cdot \text{Infusion Rate (ml/min)}}{S_{PAH}\ (mg/ml)}$$

where
S_{PAH} (mg/ml) = Serum PAH concentration
I_{PAH} (mg/ml) = Actual maintenance dose administered derived from the infusate concentration of PAH

Pharmacokinetic/Pharmacodynamic Analysis
A measure of the inhibitory effect of eprosartan on angiotensin II induced decreases in ERPF (ΔCL_{PAH}) was derived to express the change in CL_{PAH} associated with eprosartan relative to that associated with angiotesin II alone:

$$\Delta CL_{PAH,t} = 100\% \frac{(CL_{PAH,t} - CL_{PAH,0})}{(CL_{PAH,-1} - CL_{PAH,0})} \qquad [t = 1, 2, 3 \text{ hours post dosing})$$

The relationship between ΔCL_{PAH} and eprosartan plasma concentrations at 1, 2, and 3 hours post dose (Part 2 of the study) was explored using an inhibitory E_{max} model or inhibitory E_{max} mode which adjusted for baseline $\Delta CL_{PAH,t}$ (E_0) :

$$E = \Delta CL_{PAH,t} = \frac{E_{max} \cdot C}{IC_{50} + C} \quad \text{or} \quad E = \Delta CL_{PAH,t} = E_0 = \frac{E_{max} \cdot C}{IC_{50} + C}$$

where Emax = maximum inhibition of angiotensin II induced decrease in ERPF ,
IC_{50} = eprosartan plasma concentration associated with 50% Emax

The inhibitory effect of eprosartan on angiotensin II induced changes in ERPF relative to placebo (ΔCL^{pl}_{PAH}) for t=12, 13, 14 and 15 was computed as follows:

$$\Delta CL^{pl}_{PAH,t} = 100\% \frac{(CL_{PAH,t} - CL_{PAH,placebo})}{(CL_{PAH,placebo})}$$

RESULTS: Tables 1- 5 summarize the pharmacokinetic/pharmacodynamic data obtained from the study while Figures 1-9 show the individual plasma concentration-time profiles following the administration of eprosartan and Figures 10-12 show concentration-effect relationships.

Table 1. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Healthy Volunteers

PART 1

PARAMETER	DOSE (MG)					
	10	30	50	70	100	200
Cmax (ng/ml)	94.5 (38.8)	221.5 (96.6)	273.4 (142.8)	462.2 (324.5)	461.6 (135.5)	818.9 (471.1)
$AUC_{(0-t)}$ (ng*h/ml)	286 (125)	590 (335)	873 (723)	1165 (1000)	1182 (435)	2658 (1718)
Tmax (h)	1.94 (1.29)	1.88 (1.33)	1.38 (1.06)	1.31 (0.59)	1.56 (1.05)	1.88 (0.99)

Table 2. Mean (SD) Parameter Values for Eprosartan Following Oral Administration to Healthy Volunteers

PART 3

PARAMETER	DOSE (MG)		
	50	100	200
Cmax (ng/ml)	365.6 (182.2)	566.2 (319.0)	1195.2 (334.0)
$AUC_{(0-t)}$ (ng*h/ml)	1305 (964)	3242 (2564)	7983 (4266)
Tmax (h)	1.88 (0.85)	2.88 (2.10)	3.25 (1.89)

Table 3
PAH Infusion (Day 2)
Mean PAH Clearance and Regimen Comparisons
Part 1

TIME[1]	ID	MEAN REG_C	MEAN REG_D	DIFF	SED	90% LOWER LIMIT	90% UPPER LIMIT
9	C - D	653.97	608.97	45.00	41.94		
10	C - D	730.75	617.47	113.28	51.60		
11	C - D	785.44	620.08	165.36	52.38		
12	C - D	772.44	606.99	165.45	50.42		
13	C - D	724.28	637.62	86.66	89.58		

TIME	ID	MEAN REG_A	MEAN REG_D	DIFF	SED	95% LOWER LIMIT	95% UPPER LIMIT
9	A - D	422.33	608.97	-186.64	41.94		
10	A - D	548.61	617.47	-68.85	51.60		
11	A - D	610.41	620.08	-9.67	52.38		
12	A - D	639.72	606.99	32.73	50.42		
13	A - D	725.16	637.62	87.54	89.58		

TIME	ID	MEAN REG_B	MEAN REG_D	DIFF	SED	95% LOWER LIMIT	95% UPPER LIMIT
9	B - D	402.61	608.97	-206.36	41.94		
10	B - D	362.96	617.47	-254.51	51.60		
11	B - D	349.75	620.08	-270.34	52.38		
12	B - D	342.98	606.99	-264.01	50.42		
13	B - D	549.37	637.62	-88.26	89.58		

1. Actual time of day. PAH infusion 0700-1300; angiotensin-II infusion (regimens A, B and E only) 0800-1200; study medication administered at 0900 (regimens A,B,C,D) or 2100 the prior evening (regimen E)
2. Regimen key:

A: 350 mg of SK&F 108566 with PAH and Angiotensin-II infusions
B: placebo with PAH and angiotensin-II infusions
C: 350 mg of SK&F 108566 with PAH infusion
D: placebo with PAH infusion
E: 350 mg of SK&F 108566 (given 12 hours prior to infusions of PAH and angiotensin-II) with PAH and angiotensin-II infusions

Table3 (Continued)

PAH Infusion (Day 3)

Mean PAH Clearance and Regimen Comparisons

Part 1

TIME[1]	ID	MEAN REG_C	MEAN REG_D	DIFF	SED	90% LOWER LIMIT	90% UPPER LIMIT
8	C - D	633.93	660.83	-26.90	56.52		
9	C - D	651.38	634.15	17.23	37.24		
10	C - D	635.30	642.28	-6.99	37.94		
11	C - D	624.97	643.10	-18.13	38.09		
12	C - D	642.82	617.36	25.46	33.58		
13	C - D	653.01	658.69	-5.68	49.32		

TIME	ID	MEAN REG_A	MEAN REG_D	DIFF	SED	95% LOWER LIMIT	95% UPPER LIMIT
8	A - D	652.07	660.83	-8.76	56.52		
9	A - D	439.48	634.15	-194.67	37.24		
10	A - D	395.68	642.28	-246.60	37.94		
11	A - D	377.91	643.10	-265.20	38.09		
12	A - D	378.28	617.36	-239.08	33.58		
13	A - D	643.00	658.69	-15.69	49.32		

TIME	ID	MEAN REG_B	MEAN REG_D	DIFF	SED	95% LOWER LIMIT	95% UPPER LIMIT
8	B - D	654.92	660.83	-5.91	56.52		
9	B - D	403.31	634.15	-230.83	37.24		
10	B - D	364.37	642.28	-277.91	37.94		
11	B - D	349.05	643.10	-294.05	38.09		
12	B - D	349.84	617.36	-267.52	33.58		
13	B - D	628.77	658.69	-29.92	49.32		

TIME	ID	MEAN REG_E	MEAN REG_D	DIFF	SED	95% LOWER LIMIT	95% UPPER LIMIT
8	E - D	697.67	660.83	36.84	56.52		
9	E - D	564.87	634.15	-69.28	37.24		
10	E - D	546.35	642.28	-95.93	37.94		
11	E - D	516.17	643.10	-126.93	38.09		
12	E - D	487.73	617.36	-129.63	33.58		
13	E - D	680.59	658.69	21.90	49.32		

1. Actual time of day. PAH infusion 0700-1300; angiotensin-II infusion (regimens A, B and E only) 0800-1200; study medication administered at 0900 (regimens A,B,C,D) or 2100 the prior evening (regimen E)
2. Regimen key:
   - A: 350 mg of SK&F 108566 with PAH and Angiotensin-II infusions
   - B: placebo with PAH and angiotensin-II infusions
   - C: 350 mg of SK&F 108566 with PAH infusion
   - D: placebo with PAH infusion
   - E: 350 mg of SK&F 108566 (given 12 hours prior to infusions of PAH and angiotensin-II) with PAH and angiotensin-II infusions

Table 4
3 Hours After Dosing
Mean PAH Clearance and Regimen Comparisons
Part 2

Regimen Comparison	Simultaneous 95% Lower Confidence Limit	Difference Between Means	Simultaneous 95% Upper Confidence Limit
F - E		58.69	
F - D		118.59	
F - C		210.74	
F - B		143.20	
F - A		186.55	
F - G		342.86	
E - D		59.90	
E - C		152.04	
E - B		84.51	
E - A		127.86	
E - G		284.16	
D - C		92.14	
D - B		24.61	
D - A		67.96	
D - G		224.26	
C - B		-67.54	
C - A		-24.18	
C - G		132.12	
B - A		43.35	
B - G		199.66	
A - G		156.30	

1. Regimen key:

A: SK&F 108566 - 10 mg
B: SK&F 108566 - 30 mg
C: SK&F 108566 - 50 mg
D: SK&F 108566 - 70 mg
E: SK&F 108566 - 100 mg
F: SK&F 108566 - 200 mg
G: Placebo

2. Comparisons significant at the 0.05 level are indicated by '***' based on Tukey's procedure.

Table 5

Mean PAH Clearance and Regimen Comparisons
Part 3

TIME[2]	ID[1]	MEAN REG_	MEAN REG_P	DIFF	SED	95% LOWER LIMIT	95% UPPER LIMIT
9	A - D	436.80	362.83	73.97	36.15		
9	B - D	458.68	362.83	95.86	36.15		
9	C - D	515.90	362.83	153.07	36.15		

TIME[2]	ID[1]	MEAN REG_	MEAN REG_P	DIFF	SED	95% LOWER LIMIT	95% UPPER LIMIT
12	A - D	343.79	316.95	26.83	37.88		
12	B - D	420.14	316.95	103.19	37.88		
12	C - D	422.72	316.95	105.77	37.88		

1. Regimen key:

A: SK&F 108566 - 50 mg
B: SK&F 108566 - 100 mg
C: SK&F 108566 - 350 mg
D: Placebo

2. Actual time of day following dosing. Study medication is administered at 21.00 on the previous night.

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CONCLUSIONS: The results obtained from the study show that the concentration-effect relationship was not well characterized due to insufficient number of data points resulting from limited number of subjects, short duration of angiotensin II infusions, and small number of plasma concentration sampling points. Eprosartan inhibited the decrease in ERPF (measured as PAH clearance) induced by exogenous angiotensin II in a dose-related fashion. The effect of eprosartan was maximum at one to two hours after dosing (Part 2 of the study), was maintained for at least 15 hours but was absent at 24 hours after dosing (Part 3 of the study). AUC and Cmax of eprosartan increased with dose (10 to 350 mg) in a nonproportional manner.

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IN VITRO METABOLIC STUDIES

PROTOCOL NUMBER: D940634/108566 VOLUME: 1.077 PAGES: 2 - 36

INVESTIGATOR AND LOCATION: ANDREW D. AYTON AND RANDALL S. SOZIO
SMITHKLINE BEECHAM PHARMACEUTICALS
KING OF PRUSSIA, PA, USA.

STUDY DATES: August 1 to September 11, 1994.

OBJECTIVE: To investigate the inhibitory potential of eprosartan (SK&F 108566) on the human cytochrome P450 enzymes and to provide information which may assist in the prediction of potential intereactions between eprosartan and specific drugs *in vivo*.

PROCEDURES:

Assays for ethoxyresorufin O-dealkylase (CYP1A), caffeine N3-demethylase (CYP1A2), coumarin 7-hydroxylase (CYP2A6), tolbutamide hydroxylase (CYP2C8-9) S-mephentoin 4-hydroxylase (CYP2C19), (+/-)-bufuralol 1'-hydroxylase (CYP2D6), chlorzoxazone 6-hydroxylase (CYP2E), and cyclosporine oxidase (CYP3A4) were performed by incubations with microsomes from three human livers. Aliquots of eprosartan solution (50 mM) in phosphate buffer (pH 7.4) were added to incubates to give final concentrations of 100, 10, 0.1 and 0 μM. The percentage inhibition of each enzyme was determined by comparison to concurrent control activities.

Additional incubations were performed to investigate the potential of eprosartan as a mechanism-based inhibitor of cytochrome P450 and to provide information on the inhibitory potential of any microsomal oxidative metabolites of eprosartan produced during a 10 minute pre-incubation period.

RESULTS: Tables 1-7 and Figure 1 summarise the results obtained from the study.

Table A1 The effect of SK&F 108566 on ethoxyresorufin O-dealkylase activity in human liver microsomes H31, H53 and H54.

SK&F 108566 (uM)	Ethoxyresorufin O-dealkylase (nmol.hr.$^{-1}$mg protein^{-1})		
	H31	H53	H54
0+	8.26 (100.0)	1.25 (100.0)	1.15 (100.0)
100+	9.45 (114.5)	0.82 (65.5)	1.05 (91.5)
0*	5.08 (100.0)	0.60 (100.0)	0.75 (100.0)
100*	5.04 (99.1)	0.55 (92.5)	0.75 (100.2)

Values in brackets represent % control activity

+ SK&F 108566 was pre-incubated with substrate, microsomes and buffer for 2 minutes, before adding prewarmed cofactor to start the reaction.

* SK&F 108566 was pre-incubated with microsomes, cofactor and buffer for 10 minutes, before adding prewarmed substrate to start the reaction.

Table A2 The effect of SK&F 108566 on coumarin 7-hydroxylase activity in human liver microsomes H31, H53 and H54.

SK&F 108566 (uM)	Coumarin 7-hydroxylase (nmole.hr.$^{-1}$mg protein^{-1})		
	H31	H53	H54
0+	20.89 (100.0)	4.18 (100.0)	13.60 (100.0)
100+	12.87 (61.6)	3.77 (90.3)	10.86 (79.9)
0*	13.05 (100.0)	2.14 (100.0)	9.70 (100.0)
100*	12.61 (96.6)	2.31 (108.2)	9.47 (97.6)

Values in brackets represent % control activity.

+ SK&F 108566 was pre-incubated with substrate, microsomes and buffer for 2 minutes, before adding prewarmed cofactor to start the reaction.

* SK&F 108566 was pre-incubated with microsomes, cofactor and buffer for 10 minutes, before adding prewarmed substrate to start the reaction.

Table A3 The effect of SK&F 108566 on tolbutamide hydroxylase activity in human liver microsomes H31, H53 and H54.

SK&F 108566 (uM)	Tolbutamide hydroxylase (nmol.hr^{-1}.mg protein^{-1})		
	H31	H53	H54
0+	50.53 (100.0)	39.85 (100.0)	40.90 (100.0)
0.1+	49.34 (97.6)	42.79 (107.4)	39.97 (97.7)
1+	47.48 (94.0)	41.18 (103.3)	42.82 (104.7)
10+	47.18 (93.4)	40.52 (101.7)	41.64 (101.8)
100+	41.59 (82.3)	36.05 (90.5)	35.39 (86.5)
0*	28.00 (100.0)	28.91 (100.0)	25.61 (100.0)
100*	29.17 (104.2)	29.36 (101.6)	33.15 (129.5)

Values in brackets represent % control activity.

Values are a mean of duplicate determinations

+ SK&F 108566 was pre-incubated with substrate, microsomes and buffer for 5 minutes, before adding prewarmed cofactor to start the reaction.

* SK&F 108566 was pre-incubated with microsomes, cofactor and buffer for 10 minutes, before adding prewarmed substrate to start the reaction.

Table A4 The effect of SK&F 108566 on S-mephenytoin 4-hydroxylase activity in human liver microsomes H31, H53 and H54.

SK&F 108566 (uM)	S-mephenytoin 4-hydroxylase (nmol.hr^{-1}.mg protein^{-1})		
	H31	H53	H54
0+	8.64 (100.0)	2.79 (100.0)	1.06 (100.0)
0.1+	8.70 (100.7)	2.82 (101.0)	0.99 (93.8)
1+	8.38 (97.0)	2.77 (99.3)	1.02 (96.7)
10+	8.30 (96.1)	2.74 (98.3)	0.99 (93.7)
100+	8.13 (94.1)	2.65 (94.8)	0.92 (87.0)
0*	6.01 (100.0)	2.38 (100.0)	0.72 (100.0)
100*	5.97 (99.3)	2.19 (91.9)	0.70 (100.0)

Values in brackets represent % control activity.

Values are a mean of duplicate determinations

+ SK&F 108566 was pre-incubated with substrate, microsomes and buffer for 5 minutes, before adding prewarmed cofactor to start the reaction.

* SK&F 108566 was pre-incubated with microsomes, cofactor and buffer for 10 minutes, before adding prewarmed substrate to start the reaction.

Table A5 The effect of SK&F 108566 on (+/-)-bufuralol 1'hydroxylation activity in human liver microsomes H31, H53 and H54.

SK&F 108566 (uM)	(+/-)-Bufuralol 1'-hydroxylase (nmol.hr^{-1}.mg protein^{-1})		
	H31	H53	H54
0+	28.46 (100.0)	7.28 (100.0)	2.12 (100.0)
0.1+	28.41 (99.8)	7.17 (98.5)	2.02 (95.6)
1+	31.74 (111.5)	7.15 (98.2)	1.99 (94.2)
10+	28.99 (101.9)	7.24 (99.5)	2.14 (101.1)
100+	30.55 (107.3)	6.24 (85.8)	1.74 (82.2)
0*	19.75 (100.0)	4.74 (100.0)	2.25 (100.0)
100*	19.02 (96.3)	4.09 (86.4)	2.28 (101.4)

Values in brackets represent % control activity.

+ SK&F 108566 was pre-incubated with substrate, microsomes and buffer for 5 minutes, before adding prewarmed cofactor to start the reaction.

* SK&F 108566 was pre-incubated with microsomes, cofactor and buffer for 10 minutes, before adding prewarmed substrate to start the reaction.

Table A6 The effect of SK&F 108566 on chlorzoxazone 6-hydroxylase activity in human liver microsomes H31, H53 and H54.

SK&F 108566 (uM)	Chlorzoxazone 6-hydroxylase (nmol.hr.min^{-1}.mg protein^{-1})		
	H31	H53	H54
0+	107.43 (100.0)	98.09 (100.0)	75.62 (100.0)
0.1+	107.69 (100.2)	93.76 (95.6)	74.31 (98.3)
1+	97.92 (91.2)	92.30 (94.1)	72.36 (95.7)
10+	91.07 (84.8)	91.51 (93.3)	61.33 (81.1)
100+	96.22 (89.6)	78.38 (79.9)	73.42 (97.1)
0*	85.45 (100.0)	97.78 (100.0)	66.46 (100.0)
100*	91.22 (106.8)	94.50 (96.7)	57.78 (86.9)

Values in brackets represent % control activity.

Values are a mean of duplicate determinations

+ SK&F 108566 was pre-incubated with substrate, microsomes and buffer for 5 minutes, before adding prewarmed cofactor to start the reaction.

* SK&F 108566 was pre-incubated with microsomes, cofactor and buffer for 10 minutes, before adding prewarmed substrate to start the reaction.

Table A7 The effect of SK&F 108566 on cyclosporine oxidase activity in human liver microsomes H31, H53 and H54.

SK&F 108566 (uM)	Cyclosporine oxidase (nmol.hr^{-1}mg protein^{-1})		
	H31	H53	H54
0+	4.02 (100.0)	0.75 (100.0)	0.85 (100.0)
0.1+	4.09 (101.7)	0.78 (104.4)	1.04 (122.3)
1+	3.93 (97.8)	0.75 (100.4)	0.97 (114.2)
10+	3.79 (94.4)	0.75 (99.5)	1.04 (122.7)
100+	3.53 (87.7)	0.69 (91.9)	0.89 (104.4)
0*	4.05 (100.0)	0.65 (100.0)	1.10 (100.0)
100*	3.82 (94.3)	0.68 (104.7)	0.97 (88.4)

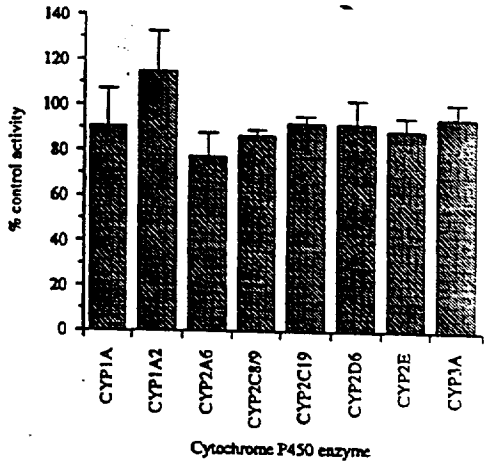
Values in brackets represent % control activity.

Values are a mean of duplicate determinations

+ SK&F 108566 was pre-incubated with substrate, microsomes and buffer for 5 minutes, before adding prewarmed cofactor to start the reaction.

* SK&F 108566 was pre-incubated with microsomes, cofactor and buffer for 10 minutes, before adding prewarmed substrate to start the reaction.

Figure 1. The inhibitory potential of SK&F 108566 (100 uM) against cytochrome P450 related activities in human liver microsomes+



Data is presented as mean value with SEM for three human livers. The raw data used to construct this figure are presented in Appendix A.

+ Only data using 100 uM are displayed graphically. Data using additional lower concentrations are included in Appendix A.

CONCLUSIONS: The results obtained from the study showed that eprosartan did not cause significant inhibition of CYP1A, CYP2A6, CYP2C9/8, CYP2C19, CP2E and CYP3A and there is no indication that oxidative metabolism of eprosartan would produce a metabolite with significant potential to inhibit cytochrome P450 enzymes.

IN VITRO PROTEIN BINDING

PROTOCOL NUMBER: D92034/108566 VOLUME:1.077 PAGES: 37 - 67

INVESTIGATOR AND LOCATION: MICHAEL CARBONARO
SMITHKLINE BEECHAM PHARMACEUTICALS
UPPER MERION, USA.

STUDY DATES: March 4 to April 17, 1992.

PROCEDURES:

Protein Binding: Pooled rat, dog, or human plasma (12 ml) was spiked with 100 μl of ethanolic stock solution of ^{3}H-eprosartan (100 μg(acid)/200 μCi/ml) to produce final plasma concentration of approximately 0.83 μg(acid)/1.66 μCi/ml. Three replicate aliquots (800 μl) of the spiked plasma were dialyzed in Spetra/Por semimicro dialysis cell at 37°C in and the following time points: 1, 2, 4, and 6 hours. Radioactivity was determined using a scintillation counter.

The concentration dependence of the plasma protein binding was investigated at plasma concentrations of 1000 (rat and dog only), 100, 10, 1, 0.1, and 0.01 μg(acid)/ml.

Blood Cell Partitioning: Blood was collected from rats, dogs and human volunteers (n=4 males). ^{3}H-eprosartan at concentrations of 100 (rat and dog only), 10, 1, 0.1, 0.01 and 0.001 mg(acid)/ml were diluted 1:100 into 3 ml of blood, resulting in blood concentrations of 1000 (rat and dog), 100, 10, 1, 0.1, and 0.01 μg(acid)/ml. Spiked blood was incubated at 37°C for 1 hour and radioactivity was quantitated (triplicate aliquots of 25 μl) in blood and plasma. Radioactivity was determined using a scintillation counter.

RESULTS: Tables 1-6 and Figures 1-4 summarise the results obtained from the study.

Appendix Table 1

Protein Binding of ^{3}H-SK&F 108566 in Rat Plasma[a]
Effect of Incubation Time
Results of Individual Incubations

Replicate Number	Time (hrs)	Equilibrium Plasma Conc. (D_{Te}) (µg/ml)	Equilibrium Buffer Conc. (D_F) (µg/ml)	V_{pe}/V_{pi}[b]	Fraction Bound X 100 (%)	Fraction Free X 100 (%)
1	1	0.7864	0.0218	0.9086	96.96	3.04
2	1	0.7939	0.0218	1.0119	97.29	2.71
3	1	0.7916	0.0220	1.0329	97.31	2.69
1	2	0.7554	0.0229	0.9324	96.76	3.24
2	2	0.7799	0.0237	1.0486	97.10	2.90
3	2	0.7848	0.0242	1.0148	96.96	3.04
1	4	0.7002	0.0240	1.1179	96.92	3.08
2	4	0.7089	0.0260	1.1074	96.68	3.32
3	4	0.7107	0.0256	1.0955	96.70	3.30
1	6	0.6968	0.0259	1.0825	96.56	3.44
2	6	0.7252	0.0254	1.1736	97.00	3.00
3	6	0.7240	0.0269	1.1079	96.63	3.37

[a] Replicate analyses of incubations of plasma pooled from 10 rats.
[b] Volume of plasma at equilibrium divided by the initial plasma volume.

Appendix Table 2

Protein Binding of ^{3}H-SK&F 108566 in Dog Plasma[a]
Effect of Incubation Time
Results of Individual Incubations

Replicate Number	Time (hrs)	Equilibrium Plasma Conc. (D_{Te}) (µg/ml)	Equilibrium Buffer Conc. (D_F) (µg/ml)	V_{pe}/V_{pi}[b]	Fraction Bound X 100 (%)	Fraction Free X 100 (%)
1	1	0.8556	0.0576	1.0154	93.36	6.64
2	1	0.8741	0.0675	1.0051	92.31	7.69
3	1	0.8774	0.0581	1.0188	93.49	6.51
1	2	0.8262	0.0819	1.0169	90.24	9.76
2	2	0.8288	0.0837	1.0148	90.03	9.97
3	2	0.8410	0.0865	1.0128	89.83	10.17
1	4	0.7705	0.0993	1.0124	87.25	12.75
2	4	0.7746	0.1028	1.0372	87.14	12.86
3	4	0.7952	0.1032	1.0260	87.31	12.69
1	6	0.8273	0.1134	1.0530	86.89	13.11
2	6	0.8305	0.1142	1.0431	86.74	13.26
3	6	0.8173	0.1140	1.0496	86.62	13.38

[a] Replicate analyses of incubations of plasma pooled from (n≥4) dogs.
[b] Volume of plasma at equilibrium divided by the initial plasma volume.

Appendix Table 3

Protein Binding of ^{3}H-SK&F 108566 in Human Plasma[a]
Effect of Incubation Time
Results of Individual Incubations

Replicate Number	Time (hrs)	Equilibrium Plasma Conc. (D_{Te}) (µg/ml)	Equilibrium Buffer Conc. (D_F) (µg/ml)	V_{pe}/V_{pl}[b]	Fraction Bound X 100 (%)	Fraction Free X 100 (%)
1	1	0.9072	0.0105	1.0206	98.87	1.13
2	1	0.9080	0.0109	1.0161	98.82	1.18
3	1	0.9199	0.0109	1.0049	98.82	1.18
1	2	0.8919	0.0146	1.0362	98.42	1.58
2	2	0.9024	0.0143	1.0213	98.45	1.55
3	2	0.8975	0.0142	1.0271	98.46	1.54
1	4	0.8784	0.0163	1.0404	98.22	1.78
2	4	0.8790	0.0165	1.0399	98.19	1.81
3	4	0.8816	0.0168	1.0446	98.17	1.83
1	6	0.8559	0.0164	1.0633	98.20	1.80
2	6	0.8720	0.0166	1.0689	98.22	1.78
3	6	0.8816	0.0167	1.0536	98.20	1.80

[a] Replicate analyses of incubations of plasma from a single male volunteer.
[b] Volume of plasma at equilibrium divided by the initial plasma volume.

Appendix Table 4

Blood Cell Association of ^{3}H-SK&F 108566 in Rat Blood[a]
Effect of Incubation Time
Results of Individual Incubations

Replicate Number	Time (hrs)	C_B (µg/ml)	C_P (µg/ml)	C_B/C_P
1	0.25	0.9098	1.381	0.66
2	0.25	0.8455	1.383	0.61
3	0.25	0.8624	1.386	0.62
1	0.5	0.9194	1.414	0.65
2	0.5	0.9158	1.337	0.69
3	0.5	0.9078	1.369	0.66
1	1	0.8644	1.408	0.61
2	1	0.8904	1.411	0.63
3	1	0.9094	1.359	0.67
1	2	0.8866	1.346	0.66
2	2	0.8892	1.319	0.67
3	2	0.8991	1.381	0.65

[a] Replicate analyses of incubations of rat blood pooled from 10 rats.

Appendix Table 5

Blood Cell Association of ^{3}H-SK&F 108566 in Dog Blood[a]
Effect of Incubation Time
Results of Individual Incubations

Replicate Number	Time (hrs)	C_B (µg/ml)	C_P (µg/ml)	C_B/C_P
1	0.25	0.7905	1.399	0.57
2	0.25	0.9118	1.389	0.66
3	0.25	0.8652	1.398	0.62
1	0.5	0.9113	1.387	0.66
2	0.5	0.8523	1.412	0.60
3	0.5	0.8619	1.375	0.63
1	1	0.9448	1.364	0.69
2	1	0.9483	1.434	0.66
3	1	0.9565	1.423	0.67
1	2	0.9043	1.361	0.66
2	2	0.9162	1.345	0.68
3	2	0.9193	1.342	0.69

[a] Replicate analyses of incubations from blood pooled from (n≥2) dogs.

Appendix Table 6

Blood Cell Association of ^{3}H-SK&F 108566 in Human Blood[a]
Effect of Incubation Time
Results of Individual Incubations

Replicate Number	Time (hrs)	C_B (µg/ml)	C_P (µg/ml)	C_B/C_P
1	0.25	0.9136	0.9536	0.96
2	0.25	0.9005	1.192	0.76
3	0.25	0.8959	1.201	0.75
1	0.5	0.9031	1.242	0.73
2	0.5	0.9011	1.236	0.73
3	0.5	0.8859	1.189	0.75
1	1	0.9153	1.215	0.75
2	1	0.8749	1.172	0.75
3	1	0.8782	1.143	0.77
1	2	0.9015	1.173	0.77
2	2	0.8578	1.075	0.80
3	2	0.8564	1.208	0.71

[a] Replicate analyses of incubations of blood from a single male volunteer.

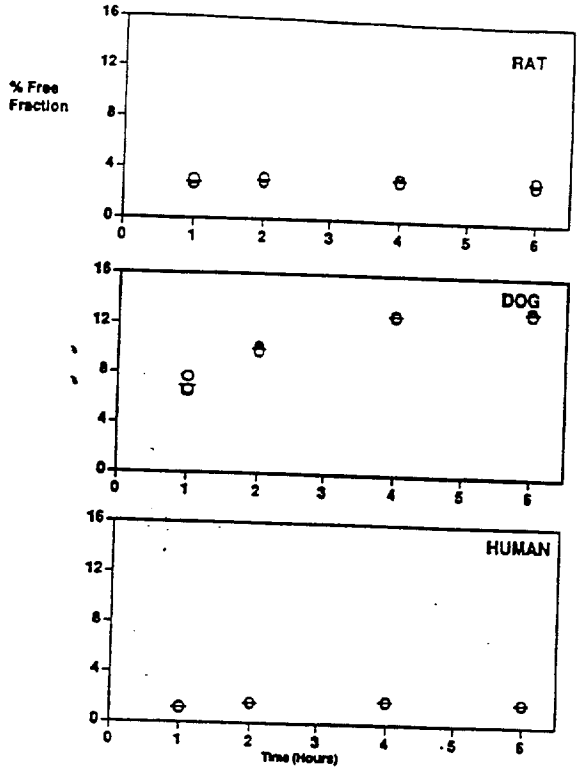


Figure 1. Effect of incubation time on the free (unbound) fraction of SK&F 108566 in plasma.

Data points displayed are replicate analyses of pooled plasma from rat, dog and human male volunteers. The blood concentration of ^{3}H-SK&F108566 was approximately 1 ug(acid)/mL

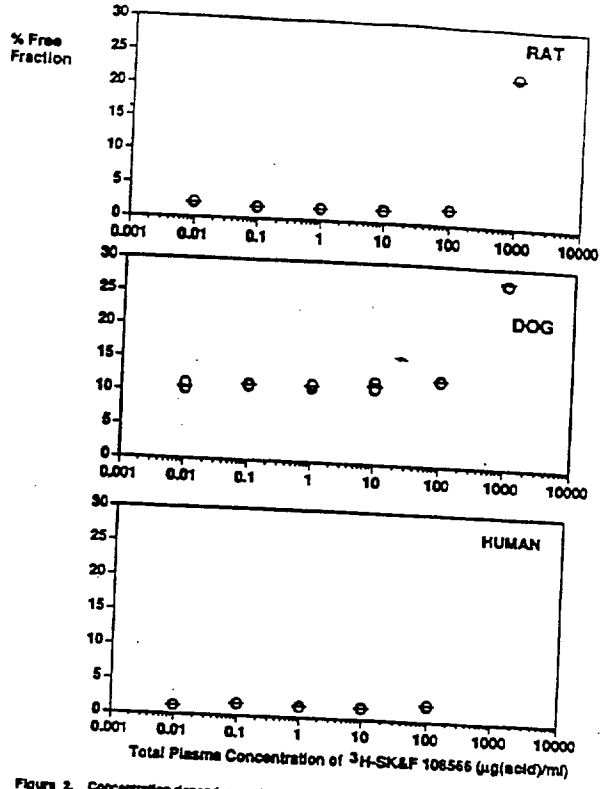


Figure 2. Concentration dependence of the plasma protein binding of ^{3}H-SK&F 108566.

Data points displayed are analyses of pooled rat, dog and human plasma samples.

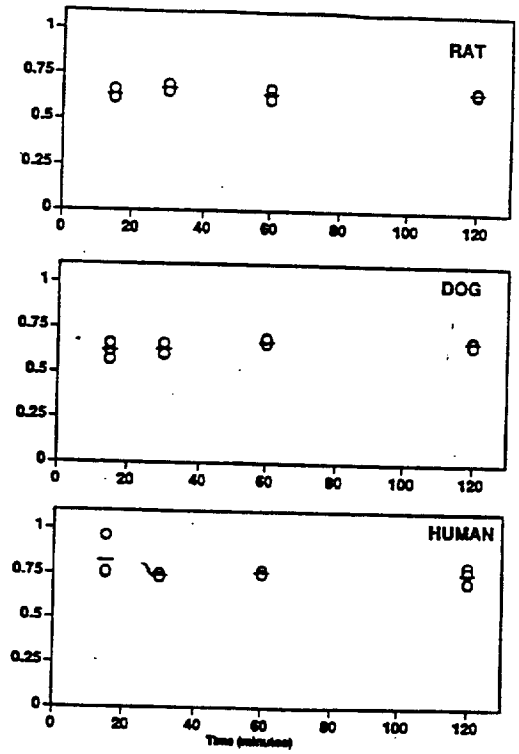


Figure 3. Effect of incubation time on the blood/plasma ratio of ^{3}H-SK&F 108566.

Data points displayed are replicate analyses of pooled blood from rat, dog and human male volunteers. The blood concentration of ^{3}H-SK&F108566 was approximately 1 ug(acid)/ml.

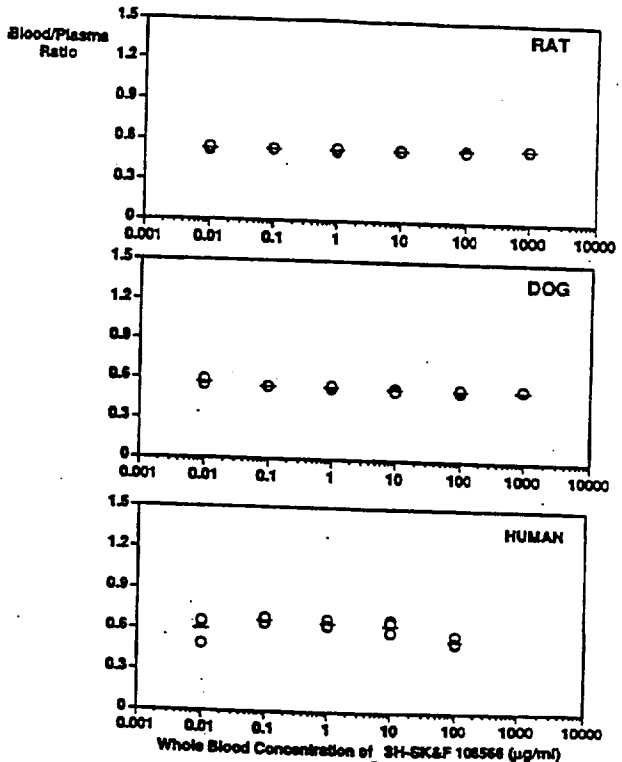


Figure 4. Blood/Plasma Ratio of ^{3}H-SK&F 108566.

Data points displayed are analyses of pooled rat, dog and human blood samples from normal male volunteers.

CONCLUSIONS: The data obtained from the study show that;

(i) Plasma protein binding of eprosartan was extensive but varied between species (% free fraction in rat, dog and human were 1.9, 11.1, and 1.6% respectively at 10 μg(acid)/ml)

(ii) The free fraction in all species remained approximately linear up to 10 μg(acid)/ml but increased in a non-linear fraction above at concentrations above 100 μg(acid)/ml.

(iii) The blood/plasma ratio remained constant for all three species and was approximately 0.54 in rat and dog blood (0.01 - 1000 μg(acid)/ml) and approximately 0.62 in human blood (0.01 - 100 μg(acid)/ml) thus suggesting little association with blood cells..

RENAL IMPAIRMENT STUDY

STUDY 108566/ 099 VOLUME: 21.1

INVESTIGATOR AND LOCATION: BERNARD ILSON, M.D.
SMITHKLINE BEECHAM CLIN. RES. UNIT
PHILADELPHIA, USA.

STUDY DATE: October 22 to December 4, 1996.

OBJECTIVES: (1) To compare the pharmacokinetics of eprosartan in hemodialysis-dependent patients with end stage renal disease between hemodialysis treatments (non-dialysis day) relative to age- and weight-matched volunteers with normal renal function; (2) to compare protein binding characteristics of eprosartan in hemodialysis-dependent patients with end stage renal disease between hemodialysis treatments (non-dialysis day) relative to age- and weight-matched volunteers with normal renal function; (3) to determine the hemodialysis clearance and protein binding characteristics of eprosartan during dialysis (dialysis day); (4) to assess the safety and tolerability of eprosartan in subjects with end stage renal disease maintained on hemodialysis.

FORMULATIONS:
Eprosartan 400 mg tablet, Lot numbers U-95113.

STUDY DESIGN:
An open label, parallel group, single dose study in 9 hemodialysis-dependent patients with end stage renal disease and 10 volunteers with normal renal function. Each subject received 400 mg oral dose of eprosartan each study day. Hemodialysis patients completed two study days: a non-dialysis day and a dialysis day while volunteers with normal renal function completed only one study day. In volunteers with normal renal function and hemodialysis patients (non-dialysis day) blood samples (5 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours following dosing. In hemodialysis patients on the dialysis day blood samples (5 ml) were collected at 0 (predose), 0.5, 1, 1.5, 2, 3 (immediately pre-dailysis), 7.5, 8, 9, 10, 12, 18, and 24 hours following dosing. Pre-dialyzer (arterial line) and post-dialyzer (venous line) blood samples were obtained at 4, 5, 6, and 7 hours after drug administration. Dialyzate effluent was collected prior to the start of hemodialysis and then in the intervals 0-1, 1-2, 2-3, and 3-4 hours after initiation of hemodialysis. In addition, blood samples (7 ml) were obtained post-dosing at 3 and 7 hours for the determination of *ex vivo* (post-dose samples) plasma protein binding of eprosartan. Plasma and urine samples were stored at -20°C until assayed for eprosartan.

ASSAYS:

The assay has been validated over the range of eprosartan plasma concentrations observed in the study.

DATA ANALYSIS: AUC, Cmax, Tmax, %fu, and $t_{1/2}$ were calculated.

RESULTS: Tables 1- 3 summarise the pharmacokinetic data obtained from the study while Figures 1 and 2 show the plasma concentration-time profiles following the administration of eprosartan to the two groups of subjects..

Table 1 Arithmetic Mean (SD) Pharmacokinetic Parameter Values for Eprosartan and Statistical Results in Normals and Hemodialysis Patients (Non-Dialysis Day)

Parameter	Non-Dialysis Day (n = 9)	Normals (n = 10)	Point Estimate (95% CI)
AUC(0-t) (ng·h/mL)	15075 (17375)	6672 (3071)	1.60 [a] (0.78, 3.25)
Cmax (ng/mL)	2180 (1626)	1780 (585)	1.01 [a] (0.60, 1.71)
Tmax [c] (h)	1.55 (1.03 - 4.02)	1.49 (1.02 - 3.05)	0.45 h [b] (-0.45, 1.52 h)

[a] data presented as the ratio of the geometric means (Non-Dialysis Day:Normal)
[b] data presented as the median difference (Non-Dialysis Day-Normal)
[c] data presented as median (range)

Table 2 Arithmetic Mean (SD) Pharmacokinetic Parameter Values for Unbound Eprosartan and Statistical Results in Normals and Hemodialysis Patients (Non-Dialysis Day).

Parameter	Non-Dialysis Day (n = 9)	Normal (n = 10)	Point Estimate (95 % CI)
%fu	3.02 (0.64)	1.74 (0.17)	1.27 [a] (0.83, 1.72)
Unbound AUC (ng·h/mL)	506 (716)	116 (55)	2.72 [b] (1.28, 5.79)
Unbound Cmax (ng/mL)	68.6 (64.9)	31.0 (10.7)	1.73 [b] (0.99, 2.99)

[a] data presented as the difference in arithmetic means (Non-Dialysis Day-Normal)
[b] data presented as the ratio of the geometric means (Non-Dialysis Day:Normal)

Table 3 Arithmetic Mean (SD) Pharmacokinetic Parameter Values for Eprosartan in Hemodialysis Patients

	AUC(0-t) (ng·h/mL)	Cmax (ng/mL)	Tmax [a] (h)	% fu (3 h)	% fu (7 h)	CLhd (mL/min)
Dialysis Day (n = 8)	20593 (17423)	2900 (1520)	3.98 (1.98 - 7.50)	3.19 (0.78)	2.01 (0.43)	11.22 (7.10)
Non-Dialysis Day (n = 9)*	15075 (17375)	2180 (1626)	1.55 (1.03 - 4.02)	2.81 (0.83)	3.26 (0.72)	—

[a] data presented as median (range)
Source: Tables 10.11-10.15, 10.18
*Subject 002 did not have a reportable %fu value at the 7 hour sample timepoint on the Non-Dialysis Day

Figure 1

Mean Plasma Eprosartan Concentration-Time Profiles Following Oral Administration of 400 mg Eprosartan

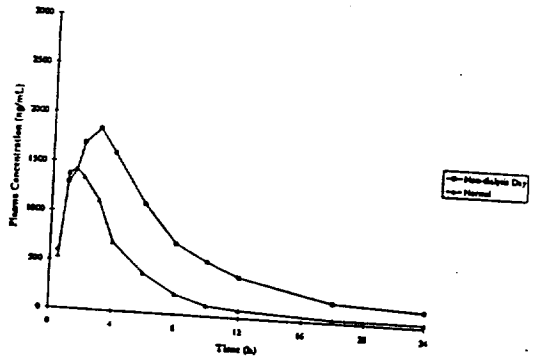
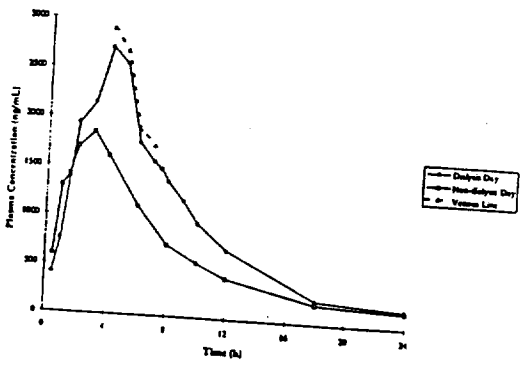


Figure 2

Mean Plasma Eprosartan Concentration-Time Profiles Following Oral Administration of 400 mg Eprosartan



On dialysis days, patient underwent dialysis from 3 to 7 hours post-dose

CONCLUSIONS: The data obtained from the study showed that: (i) AUC increased more than 2-fold and Cmax increased by 22% in hemodialysis patients when compared to healthy volunteers; (ii) the %fraction unbound increased by 74% in hemodialysis patients when compared to healthy volunteers; (iii) unbound AUC increased more than 4-fold and unbound Cmax increased more than 2-fold in hemodialysis patients when compared to healthy volunteers; (iv) compared to non-dialysis day, AUC and Cmax increased by about 35% and $T_{1/2}$ increased 2-fold on dialysis day; (v) compared to pre-hemodialysis sample, the observed %fraction unbound was lower (about 40% decrease) when assessed immediately post-hemodialysis (7 hours post-dose); (vi) CL_{hd} of eprosartan determined by dialysate measurement was 11.22 ml/min; (vi) the pharmacokinetics of eprosartan in hemodialysis patients were highly variable compared to healthy volunteers.

DRUG PRODUCT DISSOLUTION TESTING

Table 1 Dissolution Data for Batch U95110, 300 mg Tablet, Formula Code AH, used in Protocols 089 and 092, Dissolution Method PDMU-0154

Tablet	Dissolution (percent dissolved)			
	15 minutes	30 minutes	45 minutes	60 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
mean	*98*	*100*	*100*	*100*

Table 2 Dissolution Data for Batch U94175, 200 mg Tablet, Formula Code AG, used in Protocol 034, Dissolution Method PDMU-0085

Tablet	Dissolution (percent dissolved)			
	15 minutes	30 minutes	45 minutes	60 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
mean	*90*	*95*	*96*	*96*

Table 3 Dissolution Data for Batch U95111, 400 mg Tablet, Formula Code AJ, used in Protocol 035, Dissolution Method PDMU-0154

Tablet	Dissolution (percent dissolved)			
	15 minutes	30 minutes	45 minutes	60 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
mean	*98*	*100*	*100*	*101*

Table 4 Dissolution Data for Batch U94190, 200 mg Tablet, Formula Code AG, used in Protocols 035 and 092, Dissolution Method PDMU-0085

Tablet	Dissolution (percent dissolved)			
	15 minutes	30 minutes	45 minutes	60 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
mean	*92*	*96*	*97*	*97*

Table 5 Dissolution Data for Batch U93174, 100 mg tablet, Formula Code G, used in Protocol 018, Dissolution Method PDMU-0085

Tablet	Dissolution (percent dissolved)				
	5 minutes	10 minutes	15 minutes	30 minutes	45 minutes
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
mean	*56*	*71*	*80*	*91*	*95*

Table 6 Dissolution Data for Batch U93180, 50 mg tablet, Formula Code H, used in Protocol 018, Dissolution Method PDMU-0085

Tablet	Dissolution (percent dissolved)			
	10 minutes	15 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
mean	*59*	*70*	*86*	*93*

Table 7 Dissolution Data for Batch U93235, 100 mg Tablet, Formula Code L, used in Protocol 035, Dissolution Method PDMU-0085

Tablet	Dissolution (percent dissolved)			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
mean	*79*	*94*	*98*	*100*

Table 8 Dissolution Data for Batch U94068, 100 mg Tablet, Formula Code AB, used in Protocols 034 and 089, Dissolution Method PDMU-0085

Tablet	Dissolution (percent dissolved)			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
mean	*73*	*93*	*98*	*99*

Figure 1

Dissolution Profiles in pH 7.5 Phosphate Buffer of Eprosartan Tablets Used in Clinical Study 089

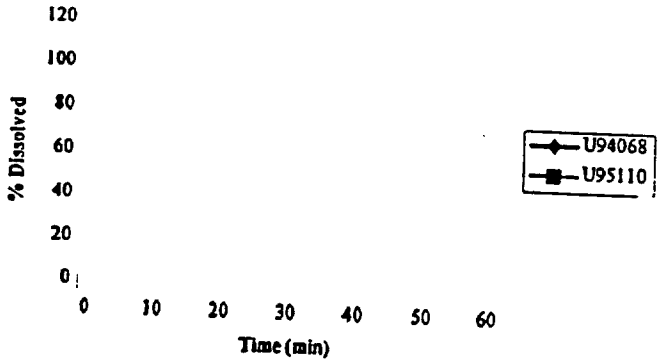


Figure 2

Dissolution Profiles in pH 7.5 Phosphate Buffer of Eprosartan Tablets Used in Clinical Study 035

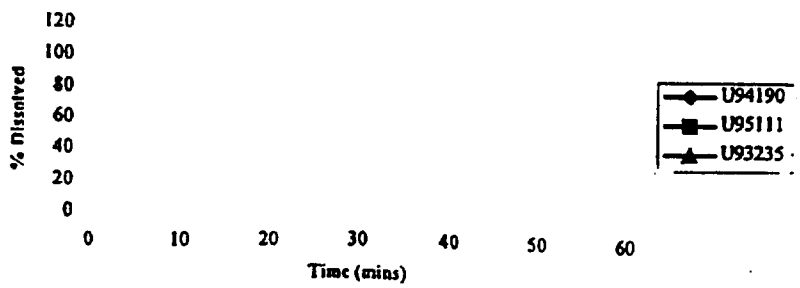


Figure 3

Dissolution Profiles in pH 7.5 Phosphate Buffer of
Eprosartan Tablets Used in Clinical Study 034

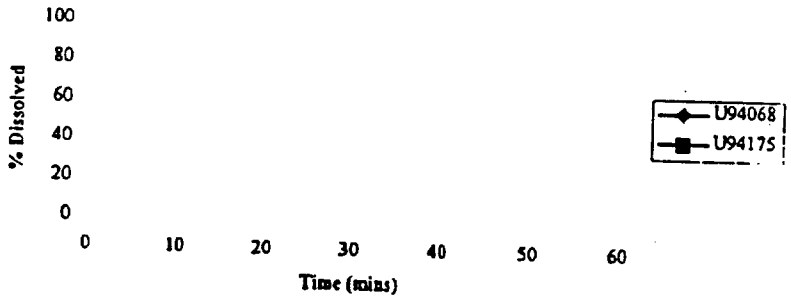


Figure 4

Dissolution Profiles in pH 7.5 Phosphate Buffer of
Eprosartan Tablets Used in Clinical Study 092

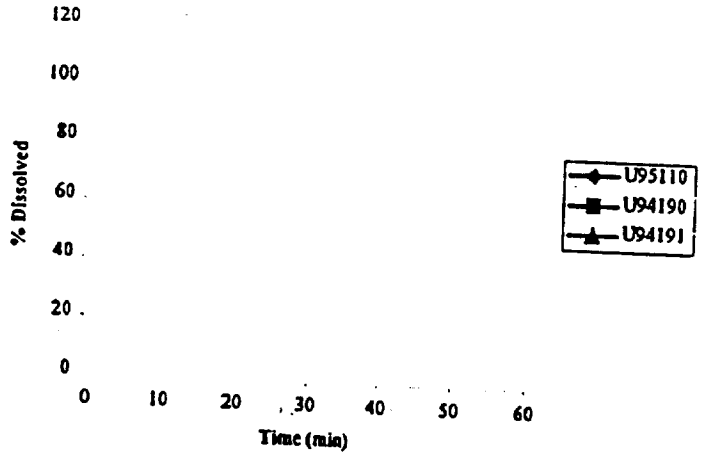


Figure 5

Dissolution Profiles in pH 7.5 Phosphate Buffer of
Eprosartan Tablets Used in Clinical Study 018

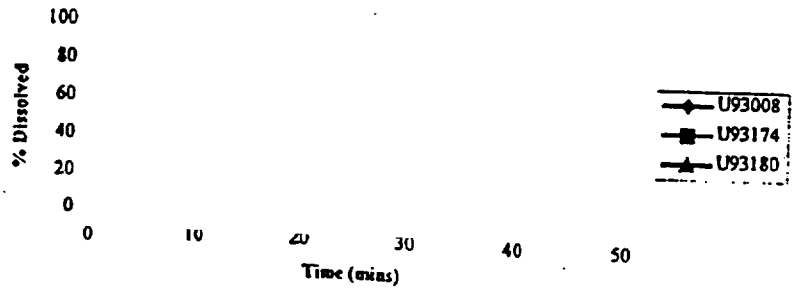
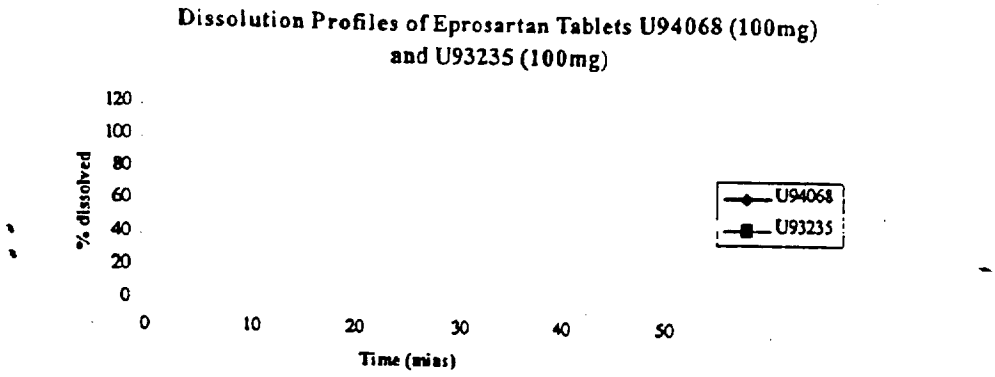


Figure 6



Based on the above results the sponsor is proposing the following method and specifications:

Dosage Form, Strength:

Dissolution Apparatus:

Speed of Rotation:

Dissolution Medium:

Volume:

Sampling Time:

Procedure:

Recommended Specification: Not less than in 45 min. (Q) of the label claim should be released

COMMENTS: The dissolution specification should be changed to not less than (Q) at 30 min.