CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20738

MEDICAL REVIEW(S)

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Secondary Medical Review of NDA

NDA #: 20-738
Date Completed: 9/9/97
Medical Reviewer: Charles J. Ganley, M.D.

Drug Name: Eprosartan Mesylate (TEVETEN™)
Sponsor: SmithKline Beecham

NDA Primary Reviewers

Discipline	Reviewer	Summary Page
Chemistry	James Short, Ph.D	1
Pharmacology	John Koerner, Ph.D Anthony Proakis, Ph.D	1
Biopharmacology	Emmanuel Fadiran, Ph.D	2
Statistics	Walid Nuri, Ph.D	-
Clinical Pharmacology	Khin U, M.D.	4
Clinical Efficacy	Isaac Hammond, M.D.	4
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Chemistry

Eprosartan mesylate is a non-biphenyl tetrazole molecule with the chemical name: (E)-α-[[2-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene]-2-thiophenepropanoic acid monomethanesulfonate. Film-coated, scored tablets contain eprosartan mesylate equivalent to eprosartan zwitterion in strengths equal to . 300 mg and 400 mg[1].

There are no major outstanding chemistry issues. Requests for additional data were submitted to the sponsor for information regarding the wavelength of light used in the photostability tests and photostability tests for the tablets outside of the bottles using UV and visible light.

An acceptable EER for the manufacturing site of the drug substance and drug product was received on May 2, 1997. Methods validation has been requested.

Eighteen month stability data for the drug product qualification lots support a two year expiration date for drug product packaged in HDPE bottles. Studies at 25°C/60%RH and 30°C/60%RH are ongoing. There was a slight increase in impurities and decreased dissolution at the 18 month time points @ 30°C for drug product packaged in blister packs[2]. This supports a 12 month expiration date for blister packs.

Pharmacology

Genotoxicity

The AMES Bacteria Mutation test (@ ≤ 5000 ug/ml +/- metabolic activation using S-9) and the Mouse Lymphoma assay (@ ≤ 2750 ug/ml with metabolic activation using S-9 and @ ≤ 2750 ug/ml without metabolic activation) were negative. The Mouse Bone Marrow Micronucleus Test was negative at doses of 2500 mg/kg/day for two days.

The Human lymphocyte test gave equivocal results @ 2000 ug/ml with metabolic activation for clastogenicity. Three different assays were performed yielding a positive, a negative and an equivocal assay result. Without metabolic activation, clastogenicity was negative at the same concentration. Polyploidy was positive with metabolic activation and equivocal without metabolic activation (@ 2500 ug/ml).

Carcinogenicity

Carcinogenicity studies were performed in the rat and mouse. The exposure in rats at 600 mg/kg was less than human exposure at 800 mg/day based on AUC. The exposure in rats did not increase with diet restriction. The exposure in the mouse at 2000 mg/kg/day was at least 3 fold greater than human exposure at 800 mg/day based on AUC. The was no evidence of carcinogenicity in either species.

Pharmacodynamics

The activity of eprosartan was documented in vitro and in vivo as illustrated in table P.1.

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[1] Data on 50 mg and 100 mg tablets are also contained in the submission. Approval on these strengths are not requested in the NDA.

[2] This was not observed @ 25°C.

Table P.1. In Vitro And In Vivo Assessment Of Eprosartan Activity

In vitro	In vivo
• eprosartan displaced I^{125} AII bound to glomerulus, tubule, outer medulla and cortex of rat kidney • no displacement of vasopressin, endothelin from receptors • shifted concentration response curve of rabbit aortic rings to angiotensin but not norepinephrine and endothelin 1 • no effect on rabbit lung ACE activity at 1 uM • eprosartan inhibited uric acid uptake into rat proximal tubule brush border membrane vesicles (IC_{50} = 60 uM for eprosartan; IC_{50} = 9.5 uM for losartan)	• decreased MAP in rats and dog with ligated renal artery • no change in spontaneous hypertensive dog unless volume depleted and with HCTZ • in rats and dogs, eprosartan produced dose dependent shift in AII dose response curve

Pharmacokinetics

In rats and dogs, the C_{max} and AUC increased with dose but not in a dose proportional manner. In studies with ^{14}C eprosartan, the majority (88% - 94%) of radioactivity was collected in the feces with the remainder collected in the bile or urine. The absolute bioavailability in the rat was rather dismal with only 8% absorbed after administration of 100 mg/kg. The absolute bioavailability ranged from 25% for intraduodenal administration to 13% for oral administration. The terminal $t_{1/2}$ after intravenous administration in the dog was 2.3 hours. Placental transfer and secretion into milk was low in rats.

Protein Binding

Protein binding in humans was 98% at concentrations of .01 - 100 ug/ml.

Effect in Human Microsomes

Eprosartan did not inhibit the metabolism of agents metabolized by the cytochrome P-450 enzymes 1A, 2A6, 2C8/9, 2C19, 2D6, 2E and 3A.

Toxicology

The repeat oral dose studies in rats and dogs up to 1000 mg/kg/day were rather unremarkable. No adverse drug effect was observed in the rat. In the dog, doses ≥ 30 mg/kg/day caused a mild decrease in RBC count, hematocrit and hemoglobin throughout the one year study. The effect being slightly more pronounced in male animals. The effect on hematological parameters is thought to be a physiologic effect similar to that observed with ACE inhibitors.

Reproductive Toxicity

There was no effect on mating, fertility and development in rats given 1000 mg/kg/day. In rabbits treated with 30 mg/kg/day on days 6 - 28 of gestation, there was maternal toxicity that included decreased body weight, abortions and death. Fetal toxicity in the rabbit was manifested by an increase in the # resorptions/litter and the # dead fetuses/litter. There were no external, visceral or skeletal malformations.

Biopharm

The absolute bioavailability of the commercial formulation of eprosartan is 14% (study 005). Five trials[3] studied the dose proportionality of eprosartan in healthy or hypertensive subjects. After single or multiple doses, there is an increase in C_{max} and AUC with dose but not in a dose proportional manner. Accumulation of eprosartan with multiple dosing was studied in protocol 009 and 048. There was minimal accumulation of eprosartan. The mean accumulation ratios ranged fron. in study 009 and study 048 respectively. The elimination half-life ($t_{1/2}$) for an intravenous formulation ranged from 1.2 - 2.2 hours. The elimination half for various oral formulations ranged from hours. In a study of the final commercial formulation, the $t_{1/2}$ ranged from hours for single dose of 100 - 800 mg.

Two food effect studies were performed plus another that evaluated absolute bioavailability and food effect (high fat diet). Study 007 (N=12; seven 50 mg tablets) evaluated the tablet

[3] Studies 003, 004, 008, 009, 048

formulation used in phase II trials. Study 086 (N = 20; two 400 mg tablets) and study 005 (N = 18; three 100 mg tablets) evaluated single doses of the of commercial formulation of eprosartan under fast and fed (fat meal) conditions. All three studies showed an increase in T_{max} with food. The study of the tablets (study 007) used in phase II trials showed a marked increase in both C_{max} (80%) and AUC (54%) under fed conditions. This result actually prompted the administration of eprosartan with food in the phase III trials. The two studies of the commercial products yielded somewhat divergent results for the AUC. Study 086 showed an increase in AUC (20%) with food whereas study 005 showed a decrease in AUC (16%) with food. C_{max} decreased by 7% in study 086 with food. Study 005 showed an decrease in Cmax (25%) with food. There was no change in $t_{1/2}$. In conclusion, for the formulation, there appears to be little or no food effect. For the formulation, there appears to be a dramatic food effect (increased with food).

Three studies evaluated the bioequivalence of the commercial formulation to the formulation included in the clinical trials. Both are formulations. Table B.1 shows that the 90% C.I. for C_{max} and AUC of the commercial formulation is not bioequivalent using the usual FDA standard of .8 to 1.25 for the 90% C.I. The deviation outside the .80 - 1.25 standard is minimal, except for study 89, and should not affect approvability since the drug is titrated to affect.

Table B.1. AUC and C_{max} 90% C.I. for Comparison of Commercial/Clinical Trial Formulations.

Study	AUC 90% C.I	C_{max} 90% C.I.
034	1.02 - 1.19	1.05 - 1.28
089	1.02 - 1.29	1.11 - 1.55
092	.84 - 1.28	.86 - 1.27

Patients with various degrees of renal insufficiency were studied with multiple doses (seven days of dosing) of eprosartan in study 021. Patients with severe (creatinine clearance 5 - 29 ml/min; N = 3) and moderate (creatinine clearance 39 - 59 ml/min; N = 11) renal insufficiency had increased Cmax (35 - 51%) and AUC (25 - 55%) compared to normal (creatinine clearance > 80 ml/min; N = 7) subjects. Patients with mild (60 - 80 ml/min; N = 8) renal insufficiency were no different than normal subjects. The difference between groups was even greater when free AUC and free Cmax were calculated. The mean elimination half-life in the severe renal insufficiency subjects was approximately double that of the normal subjects.

In a study comparing the kinetics of patients with hepatic insufficiency with normals, there was no difference in the Cmax but the AUC was approximately doubled in the hepatic patients. The elimination half-life, however, was similar in both groups.

In a study comparing the kinetics of elderly men to young men and women, the free and total Cmax and AUC for elderly men was approximately double that of young subjects (male or female). The elimination half-life was also increased (6.19 hours in elderly vs. 2.8 hours in young men).

Drug interaction studies were performed between eprosartan and digoxin, warfarin, glyburide, ranitidine and fluconazole. There was no change in digoxin pharmacokinetics when administered with eprosartan. There was no pharmacodynamic interaction between eprosartan and warfarin (change in INR) or glyburide (change in glucose). Pharmacokinetic interactions with warfarin and glyburide were not evaluated. Fluconazole did not affect the pharmacokinetics of eprosartan. Fluconazole, however, increased the Cmax (30%) and AUC $_{0\rightarrow t}$ (70%) of losartan.[4] Urine uric acid excretion was evaluated in the two studies evaluating the pharmacokinetic affect of fluconazole (study 94) and ketoconazole (study 95) on eprosartan and losartan. Losartan 100 mg caused a slight increase in $U_{uric\ acid}/U_{creat}$ throughout a 20 day treatment period. Eprosartan 300 mg BID caused an initial increase in $U_{uric\ acid}/U_{creat}$ (day 1 compared to baseline) that returned to baseline with continued treatment.

Eprosartan did not cause significant inhibition of CYP1A, CYP2A6, CYP2C9/8, CYP2E and CYP3A at concentration of 100 uM in human microsomes.

Eprosartan is approximately 98% protein bound in human plasma.

The dissolution of eprosartan in pH 7.5 phosphate buffer wa within 20 minutes. The proposed dissolution specification o @ 45 minutes will not adequately discriminate unacceptable lots of the commercial product.

Because of the differences in the results of the food studies and the lack of bioequivalence between two wet granulation formulations, the biopharm reviewer has requested addition information on the formulations used in the trials.

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[4] E-3174, the losartan metabolite, AUC and Cmax were decreased

Clinical Pharmacology

Dr. U has provided a comprehensive review of all of the clinical pharmacology studies. Many of the studies have been reviewed by Dr. Fadiran and the conclusions of the two reviewers do not differ. There are several issues that require comment.

Eprosartan decreased serum aldosterone levels in a dose related fashion in the dose range of 10 - 200 mg. A dose of 350 mg eprosartan decreased serum aldosterone but the effect did not persist for greater than 12 hours. Eprosartan effectively blocked the angiotensin II induced decrease on effective renal plasma flow (ERPF) and did not decrease ERPF alone (suggesting no agonist activity on this parameter).

The pharmacokinetic parameters (Cmax, AUC) are sensitive to changes in formulation. This is evident in all of the bioequivalence studies directly comparing various formulations and in the food and fasting studies. Depending on the formulation, a food effect may or may not be present. For the formulations used in the phase II trials , a food effect was prominent (study 007). This, however, is not the case for the commercial formulation where differences in absorption with food were contradictory in two studies (Study 086 and 005).

In a study of ^{14}C - eprosartan comparing intravenous (IV) to oral dosing, an acyl glucuronide was the only metabolite detected. Surprisingly, it was only detected in the urine (accounting for approximately 20% after an IV dose) and not in the plasma or feces. The absence of the glucoronide in the feces may be explained by intraluminal hydrolysis to the parent compound.

Numerous studies evaluated the effect eprosartan on $U_{uric\ acid}/U_{creat}$. At doses up to 1200 mg once a day, uric acid excretion did not increase.

The elimination half-life with oral dosing is greater than the intravenous dosing. This suggests that the elimination half life may be absorption limited and dependent on the formulation used.

Study 090 evaluated the effect of eprosartan 300 mg BID and placebo on proteinuria in patients with Type II diabetes mellitus and proteinuria (300 - 300 mg/24 hr.). This study randomized 85 patients, of which, 39 were randomized by a center operated by Dr. Fiddes. Dr. Fiddes is currently under investigation for data fraud. Regardless, with or without Dr. Fiddes data, there was no significant difference in the percent decrease in proteinuria after 6 weeks of treatment.

Study 051 evaluated the effect of eprosartan or enalapril on left ventricular hypertrophy. Without going into further detail about the deficiencies of the study, there was no significant change in left ventricular mass index between treatments.

Medical - Efficacy

The NDA included seven (study # 10, 11, 13, 16, 17, 45, 49) double-blind, placebo controlled, two double-blind, active controlled studies (41, 47) and two cough studies (14, 53) in patients with a diagnosis of essential hypertension. These studies randomized a total 1794 patients to eprosartan and 896 to the control therapies. The daily dose studied ranged from 50 mg to 1200 mg either as once a day (OD) or twice a day (BID) dosing. The duration of the double-blind treatment period ranged from 4 - 13 weeks. Table E.1 lists the double-blind, placebo controlled trials included in the NDA and the number of patients randomized to each treatment group. Studies 10 and 45 enrolled males only and DBP was measured by ABPM after 4 weeks of treatment. Study 16 added eprosartan or placebo therapy to patients who were considered non-responders to HCTZ therapy. Studies 13 and 17 were dose titration trials where patients had the dose doubled after 3 weeks of treatment if they had not responded adequately to therapy. As a consequence, the week 3 blood pressure measurements provided the only values for the initial randomized dose. Study 17 is further confounded because it enrolled only elderly (≥ 65 yrs.) subjects. Study 13 provides the only head to head comparison of OD versus BID dosing. Studies 11 and 49 provide the most important information with regard to a dose response relationship. Both studies had 8 week double-blind treatment periods. Study 11 evaluated BID dosing regimens whereas study 49 studied OD dosing regimens.

Table E.1. Number of Patients Randomized to Placebo Controlled Trials in Hypertensive Patients

		Number of Patients Randomized										
		Total Daily Dose (mg) BID*							Total Daily Dose (mg) OD			
Study		50	100	200	300	400	600	800	400	600	800	1200
10	• male only • ABPM • 4 wk Rx.		26	26	22	22						
11	• 8 wk Rx.	91		87		90	86	91				
13	• titration • 13 wk Rx.					79			78			
16	• add on to HCTZ • 4 wk Rx.		53	51								
17	• titration • ≥ 65 years • 9 wk Rx.			92		91						
45	• ABPM • male only • 4 wk Rx.								31			
49	• 8 wk Rx.								72	73	73	72

* for example, 800 mg total daily dose equals 400 mg BID

Data is presented in this review as a function of total daily dose. For example, a total daily dose of 400 mg for a BID regimen is equivalent to 200 mg BID. This is done to compare the effects of BID versus OD dosing schedules.

Diastolic Blood Pressure

Table E.2. lists the mean change in siDBP at endpoint[5] for studies 11 and 49. There is no difference in the treatment effect of eprosartan 25 mg BID and 100 mg BID in study 11. There is no other support in the NDA for the 25 mg BID regimen. The 100 mg BID regimen was also evaluated in study 10 (males only) and 17 (≥ 65 yrs.). The placebo subtracted change in DBP for 100 mg BID was -1.6 mmHg and -0.7 mmHg in study 10 (siDBP at trough) and 17 respectively. This data does not support the use of 100 mg BID and the 25 mg BID dose. Eprosartan doses of 200 mg BID - 400 mg BID (total daily dose = 400 - 800 mg) effectively lowered blood pressure by 4 mmHg or more. There is supporting data for the 200 mg BID dose in study 10 and 17. Other than study 11, no other studies evaluated BID doses greater than 200 mg BID.

The once a day dosing data is somewhat more confusing because few studies evaluated the once a day regimens. In study 49, the 1200 mg and 600 mg doses are the only doses significantly different from placebo. There are no other studies in the NDA that confirm the efficacy of the 600 or 1200 mg once a day dose regimen. The change in siDBP for the 400 mg once a day dose was not significantly different from placebo in study 49. In study 45, the mean change in siDBP for 400 mg OD was not significantly different from placebo. In study 13, the mean change in siDBP for 400 mg OD at week 3 (after week 3, some patients had dose titrated) was significantly different from placebo.

[5] last measurement carried forward

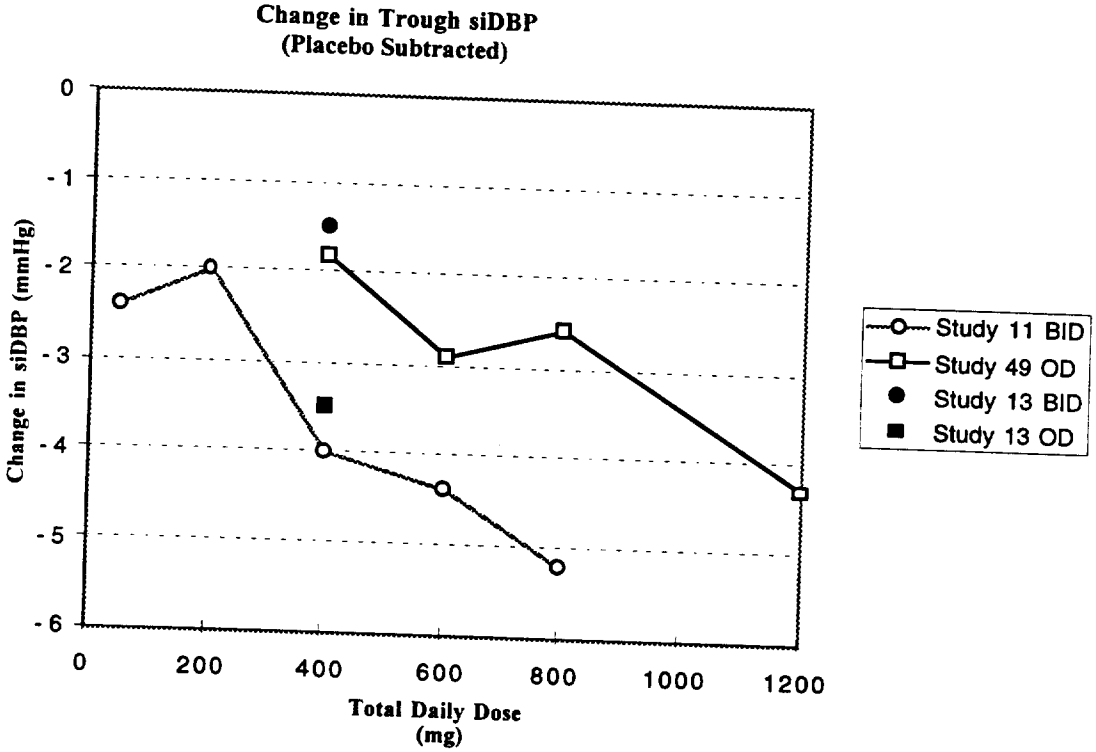
Table E.2. Change in siDBP (mmHg) from Baseline for Study 11 (BID Dosing) and Study 49 (Once Daily Dosing) at Endpoint

	Study 11 BID			Study 49 OD		
Total Daily Dose	N	Change from Baseline	Placebo Subtracted Change	N	Change from Baseline	Placebo Subtracted Change
Placebo	93	-2.8 (.7)			-3.3 (1.0)	
50	91	-5.2 (.8)*	-2.4			-
200	87	-4.8 (.8)	-2.0			
400	90	-6.8 (.7)*	-4.0	72	-5.1 (.9)	-1.8
600	86	-7.2 (.7)*	-4.4	73	-6.2 (.9)*	-2.9
800	91	-8.0 (.8)*	-5.2	73	-5.9 (.8)	-2.6
1200				72	-7.6 (.9)*	-4.3

* Significant Difference from Placebo

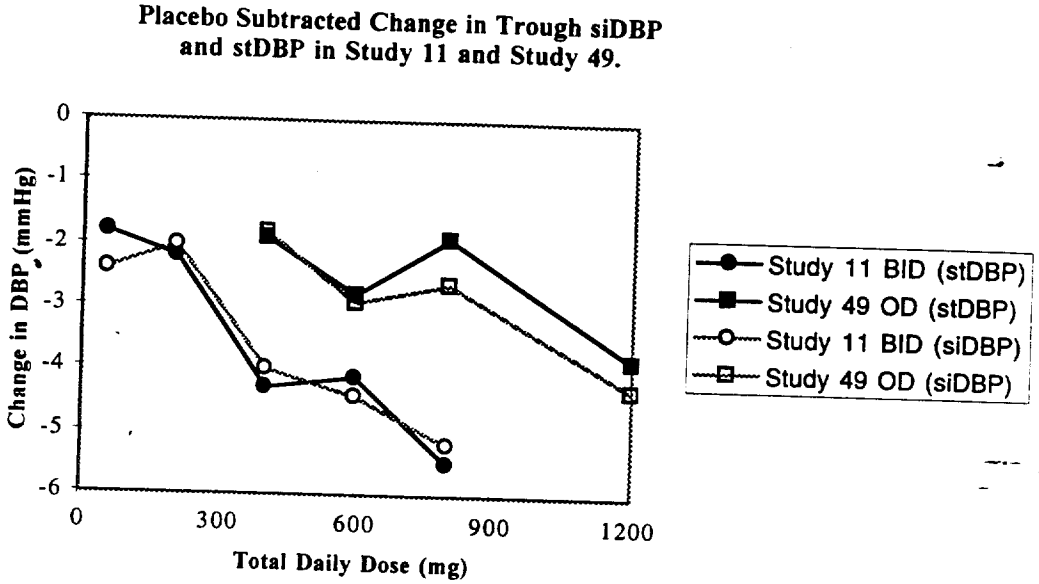
The placebo subtracted change in siDBP for studies 11, 49 and 13 are plotted in figure E.1. Based on the dose response curves, the BID regimen appears preferable to the OD regimen. There are obviously limitations in concluding this because the difficulties associated with comparing the results from different studies.

Figure E.1. Placebo Subtracted Change in siDBP in Study 11 (BID) and 49 (OD).



The standing DBP data for studies 11 and 49 are similar to the sitting DBP data as illustrated in figure E.1a.

Figure E.1a. Placebo Subtracted Change in sitting DBP and standing DBP in Study 11 (BID) and 49 (OD).



The 400 mg OD dose was evaluated in studies 13, 45 and 49. Study 13 was the only trial that included a direct comparison of once a day dosing (400 mg) versus twice a day (200 mg BID) dosing. Table E.2 lists the week 3 and 9 siDBP changes for study 13. In this study, patients who did not respond[6] to the initial dose regimen had the dosage adjusted after week 3 to a total daily dose of 600 mg or 800 mg. Week 3 measurements offer the best comparison because all patients were on the same randomized dose. At week 3, the OD regimen appears numerically (but not statistically) superior to the BID regimen. The placebo subtracted change for 400 mg OD at week 3 and week 9 are similar. This is unusual because the week 9 measurement included doses of 600 mg and 800 mg in patients who were deemed non-responders at week 6 and week 9. At week 9, the BID and OD dose regimens are indistinguishable. The similarity of the regimens at week 9 may be more a reflection of the study design than the similarity of effect. Although the dose titration design mimics the practice of physicians, it is not able to adequately compare the efficacy of two different dose regimens because it does not factor in the number of patients requiring higher doses and the amount of the higher dose.

Table E.2. Change In siDBP (mmHg) At Week 3 And Week 9 In Study 13.

Treatment	N	siDBP (mmHg) at Week 3		siDBP (mmHg) at Week 9	
		Change from Baseline	Placebo Subtracted Change	Change from Baseline	Placebo Subtracted Change
Placebo	86	-3.7	-	-4.4	-
200 mg BID	79	-5.2	-1.5	-9.2	-4.8
400 mg OD	78	-7.2*	-3.5	-8.3	-3.9

* Significant Difference from Placebo

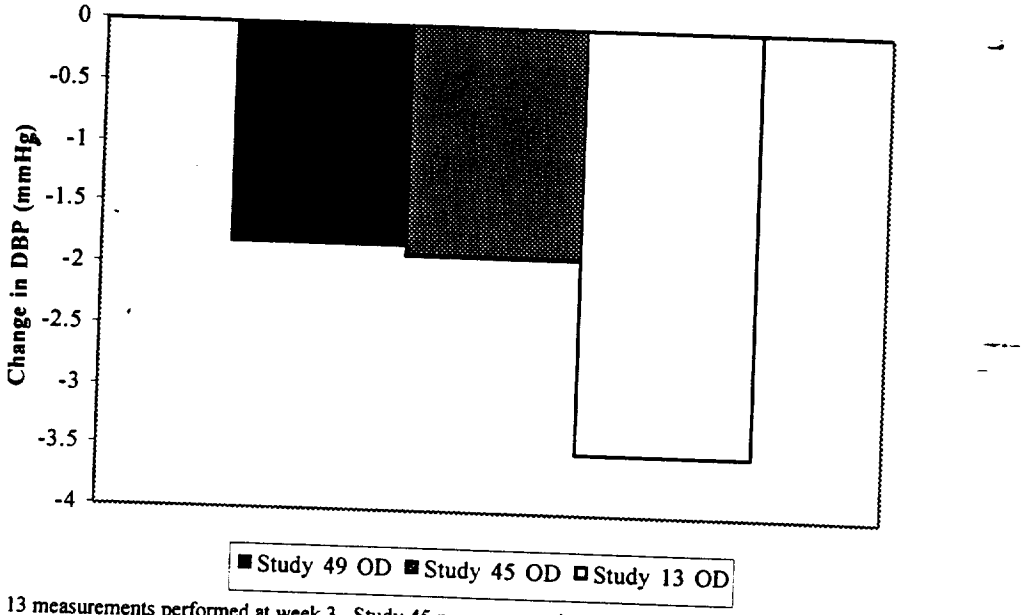
The week 3 results for the 400 mg OD dose regimen in study 13 are not consistent with the results observed in study 49 and study 45 where 400 mg OD had a minimal effect.[7] This is illustrated in figure E.2.

[6] response = siDBP < 90 mmHg or siDBP < 100 mmHg and change from baseline ≥ 10 mmHg

[7] Study 13 , 49 and 45 are siDBP at trough. Study 45 had also DBP measured by ABPM at 20 - 24 hours post dosing.

Figure E.2. Placebo Subtracted Change in DBP for OD Dosing Regimens

Placebo Subtracted Change from Baseline in Trough siDBP for Eprosartan 400 mg OD Dosing Regimen.

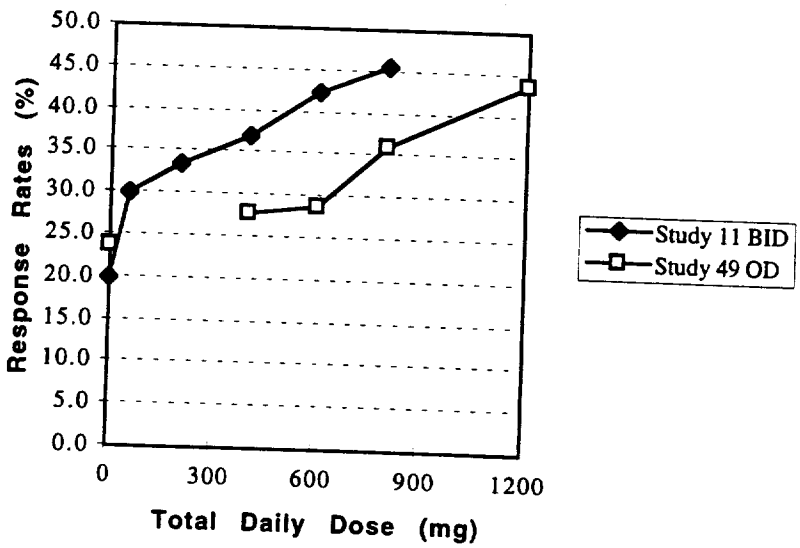


Study 13 measurements performed at week 3. Study 45 measurement is siDBP at trough (not ABPM; obtained from Dr. Nuri's review table 1).

To further assess the BID versus OD dosing, figure E.3 plots the response rates at endpoint for study 11 (BID) and study 49 (OD). For comparable total daily doses, BID dosing appears to be more effective than OD.

Figure E.3. Response Rates in Study 11 and Study 49 at Endpoint.

Response Rates for Study 11 (BID) and 49 (OD)



Studies 10 and 45 utilized ABPM measurements in male patients. The mean values were obtained at different times of the ABPM recording. In study 10, the mean measurements were calculated from measurements obtained between 0 - 12 hours post-dosing. This time period included both peak and trough measurements. In study 45, the mean measurements were calculated from measurements obtained between 20 - 24 hours post-dosing (trough). Study 10 appears to confirm that a eprosartan 200 mg BID dose is effective. The 400 mg OD regimen in study 45 was not significantly different from placebo. The study was to small to detect a significant difference. It should be noted, however, that the placebo subtracted change in siDBP at trough in study 45 was -1.6 mmHg.

Table E.3. Mean Change in DBP (mean ABPM) in Study 10 and Study 45

	Study 10 BID [A]			Study 45 OD [B]		
Total Daily Dose	N	Change from Baseline	Placebo Subtracted Change	N	Change from Baseline	Placebo Subtracted Change
Placebo	22	-.4 (6.5)		30	-.3 (8.1)	
100	26	-3.8 (5.9)	-3.4			
200	26	-1.8 (5.3)	-1.4			
300	22	-5.1 (5.7)*	-4.7			
400	22	-5.8 (8.0)*	-5.4	31	-4.0 (6.9)	-3.7

[A] = mean of ABPM measurements between 0 - 12 hours post-dosing; Dr. Hammond's Review table 10.3, p. 17
[B] = mean of ABPM measurements between 20 - 24 hours post-dosing; Dr. Hammond's Review table 45.2, p. 54
* Significant Difference from Placebo

Based on Emax and logistic models for dose response constructed for study 11 and 49 (figure 1 and 2 in Dr. Nuri's review; discussion on p. 8 and 9 Dr. Nuri review), the maximum effective dose of eprosartan is not established for the BID or OD dosing regimens.

A summary table of the change in siDBP from baseline is provided in table E.3a.

Table E.3a. Mean Change in siDBP for Placebo Controlled Studies

			Change in DBP										
			Total Daily Dose (mg) BID							Total Daily Dose (mg) OD			
Study			P	50	100	200	300	400	600	800	400	600	800	1200
10	• males • ABPM • 4 wk Rx.	N Δ	22 -3.4		26 -5.9	26 -1.8	22 -4.9	22 -9.5*						
11	• 8 wk Rx.	N Δ	93 -2.8	91 -5.2*		87 -4.8*		90 -6.8*	86 -7.2*	91 -8.0*				
13 [A]	• titration	N Δ	86 -3.7					79 -5.2			78 -7.2*			
16	• add on to HCTZ	N Δ	52 -4.9		53 -7.9*	51 -7.7*								
17 [A]	• titration • ≥ 65 years	N Δ	47 -8.6			92 -9.3		91 -11.3						
45	• ABPM • males • 4 wk Rx.	N Δ	30 -3.0								31 -4.9			
49	• 8 wk Rx.	N Δ	74 -3.7								72 -4.6	73 -6.0*	73 -5.3	72 -6.9*

* P < .05 ; [A] at week 3

Systolic Blood Pressure

The change in trough siSBP is listed in table E.4. Doses of eprosartan greater than 200 mg BID or 400 mg OD were significantly different from placebo.

Table E.4. Placebo Subtracted Change in SBP at Trough.

		Placebo Subtracted Change in SBP (mmHg) at Endpoint										
		Total Daily Dose (mg) BID							Total Daily Dose (mg) OD			
Study		50	100	200	300	400	600	800	400	600	800	1200
10[A]	N		26	26	22	22						
	Δ		-2.0	-1.6	-1.5	-6.1						
11	N	91		87		90	86	91				
	Δ	-.8		-3.3		-6.6	-7.6	-8.2				
13[C]	N					79			78			
	Δ					-5.8			-3.4			
17[C]	N			92		91						
	Δ			-1.9		-5.1						
45[B]	N								31			
	Δ								-4.2			
49	N								72	73	73	72
	Δ								-4.0	-7.4	-4.8	-9.2

N = number randomized. ; [A] Table 10.6 of Dr. Hammond's Review
[B] = mean ABPM between 20 - 24 hours.; [C] = week 3 measurements

Subgroups

In general, the placebo subtracted change in siDBP for female patients exceeded the change in male patients [see table 3 and discussion (p. 9) in Dr. Nuri's review].

There are a limited number of black patient's randomized in the clinical trials. As a consequence, there is insufficient evidence to suggest that eprosartan is effective in black patients (table 4 and discussion p. 10 from Dr. Nuri's review). A pooled analysis may provide from all of the placebo controlled trials may provide addition insight into the effect of eprosartan in black patients.

Fewer patients ≥ 65 years were randomized into placebo controlled trials compared those < 65. In study 11, the patients ≥ 65 years consistently had lower placebo subtracted changes in siDBP compared to patients < 65 years of age for all treatment groups (table S4, p. 7 in Dr. Hammond's review).

Trough/Peak Ratios

Peak blood pressure measurements at 1, 2 and 3 hours post-dosing were performed in studies 11 and 49. They were predominantly collected at week 4 rather than at the end of the 8 week trial. Some patients in study 49 had week 8 trough/peak measurements performed. As a consequence, there are many trough peak ratios calculated which makes it difficult to interpret because there is a wide range of ratios. Table E.5 lists the placebo subtracted trough/peak ratios for study 11 and 49 at week 4 and week 8.

Table E5. Placebo Subtracted Trough /Peak Ratio for siDBP

Week 4

Total Daily Dose	Study 49 (OD)			Study 11 (BID)		
	1 hour	2 hours	3 hours	1 hour	2 hours	3 hours
Eprosartan 50 mg				.36	.2	.21
Eprosartan 200 mg				1.33	.6	.48
Eprosartan 400 mg	.47	.56	.34	.93	.5	.56
Eprosartan 600 mg	.22	.24	.20	1.03	.59	.68
Eprosartan 800 mg	.61	.46	.66	.83	.52	.62
Eprosartan 1200 mg	.82	.52	.51			

Week 8

Total Daily Dose	Study 49 (OD)			Study 11 (BID)		
	1 hour	2 hours	3 hours	1 hour	2 hours	3 hours
Eprosartan 50 mg						
Eprosartan 200 mg						
Eprosartan 400 mg	.08	.08	.09			
Eprosartan 600 mg	.35	.24	.3			
Eprosartan 800 mg	.27	.19	.2			
Eprosartan 1200 mg	.38	.34	.4			

In general, the trough/peak ratios for BID dosing are greater than the ratios for OD dosing at comparable total daily doses.

Time to Steady State Blood Pressure

Blood pressure data from study 49 suggests that steady state is achieved by 2 weeks (figure 49.2, p. 61 Dr. Hammond's review)

Active Control Trials

Two active control trials were performed comparing eprosartan to enalapril or nifedipine XL. These studies contribute little information regarding the effectiveness of eprosartan.

Safety

Patient Exposure/Demographics

The NDA included the results from 15 phase II/III clinical trials in hypertensive patients. Of these trials, eleven were controlled and 4 were open label. A total of 2334 patients were exposed to eprosartan in these trials. Open label studies enrolled 804 subjects of which 556 had never received eprosartan previously. Table S.1 lists the number of hypertensive patients exposed in controlled and open label studies. In addition, there were 29 clinical pharmacology studies performed predominately in healthy subjects and involving single doses. The total subject exposure is 2969. The safety update provided information on an additional 33 patients for a total exposure of 3002 subjects.

Table S.1. Number of Hypertensive Patients Exposed to Eprosartan

Trial	# Patients
Placebo Controlled	1202
Positive Control	472
HCTZ Background	104
Uncontrolled	804*
Total	2334

* 556 patients were new exposure not previously on eprosartan

The most commonly studied total daily dose in the controlled trials was 400 mg and 400 - 600 mg in uncontrolled trials administered as once or twice a day dosing (p. 12, 13 Dr. Gordon's review). The hypertension trials enrolled 40% female and 10% blacks with an overall average age of 57 years.

The duration of exposure was predominately < 3 months but 572 patients had eprosartan exposure of 181 - 360 days and 166 had exposure of greater than 361 days.

Deaths

There were 19 deaths in eprosartan treated patients. In five of the patients, death occurred after the patient discontinued eprosartan therapy. In the 14 other deaths, the patients died while on therapy or they experienced an adverse event while on therapy that ultimately lead to their demise. Most of the cases were cardiovascular with the exception of 2 cancer related deaths. None of the deaths could be attributed to valsartan therapy.

Premature Withdrawals

Approximately 4 - 5% of eprosartan patients withdrew from the controlled clinical trials due to adverse events. A similar number was reported for the placebo treatment arm. Dr. Gordon's review notes a difference in the number of patients withdrawn due to lack of effect between the eprosartan and placebo treatments (p. 48 Dr. Gordon review). This number is biased by study 13 where patients who did not decrease DBP by >10 mm Hg or below 90 mm Hg were discontinued. Since there were fewer placebo patients in other studies, the denominator for the placebo group is lower and as a consequence the percent of patients discontinued for lack of effect is inflated for both treatments but more so for placebo. If all studies had the same criteria for withdrawal as study 13, the percent of withdrawals would be 50% or greater for either treatment.

Adverse Events

Adverse events are quite unremarkable. The most common adverse events reported for eprosartan in all hypertension studies include headache (12.4%), URI (10.9%), myalgia (6.7%), coughing (5.5%), pharyngitis (5.3%), rhinitis (5.2%) and dizziness (4.8%). Surprisingly, injury was reported by 4.3%. The adverse events reported with eprosartan having a greater incidence than placebo in placebo controlled trials is provided on page 19 of Dr. Gordon's review. The differences are slight and generally unimpressive. The list includes URI, injury, rhinitis, pharyngitis, depression, UTI, viral infection and coughing. There were no significant differences in adverse events based on demographic variables.

There were two reports of facial edema in eprosartan patients.

There were no significant ECG changes attributable to eprosartan. Mean heart rate did not change.

Laboratory Abnormalities

There are no surprises with regard to laboratory abnormalities. Mean BUN and creatinine did not change significantly. But there were three patients with increased creatinine while on eprosartan. Two of these withdrew and one died (patient # 050.011.001.00638, page 56 Dr. Gordon's review).

In placebo controlled trials, the percentage of patients with normal baseline ALAT and abnormal post-randomization ALAT was 2.6% and 3.0% for eprosartan and placebo respectively. For ASAT, the percentages were 1.2% and 3.0% for eprosartan and placebo respectively. Four patients withdrew because of abnormal liver function tests (page 59 Dr. Gordon's review). The relationship to eprosartan is unclear.

Mean potassium increased by .03 mmol/L in all hypertension trials with eprosartan treatment (page 60 Dr. Gordon's review). In placebo controlled trials, the percentage of patients with low or high potassium levels was not different between placebo and eprosartan treatment groups.

There was no significant difference in mean changes for total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides.

In placebo controlled trials, mean hemoglobin decreased by 1.59 g/L with eprosartan compared to .21 g/L for placebo (baseline vs. endpoint).

Cough

Two clinical trials were performed to specifically assess the incidence of cough with eprosartan compared to enalapril. Study 14 was a randomized, double-blind, parallel group study that enrolled 528 patients with hypertension to eprosartan 300 mg BID (N = 264) or enalapril 20 mg OD (N = 264). The double-blind treatment period was 26 weeks. HCTZ could be added at week 12 if blood pressure was not controlled. The primary measure of efficacy was definite cough defined as persistent, dry cough for 2 weeks as measured by an investigator's questionnaire (see appendix 3 Dr. Gordon's review)[8]. The protocol specifies analyses be performed at visits 2 (double-blind week 6) or 4 (double-blind week 12) prior to HCTZ dosing or at withdrawal if the patient had at least 2 weeks of therapy and had a cough assessment or

[8] answer yes to question 6, dry cough on question 12 and no to URI for question 17 on investigator's questionnaire (Dr. Gordon's review appendix 3)

if the patient was withdrawn for cough [9]. Table S2 lists the incidence of patients who had dry, persistent cough at visit 2 or 4. There was no significant difference between treatments at these timepoints.

Table S2. Incidence of Investigator Documented Cough

Definite Cough Timepoints	eprosartan	enalapril
Visit 2 (week 6)	2/255 (.8%)	4/253 (1.6%)
Visit 4 (week 12)	2/248 (.8%)	7/237 (3.0%)

Study 53 was the more important of the cough studies and followed a protocol similar to ones used by previous sponsors with their angiotensin II antagonists. Patients with hypertension and a history of ACE inhibitor induced cough were challenged with enalapril. Those patients who had definite cough defined by positive responses for persistent (2 weeks), dry cough on an investigator's questionnaire (appendix 4 of Dr. Gordon's review) entered a washout period during which cough was absent. Patients with cough on enalapril and no cough off of enalapril were randomized to placebo (N = 45), eprosartan 300 mg BID (N = 46) or enalapril 20 mg OD (N = 45). The primary endpoint was the incidence of persistent, dry cough at any time during the double-blind treatment period.[10] Table S3. shows the incidence of dry, persistent cough. The table excludes data from Dr. Fiddes center (24 patients) because of an ongoing investigation by DSI involving the validity of data provided by Dr. Fiddes. There is a significant difference between eprosartan and enalapril (p = .008; Cochran-Mantel-Haenszel Analysis).[11]

Table S3. Incidence of Investigator Documented Cough at Any Time in Double-Blind Treatment

Treatment	Placebo	Eprosartan 300 mg BID	Enalapril 20 mg OD
Definite Cough	1/37 (2.7%)	1/38 (2.5%)	9/36 (25%)

(from Dr. Nuri's Review, Table 6; excludes Dr. Fiddes data)

Comments

- The maximum dose range has not been adequately established. The maximum dose studied in clinical trials is 1200 mg.
- The BID dose regimen appears to be superior to the once a day regimen. The NDA supports an initial starting dose of 200 mg BID but not 400 mg OD. The superiority of the BID dose may be explained by the short elimination half-life (as low as 3 hours in some studies), the lack of an active metabolite and the failure of AUC and C_{max} to increase in a dose proportional manner (doubling the dose leads to less than double the AUC and C_{max}). The upper dose range for the BID and OD dose regimens has been inadequately explored.
- The clinical trial formulation is not bioequivalent to the to be marketed formulation. A significant food effect is observed with some formulations but not with others. The variability observed between essentially the same formulations in pharmacokinetic trials is cause for concern with respect to future minor changes in manufacturing or the development of new tablet strengths. For this reason, the dissolution specifications proposed by the sponsor are not stringent enough.

- The effect in black patients has not been adequately explored. For the most part, the response in black patients is less than the effect observed in non-black patients. The effect in females is generally greater than the effect in males.
- Few patients with severe renal insufficiency have been evaluated in the studies. As a consequence, many of the statements in the label regarding the unrestricted use of eprosartan in patients with renal insufficiency are not acceptable.

---

[9] this is ambiguous but it suggests that patients withdrawn prior to visit 4 for cough be counted or if they have a questionnaire completed at withdrawal prior to visit 4.

[10] as documented by the investigator's questionnaire

[11] [Additional data was requested from Dr. Nuri regarding the number of subjects who experienced cough during double-blind enalapril treatment. From the data provided, it appears that 16 enalapril subjects, 6 eprosartan and 6 placebo fulfilled the questionnaire criteria for cough. More information is needed from Dr. Nuri to determine the reason for the discrepancy between this information and the information included in table S3.]

[12] even though both are formulations

Conclusion

The information included in the NDA supports the approval of eprosartan for the treatment of hypertension.

Labeling

The sponsor submitted revised draft labeling for eprosartan on July 31, 1997. The major changes by the sponsor in the label include the and the change of the initial starting dose from 400 mg OD to 600 mg OD. It is clear from the data that 200 mg BID is an acceptable initial dose and that 400 mg OD is not.

A revised version of the label is attached.

Charles J. Ganley, M.D.

Lipicky

cc: orig.
HFD-110
HFD-110 / D. Willard/ C. Ganley/J. Koerner/A. Proakis/R. Lipicky/ M. Gordan/ I. Hammond
HFD-110 /Khin U; HFD-810/J. Short; HFD-860/ E. Fadiran/ A. Parekh; HFD-710/W. Nuri

APPEARS THIS WAY
ON ORIGINAL

D. WINNIKO

AUG 8 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER REVIEW

NDA #:	20-738	NDA Volume:	1.1091-6
DRUG NAME:	Teveten™ (Eprosartan) Tablets	Doc ID	BM (M19.1 - M19.6)
SPONSOR:	SmithKline Beecham Pharmaceuticals		
TYPE OF DOCUMENT:	New NDA (Clinical Pharmacology Review)		
DATE OF CORRESPONDENCE:	*03-Jul-1997*		
DATE RECEIVED:	*07-Jul-1997*	DATE ASSIGNED:	*08-Jul-1997*
MEDICAL OFFICER:	Khin Maung U, M.D.	DATE COMPLETED	*10-Jul-1997*

1. STUDY PROTOCOL

1.1 Title

Protocol 061: ***An 8-week, double-blind, double-dummy, placebo-controlled, parallel group, multicenter comparison of regimens of oral SK&F 108566 and hydrochlorothiazide given in combination in patients with mild to moderate essential hypertension (DBP ≥ 95 & ≤ 114 mmHg)***

1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. Hydrochlorothiazide (HCTZ) is a diuretic used as a standard therapy for hypertension, and is often used in combination with other antihypertensive agents. This study evaluates the efficacy and safety of adding eprosartan to HCTZ therapy in those patients whose blood pressure is not controlled with HCTZ alone.

1.3 Objectives

1. To compare the antihypertensive efficacy of eprosartan 400 mg once daily in combination with HCTZ 12.5 or 25 mg once daily in patients with mild to moderate hypertension (average sitting diastolic blood pressure ≥ 95 and ≤ 114 mmHg).
2. To assess the safety of eprosartan and HCTZ in combination with regard to adverse experiences, laboratory abnormalities and electrocardiograms (ECGs).

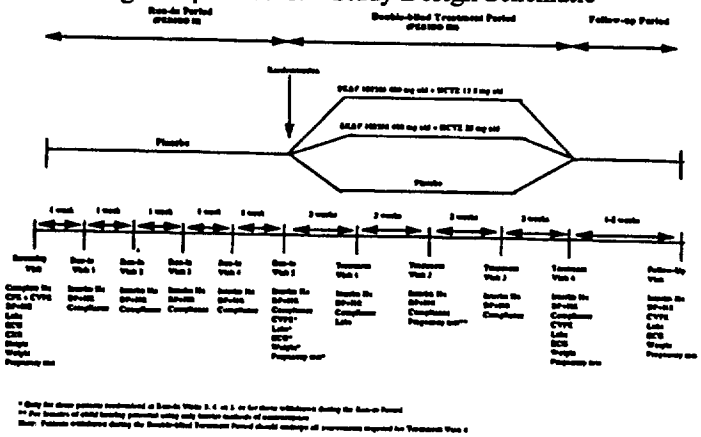
1.4 Study design

This is a Phase III, multi-center, double-blind, double-dummy, placebo-controlled, parallel group study of patients with mild to moderate essential hypertension who were randomized to receive for 8 weeks:

1. placebo (eprosartan placebo = Lot# U95146, HCTZ placebo = Lot# U95233)
2. eprosartan 400 mg (Lot# U95111) and HCTZ 12.5 mg (Lot# U 95234)
3. eprosartan 400 mg (Lot# U 95111) and HCTZ 25 mg (Lot# U 95235)

The study design is illustrated in Figure Epro-061-1 below:

Figure Epro-061-1. Study Design Schematic



After completing the double-blind treatment period, patients may enter an open-label, long-term study (protocol #105) or return within 7-14 days for follow-up visit.

1.5 **Protocol Amendments**

Amendment 1 (applied only to Canada). Sections of protocol pertaining to safety limits for withdrawal, and reasons for withdrawal were modified to conform to Canadian requirements.

Amendment 2 (applied only to France): Sections of protocol pertaining to safety limits for withdrawal, and reasons for withdrawal were modified to conform to Canadian requirements.
Amendment 3 (applied only to the US and Canada): Section of protocol pertaining to the procedure for reporting serious adverse experiences was modified to include the new office and emergency telephone numbers for contacting the Medical Monitor in North America. The procedure for emergency identification of double-blind medication was changed.

1.6 **Population enrolled/analyzed**

519 patients with newly diagnosed mild to moderate hypertension (average sitting diastolic blood pressure ≥ 95 and ≤ 114 mmHg) including women without child bearing potential or using hormonal or barrier contraceptives or IUCDs, at least 18 years of age without secondary hypertension, arrhythmias, clinical evidence of congestive heart failure, myocardial infarction or a cerebrovascular accident, angina pectoris, unstable diabetes mellitus, clinically significant renal or hepatic disease, alcohol or drug abuse, or chronic/concomitant treatment with drugs known to affect blood pressure, were enrolled.

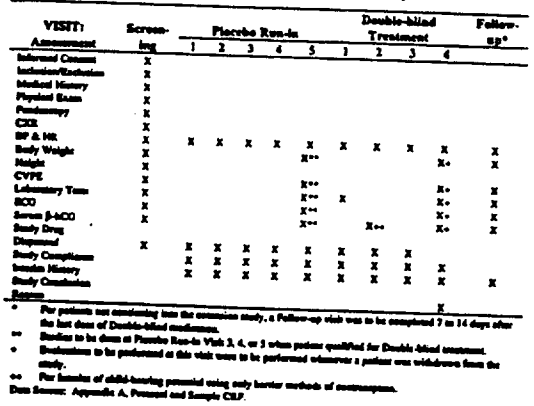
Compliance: This was determined by the number of tablets dispensed at each visit and subtracting the returned number of tablets.

Pre-study screening: All antihypertensive medication except HCTZ were discontinued at the screening visit or up to 7 days after the screening visit. Treatment with concomitant antihypertensive agents and other excluded medications (MAO inhibitors, tricyclic antidepressants, phenothiazine derivatives, sympathomimetic amines, NSAIDS (except low dose aspirin up to 325 mg/day), warfarin and other anticoagulants, etc., was not allowed.

1.7 **Study procedures**

The schedule for assessment of efficacy and efficacy parameters is given in Table Epro-061-1.

Table Epro-061-1. Schedule of study assessments



As shown in table, the study consisted of a screening period, a placebo run-in period of 3-5 weeks during which sitting blood pressure was recorded weekly and then randomized at the last visit, a double-blind period of 8 weeks during which each patient took the randomized medication and sitting blood pressures recorded every 2 weeks, and a follow-up visit 7-14 days after completion of the double-blind treatment period.

1.8 **Efficacy assessments:**

The primary efficacy parameter was the mean change from baseline to study endpoint in sitting diastolic blood pressure (SitDBP). Baseline was defined as the mean of the last two qualifying visits of the placebo run-in period.

The secondary efficacy criteria were as follows:

- Mean change from baseline in sitting systolic blood pressure (SitSBP)

- Mean change from baseline from sitting heart rate (SitHR)
- Proportion of responders in each treatment group (i.e., percent of patients whose SitDBP was <90 mmHg or ≤100 mmHg and decreased from baseline by at least 10 mmHg) using Cochran-Mantel-Haenszel statistic, adjusting for center or subgroup interaction by Breslow-Day test.

Comparisons of SitDBP were made for each of the following subgroups: age (<65 and ≥65 years), sex, race (Black, Caucasian, Oriental, Other), prior use of antihypertensives (Yes, No), and severity of hypertension at baseline (SitDBP <105 and ≥105 mmHg), using ANOVA

1.9 **Safety assessments:**

Safety assessments include adverse experiences, physical examinations, results of clinical laboratory tests (blood chemistry, hematology and urinalysis), BP and HR, and ECGs (at screening, at entry to double-blind treatment, at treatment visit 4, and at follow up or withdrawal from study) while "on therapy" (defined as the period starting from the first dose of randomized medication and including the 24-hour period after the last dose of randomized medication).

1.10 **Sample size:**

To detect a 5 mmHg difference in change from baseline between any 2 regimens, assuming a standard deviation of 8 mmHg, to provide 90% power and a 0.05 level of significance on two-sided testing with a Hochberg procedure of Bonferroni adjustment for the 3 comparisons, the sample size was estimated to be 70 evaluable patients per medication regimen.

1.11 **Investigator , Center and Study Dates:**

27 investigators in 5 countries (2 in the Netherlands, 3 in Canada, 3 in France, 6 in the United Kingdom and 13 in the United States) participated in the study. The medical monitor was Marcus B. Saltzman, MD, SmithKline Beecham Pharmaceuticals, Collegeville, Pennsylvania. Study Dates: 15-Jan-1996 to 14-Aug-1996.

2. STUDY POPULATION

2.1 **Subject disposition:**

519 patients were screened. 13 (2.5%) withdrew prior to receiving single-blind placebo run-in medication (2=protocol violation, 1= lost to follow-up, 10 = "other reasons"). 126 (24.9%) were not randomized (21=withdrawn due to adverse experiences, 21=protocol violations, 6=lack of efficacy, 1=lost to follow up and 77="other reasons").

Of 380 patients who qualified for randomization, 124 received placebo, 128 received eprosartan 400 mg/HCTZ 12.5 mg and 128 patients received eprosartan 400 mg/HCTZ 25 mg.

4 patients (#061.052.00217, #016.274.00277, #061.472.00340, and #061.573.00457) randomized to eprosartan 400 mg/HCTZ 25 mg did not have any trough (pre-dose) vital signs taken after randomization and they were no included in analysis. 352 (92.6%) patients completed the 8-week study; 28 (7.4%) patients were withdrawn.

2.2 **Withdrawals:**

28 (7.4%) patients were withdrawn (10 in placebo group, 8 in eprosartan 400 mg/HCTZ 12.5 mg group, and 10 in eprosartan 400 mg/HCTZ 25 mg group). 10 (2.6%) patients were withdrawn due to adverse experiences, 9 (2.4%) patients due to lack of efficacy, 2 patients lost to follow up, 4 patients due to protocol violations and 3 patients for "other reasons" (Table Epro-061-2).

Table Epro-061-2. The number and percentage of randomized patients who completed the study or were withdrawn by the reason for study withdrawal

	Placebo UID (n = 124)		Eprosartan 400 mg UID HCTZ 12.5 mg UID (n = 128)		Eprosartan 400 mg UID HCTZ 25 mg UID (n = 128)		Total (n = 380)	
Study Conclusion / Reason	No.	(%)	No.	(%)	No.	(%)	No.	(%)
COMPLETED STUDY	114	(91.9)	120	(93.8)	118	(92.2)	352	(92.6)
EARLY TERMINATION	10	(8.1)	8	(6.3)	10	(7.8)	28	(7.4)
Withdrawal Reason								
Adverse Experience	1	(0.8)	3	(2.3)	6	(4.7)	10	(2.6)
Lack of Efficacy	5	(4.0)	1	(0.8)	3	(2.3)	9	(2.4)
Lost to Follow-up	0	(0.0)	2	(1.6)	0	(0.0)	2	(0.5)
Other reasons	3	(2.4)	0	(0.0)	0	(0.0)	3	(0.8)
Protocol violation, including non-compliance	1	(0.8)	2	(1.6)	1	(0.8)	4	(1.1)

2.3 Protocol violations:

The most frequently occurring protocol violations (≥4.5% in any medication group) are summarized in Table Epro-061-3. The incidences of individual protocol violations were consistent across the 3 treatment groups and are therefore not expected to affect the outcome of the study. Including these frequently occurring protocol violations, 321 (84.5%) randomized patients had at least one protocol violation (106 (85.5%) in placebo group, 108 (84.4%) in eprosartan 400 mg/HCTZ 12.5 mg group, and 107 (83.6%) in eprosartan 400 mg/HCTZ 25 mg treatment group). The most common protocol violation was not taking study medication 22-24 hours before scheduled trough (pre-dose) vital sign measurements that occurred in 234 (61.6%) of randomized patients.

Table Epro-061-3

Frequency of Protocol Violations: Number (%) of Randomized Patients With At Least one Violation and Distribution of the Most Frequent (Incidence ≥4.5% in any Treatment Group) Types of Violations

	Placebo UID		EPROSARTAN 400 mg UID HCTZ 12.5 mg		EPROSARTAN 400 mg UID HCTZ 25 mg		TOTAL	
Protocol Violation	(n = 124)		(n = 128)		(n = 128)		(n = 380)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Patient medication not taken 22 - 24 hours before pre-dose vital sign measurements*	84	(67.7)	71	(55.5)	79	(61.7)	234	(61.6)
Concomitant medication affecting BP: during Placebo Run-in	13	(10.5)	6	(4.7)	9	(7.0)	28	(7.4)
Concomitant chronic treatment with sympathomimetic amines or NSAIDs (except low-dose aspirin): within 7 days prior to Screening	10	(8.1)	14	(10.9)	7	(5.5)	31	(8.2)
Concomitant chronic treatment with sympathomimetic amines or NSAIDs (except low-dose aspirin): during Placebo Run-in	11	(8.9)	15	(11.7)	10	(7.8)	36	(9.5)
Concomitant chronic treatment with NSAIDs (except low-dose aspirin): during Placebo Run-in	10	(8.1)	12	(9.4)	10	(7.8)	32	(8.4)
Concomitant chronic treatment with aspirin (except low-dose aspirin): during Placebo Run-in	2	(1.6)	6	(4.7)	3	(2.3)	11	(2.9)
Concomitant chronic treatment with other NSAIDs: during Placebo Run-in	9	(7.3)	7	(5.5)	7	(5.5)	23	(6.1)
Concomitant chronic treatment with sympathomimetic amines or NSAIDs (except low-dose aspirin): during treatment	9	(7.3)	18	(14.1)	15	(11.7)	42	(11.1)
Concomitant chronic treatment with NSAIDs (except low-dose aspirin): during treatment	9	(7.3)	14	(10.9)	14	(10.9)	37	(9.7)
Concomitant chronic treatment with aspirin (except low-dose aspirin): during treatment	3	(2.4)	6	(4.7)	3	(2.3)	12	(3.2)
Concomitant chronic treatment with other NSAIDs: during treatment	7	(5.6)	9	(7.0)	11	(8.6)	27	(7.1)
Concomitant treatment with MAO inhibitors, Tricyclic antidepressants and Phenothiazine derivatives: during Placebo Run-in	2	(1.6)	7	(5.5)	3	(2.3)	12	(3.2)
Trough vital signs taken between 12:01 and 23:59	5	(4.0)	9	(7.0)	8	(6.3)	22	(5.8)
Antihypertensives (at least one) during the Placebo Run-in period	13	(10.5)	6	(4.7)	9	(7.0)	28	(7.4)
Number of patients with no violations	18	(14.5)	20	(15.6)	21	(16.4)	59	(15.5)
Number of patients with at least one violation **	106	(85.5)	108	(84.4)	107	(83.6)	321	(84.5)

Note: A patient may have had more than one violation and may be counted twice.
**The number of patients include the 60 patients listed in Section 11.0, Errata. These patients may or may not have other violations and therefore are not subtracted from the total

2.4 Demography

The demographic characteristics of all patients (non-randomized and randomized) who entered the study are given in Table Epro-061-4.

Table Epro-061-4. Demographic characteristics of all non-randomized and randomized patients

			Randomized			
				Eprosartan 400 mg UID		
Demographics	Screening Only (n = 13)	Run-in Only (n = 136)	Placebo UID (n = 124)	HCTZ 12.5 mg UID (n = 128)	HCTZ 25 mg UID (n = 128)	Total (n = 380)
Age (years)						
≤65 years	8 (61.5)	93 (73.8)	94 (75.8)	111 (86.7)	105 (82.0)	310 (81.6)
>65 years	5 (38.5)	33 (26.2)	30 (24.2)	17 (13.3)	23 (18.0)	70 (18.4)
Mean ± SDM	59.1 ± 3.6	56.0 ± 1.1	55.6 ± 1.0	53.1 ± 0.9	55.1 ± 1.1*	54.6 ± 0.6*
Range	36 - 77	32 - 85	37 - 82	32 - 85	29 - 85	29 - 85
Sex						
Male	8 (61.5)	60 (47.6)	53 (42.7)	67 (52.3)	72 (56.3)	214 (56.3)
Female	5 (38.5)	66 (52.4)	69 (57.3)	61 (47.7)	56 (43.8)	166 (43.7)
Race						
Black	3 (23.1)	23 (18.3)	15 (12.1)	12 (9.4)	12 (9.4)	39 (10.3)
Caucasian	10 (76.9)	100 (79.4)	99 (79.8)	108 (84.4)	111 (86.7)	318 (83.7)
Oriental	0	2 (1.6)	2 (1.6)	3 (2.3)	2 (1.6)	7 (1.8)
Other**	0	1 (0.8)	8 (6.5)	5 (3.9)	3 (2.3)	16 (4.2)
Weight (kg)						
Mean ± SDM	83.6 ± 3.5+	80.2 ± 1.7	86.6 ± 1.8	86.4 ± 1.8	84.1 ± 1.6*	85.7 ± 1.0*
Range	69.4 - 108.0	48.3 - 144.4	51.8 - 150.7	44.3 - 137.4	44.5 - 134.5	44.3 - 139.7
Height (cm)						
Mean ± SDM	171.8 ± 2.8+	168.3 ± 1.0	169.8 ± 0.9	169.9 ± 1.0	168.5 ± 1.0*	169.4 ± 0.6*
Range	160.0 - 185.4	113.0 - 198.1	147.3 - 209.7	144.5 - 233.7	147.0 - 193.0	144.5 - 233.7

* Four patients randomized to eprosartan 400 mg/HCTZ 25 mg (PIDs: 061.052.00217, 061.274.00277, 061.472.00369, and 061.573.00457) did not have pre-dosetrough vital sign data, and therefore are not included in descriptive statistics for age, weight, and height.
** Other races included Hispanic, Asian, Hindustanic, White/Indonesian, 1/2 Japanese, Filipino, Guyanese, Mid-eastern, and East Indian
\+ Weight and height was available for only 10 of the 13 "Screening-only" patients.

2.5 Baseline characteristics

The sitting diastolic blood pressure was between 95 and 104 mmHg for the majority (311 or 81.8%) of randomized patients, and between 105 and 114 mmHg for the remaining (69 or 18.2%) patients. Most (294 or 77.4%) of the randomized patients had a history of prior use of antihypertensive agents (94 of 124 (75.4%) patients on placebo, 98 of 128 (76.6%) patients on eprosartan 400 mg/HCTZ 12.5 mg and 102 of 128 (79.7%) on eprosartan 400 mg/HCTZ 25 mg).

3 SAFETY RESULTS

3.1 **Deaths:** There were no deaths during the study or for 30 days following each patient's completion of the clinical trial.

3.2 **Withdrawals:** A total of 10 patients were withdrawn due to adverse experiences. Of these, 3 patients had serious, on-therapy adverse experiences which led to withdrawal (1 patient (#061.052.00257) for attempted suicide (randomized to placebo), 1 patient (#061.052.00217) for sarcoidosis, and 1 patient (#061.272.00273) for dizziness, anemia and adenocarcinoma of the esophagus, the latter two being randomized to eprosartan 400 mg/HCTZ 25 mg treatment group. 7 more patients with non-serious adverse experiences were also withdrawn. 4 had severe adverse experiences: 2 patients on eprosartan 400 mg/HCTZ 12.5 mg reported headache (#061.001.00052) and dyspepsia (#061.004.00071), 2 patients on eprosartan 400 mg/HCTZ 25 mg reported headache (#061.005.00033) and pharyngitis (061.004.00102). 2 other patients on eprosartan 400 mg/HCTZ 25 mg reported non-severe adverse experiences of nausea (#061.274.00277) and myalgia (061.573.00457), and 1 patient on eprosartan 400 mg/HCTZ 12.5 mg reported moderate abdominal pain (#061.007.00123). The details are shown in Table Epro-061-5.

Table Epro-061-5

Listing of Patients Withdrawn From the Study Due to On-therapy Adverse Experiences

Identification Patient Number	Age (years)	Sex (M/F)	Days on Double-blind	Reason for Withdrawal (Adverse Experience)	Days on Study at Onset	Duration	Intensity	Relationship
				Placebo UID				
061.052.00257*	41	F	25	Suicide Attempt	22	1 days	Severe	Not Related
				Eprosartan 400 mg/HCTZ 12.5 mg UID				
061.001.00052	62	F	21	Headache	21	2 days	Severe	Poss. Related
061.004.00071	41	M	14	Dyspepsia	1	Ongoing	Severe	Poss. Related
061.007.00123	64	M	31	Abdominal Pain	31	4 days	Moderate	Not Related
				Eprosartan 400 mg/HCTZ 25 mg UID				
061.052.00217*,**	60	F	5	Sarcoidosis	1	Ongoing	Severe	Not Related
061.004.00102	50	F	18	Pharyngitis	19(1)	4 days	Severe	Poss. Related
061.005.00033	47	F	42	Headache	16	Ongoing	Severe	Poss. Related
061.272.00273*,+	60	M	22	Dizziness	22	Ongoing	Severe	Not Related
061.274.00277	51	F	12	Nausea	2	11 days	Moderate	Poss. Related
061.573.00457	53	M	4	Myalgia	3	4 days	Mild	Poss. Related

* Adverse experience classified as serious (see Section 6.8).

** Although patient 061.052.00217 was withdrawn for adverse experience, the conclusion reason is listed as "protocol violation" in Data Source: Table 13.3, Appendix B, Listing 4, Appendix I, Listing 1. This patient did not have a screening chest x-ray (protocol violation) until the first day of double blind medication. When the results came back on Day 5 indicating sarcoidosis, the patient was withdrawn.

\+ Patient 061.272.00273 had other adverse experiences (esophageal carcinoma and anemia) that met the definition of serious.

3.3 **Serious, Non-fatal Adverse Events:** There were 8 patients with serious, on-therapy adverse experiences, 3 of which led to withdrawal (1 patient (#061.052.00257) for attempted suicide (randomized to placebo), 1 patient (#061.052.00217) for sarcoidosis, and 1 patient (#061.272.00273) for dizziness, anemia and adenocarcinoma of the esophagus, the latter two being randomized to eprosartan 400 mg/HCTZ 25 mg treatment group. Of the other 5 serious adverse experiences, 3 patients (#061.002.00157, #061.006.00046 (who had transient aphasia) , and #061.010.00017 who had atrial fibrillation) received placebo, 1 patient (#061.472.00401) received eprosartan 400 mg/HCTZ 12.5 mg and 1 patient (#061.052.00218) received eprosartan 400 mg/HCTZ 25 mg. Details are shown in Table Epro-061-6.

Table Epro-061-6

Listing of Randomized Patients With Serious On-therapy Adverse Experiences That Did Not Lead to Withdrawal From the Study

Identification Patient Number	Age (years)	Sex (M/F)	Days on Double-blind	Adverse Experience	Days on Study at Onset	Duration	Intensity	Relationship
				Placebo UID				
061.002.00157	54	M	60	Melanoma	60	1 day	Mild	Not Related
061.006.00046	75	F	51	Transient Aphasia	51	1 day	Moderate	Possibly Related
061.010.00017	66	M	55	Atrial Fibrillation	56(1)	3 days	Moderate	Not Related
				Eprosartan 400 mg/HCTZ 12.5 mg UID				
061.472.00401	50	F	56	Left Hip Prothesis due to Worsening of Arthrosis	16	14 days	Mild	Not Related
				Eprosartan 400 mg/HCTZ 25 mg UID				
061.052.00218	35	M	56	Gastroenteritis from strawberries resulting in 24 hr hospital stay	12	2 days	Severe	Not Related

3.4 **Adverse Events:** .

Headache was the most common adverse experience during the placebo run-in period, occurring in 71 of 380 (18.7%) patients (22 of 124 (17.7%) patients on placebo, 28 of 128 (21.9%) patients receiving eprosartan 400 mg/HCTZ 12.5 mg and 21 of 128 (16.4%) patients receiving eprosartan 400 mg/HCTZ 25 mg).

During the double-blind study period, the most common adverse experience was headache reported by 42 of 380 (11.1%) patients, with 17 of 124 (13.7%) patients receiving placebo, 15 of 128 (11.7%) of patients receiving

eprosartan 400 mg/HCTZ 12.5 mg, and 10 of 128 (7.8%) patients receiving eprosartan 400 mg/HCTZ 25 mg. The second most commonly reported on-therapy adverse experience was myalgia, being found in 29 of 380 (7.7%) patients (7 of 124 (5.6%) patients receiving placebo, 12 of 128 (9.4%) of patients receiving eprosartan 400 mg/HCTZ 12.5 mg and 10 of 128 (7.8%) of patients receiving eprosartan 400 mg/HCTZ 25 mg). Dizziness was reported by 17 of 380 (4.5%) patients (2 of 124 (1.6%) patients receiving placebo, 4 of 128 (3.1%) of patients receiving eprosartan 400 mg/HCTZ 12.5 mg and 11 of 128 (8.6%) of patients receiving eprosartan 400 mg/HCTZ 25 mg). Only 1 patient (#061.003.00066) receiving eprosartan 400 mg/HCTZ 25 mg reported postural hypotension.

3.5 Laboratory findings, ECGs, Vital signs

Only 3 of 376 patients whose vital signs were measured had values of clinical concern: 1 patient (#061.005.00035) on eprosartan 400 mg/HCTZ 12.5 mg had a reduction in systolic blood pressure of clinical concern, and 2 patients (#061.472.00398 and #061.472.00414) on eprosartan 400 mg/HCTZ 25 mg had heart rates (44 bpm and 48 bpm, respectively) of clinical concern.

ECG abnormalities that were not present at baseline and occurred for the first time during the double-blind on-therapy period were observed for 7 patients randomized to placebo, 7 to eprosartan 400 mg/HCTZ 12.5 mg, and 5 to eprosartan 400 mg/HCTZ 25 mg (Table Epro-061-7).

Table Epro-061-7 Number of patients with new ECG findings during the on-therapy period

ECG Abnormality	Placebo UID (n=109)		Eprosartan 400 mg UID: HCTZ 12.5 mg UID (n=106)		Eprosartan 400 mg UID: HCTZ 25 mg UID (n=113)	
	No.	(%)	No.	(%)	No.	(%)
Conduction						
First degree AV block	0	(0.0)	1	(0.9)	1	(0.9)
Left bundle branch block NOS	1	(0.9)	0	(0.0)	0	(0.0)
Left ventricular hypertrophy	3	(2.8)	1	(0.9)	1	(0.9)
Morphology						
EKG finding of ischemia	0	(0.0)	1	(0.9)	0	(0.0)
Myocardial infarction old	0	(0.0)	1	(0.9)	0	(0.0)
Rhythm						
Sinus bradycardia	1	(0.9)	3	(2.8)	1	(0.9)
Sinus tachycardia	0	(0.0)	0	(0.0)	2	(1.8)
Atrial fibrillation	2	(1.8)	0	(0.0)	0	(0.0)
Total with at least one new onset ECG abnormality	7		7		5	

There was no apparent effect of study medication on atrial rate, ventricular rate, PR interval, QRS interval or QTc in any treatment group, changes between baseline and study endpoint being minimal with the exception of the ECG abnormalities shown in Table Epro-061-8.

Table Epro-061-8 Listing of patients with on-therapy adverse experiences related to heart rate, rhythm or ECG abnormalities

Patient Identification Number	Sex	Age (years)	Days on Double-blind	Adverse Experience (Preferred Term)	Days on Study Med at Onset	Duration	Severity	Relationship	Action
				Placebo UID					
061.004.00118	Female	51	55	Palpitation	15	1 day	Mild	Possibly related	Dose interrupted
061.002.00136	Female	73	54	ECG abnormal	37	1 day	Mild	Possibly related	None
061.010.00017	Male	65	55	Fibrillation atrial**	55 (1)*		Mild	Unrelated	None
061.053.00228	Female	39	56	Palpitation	36 (1)*	3 days	Moderate	Unrelated	None
061.473.00405	Female	82	22	Fibrillation atrial	20	1 day	Severe	Unrelated	None
061.571.00432	Male	57	57	ECG abnormal, specific	23 (1)*		Mild	Unrelated	None
					56 (1)*		Mild	Unrelated	None
				Eprosartan 400 mg/HCTZ 12.5 mg UID					
061.003.00061	Female	52	57	Palpitation	36	10 days	Mild	Unrelated	None
061.473.00347	Female	51	56	Tachycardia	54	1 day	Mild	Possibly related	None
061.574.00472	Female	66	56	ECG abnormal, specific	37 (1)*		Mild	Unrelated	None
				Eprosartan 400 mg/HCTZ 25 mg UID					
061.002.00158	Male	54	41	Palpitation	36	7 days	Mild	Possibly related	None
061.053.00223	Female	48	56	Palpitation	3	12 days	Mild	Unrelated	None
061.274.00369	Male	28	56	Palpitation	44	56 days	Mild	Possibly related	None
061.472.00398	Male	58	56	Extrasystoles	29		Moderate	Possibly related	None

* ( ) indicates the number of days after the last dose of randomized medication.
** This adverse experience was considered by the investigator to be serious.

There were no marked change in baseline and endpoint values for hematology and blood chemistry tests between placebo and eprosartan/HCTZ treatments. 77 of 380 (20.3%) patients had on-therapy laboratory values of clinical concern (25 of 124 (20.2%) on placebo, 28 of 128 (21.9%) of patients receiving eprosartan 400 mg/HCTZ 12.5 mg, and 24 of 128 (18.8%) patients receiving eprosartan 400 mg/HCTZ 25 mg. The laboratory parameter most frequently found to be abnormal was fasting blood glucose.

24 of 380 (6.3%) patients reported on-therapy adverse experiences related to clinical laboratory results: (9 of 124 (7.3%) on placebo, 4 of 128 (3.1%) of patients receiving eprosartan 400 mg/HCTZ 12.5 mg, and 11 of 128 (8.6%) patients receiving eprosartan 400 mg/HCTZ 25 mg (Table Epro-061-9). All adverse experiences were mild or moderate in intensity and no patients were withdrawn because of adverse experiences related to laboratory results. Increased creatinine phosphokinase and hypokalemia were the most common on-therapy adverse experiences related to laboratory results.

Table Epro-061-9

Listing of Patients with On-therapy Adverse Experiences Related to Laboratory Results

Patient Identification Number	Adverse Experience	Days on Study Mode of Onset	Severity	Relationship	Lab Test (Reference Range)*	Baseline Value	Highest or Lowest Value [Day]	Last Value [Day]
				Placebo				
061.002.00152	Creatine phosphokinase increased	60 (1)	Moderate	Possibly related				
061.005.00133	Creatine phosphokinase increased	62 (1)	Mild	Possibly related				
061.006.00046	Diabetes	28	Mild	Unrelated				
061.007.00055	Gout	25	Mild	Unrelated				
061.011.00104	Lymphopenia	14	Mild	Unrelated				
061.052.00211	Pyuria	15	Mild	Unrelated				
061.052.00227	Hepatic enzymes increased	15	Moderate	Unrelated				
061.052.00228	Hematuria	57 (1)	Mild	Unrelated				
	Hypokalemia	57 (1)	Mild	Unrelated				
061.052.00262	Urinary tract infection**	7 44	Moderate	Unrelated				
				Eprosartan 400 mg/HCTZ 12.5 mg UID				
061.004.00008	Urinary tract infection	9	Mild	Unrelated				
061.006.00044	Gout	-8	Moderate	Unrelated				
061.008.00081	Creatine phosphokinase increased	57 (1)	Mild	Possibly related				
061.574.00469	Hyperglycemia	15	Mild	Possibly related				
				Eprosartan 400 mg/HCTZ 25 mg UID				
061.002.00036	Hypokalemia	57 (1)	Moderate	Related				
061.002.00158	Hypokalemia	16	Mild	Related				
061.002.00161	Hypokalemia**	9	Mild	Related				
		32 (1)	Moderate	Related				
	Creatine phosphokinase increased	32 (1)	Moderate	Possibly related				
061.005.00066	SGPT (ALAT) increased**	8	Mild	Not related				
	Hyperuricemia	15 15	Mild Mild	Not related Related				
061.006.00045	Urinary tract infection	14	Mild	Not related				
061.007.00060	Creatine phosphokinase increased**	16 57 (1)	Moderate Mild	Possibly related				
061.052.00496	Hypokalemia	57 (1)	Mild	Possibly related				
061.275.00302	BUN increased	13	Mild	Possibly related				
	Creatine phosphokinase increased**	13	Mild	Possibly related				
	NPH increased	13	Mild	Possibly related				
061.471.00581	Leukocytosis	13	Mild	Unrelated				
061.472.00353	Gout	34	Moderate	Possibly related				
061.571.00431	Creatine phosphokinase increased	48	Mild	Unrelated				

* Reference ranges for fasting glucose are age-dependent and reference ranges for creatine phosphokinase are gender-dependent.
** The same adverse experience occurred at least twice during the study.
Key: Investigator-designated Severity: Mild, Moderate, or Severe. Investigator-designated Relationship: Unrelated, Possibly Related, or Related. Days on study medication are presented relative to the first dose of randomized medication, numbers in ( ) indicate the number of days after the last dose of randomized medication.

4. EFFICACY RESULTS

4.1 Statistical considerations

This study was overpowered because it enrolled more patients (approximately 126 per group were randomized) than were needed (70 patients per group) to detect a difference of 5 mm Hg between two treatment groups. Thus, the statistically significant differences in efficacy parameters detected at study endpoint may be due to over-enrollment.

4.2 Primary Efficacy Parameter

The reduction in mean sitting diastolic blood pressure from baseline to endpoint ranged in a dose-related (to HCTZ) manner from 5.4 mmHg for the placebo group to 12.2 mmHg for the eprosartan 400 mg/HCTZ 25 mg once/day treatment group (Table Epro-061-10), the differences between active treatment groups and placebo being statistically significant. Table Epro-061-10 also shows that the reduction in SitDBP due to placebo effect was 5.4 mmHg, that due to HCTZ was 2.4 mmHg for the 12.5 mg dose and 4.8 mmHg for the 25 mg dose, leaving a relatively small reduction in SitDBP of 2.0 mmHg attributable to the eprosartan 400 mg once/day dose.

Analysis of SitDBPs at each visit showed that the maximum response was achieved at Week 6 with eprosartan 400 mg/HCTZ 12.5 mg treatment, and at Week 8 with eprosartan 400 mg/HCTZ 25 mg treatment.

Table Epro-061-10. Mean (±SE) trough sitting diastolic blood pressure at baseline and study endpoint, and mean change from baseline in trough sitting diastolic blood pressure at study endpoint (95% Bonferroni confidence intervals)

	MEDICATION REGIMEN		
SitDBP (mmHg)	Placebo (n=124)	Epro+HCTZ 12.5mg (n=128)	Epro + HCTZ 25 mg (n=124†)
Baseline	101.0 ± 0.3	101.3 ± 0.4	99.8 ± 0.3
Study Endpoint	95.6 ± 0.8	91.5 ± 0.7	87.6 ± 0.7
Change from Baseline	-5.4 ± 0.8	-9.8 ± 0.7	-12.2 ± 0.6
Difference from placebo (95% CI) p-value		-4.4 (-6.7, -2.1) < 0.0001*	-6.9 (-9.1, -4.6) < 0.0001*
Difference from epro + 12.5 mg HCTZ (95% CI) p-value			-2.5 (-4.7, -0.2) 0.0095*

n = number of patients with a baseline value and study endpoint value
* Indicates significance at 0.05 using modified Bonferroni procedure
† 4 patients (#061.052.00217, #016.274.00277, #061.472.00340, and #061.573.00457) randomized to eprosartan 400 mg/ HCTZ 25 mg did not have any trough (pre-dose) vital signs taken after randomization and were not included in analysis.

4.3 **Secondary Efficacy Parameters**

Decreases from baseline to study endpoint in mean sitting systolic blood pressure ranged from 5.5 mmHg for the placebo group to 16.3 mmHg for the eprosartan 400 mg/HCTZ 25 mg once/day regimen (Table Epro-061-11), the differences between active treatment groups and placebo being statistically significant. There was no change in sitting heart rate. Table Epro-061-11 also shows that the reduction in SitSBP due to placebo effect was 5.5 mmHg, that due to HCTZ was 2.3 mmHg for the 12.5 mg dose and 4.6 mmHg for the 25 mg dose, leaving a reduction in SitSBP of 6.2 mmHg attributable to the eprosartan 400 mg once/day dose.

Table Epro-061-11. Mean (±SE) trough sitting systolic blood pressure and heart rate at baseline and study endpoint, and mean change from baseline in trough sitting diastolic blood pressure at study endpoint (95% Bonferroni confidence intervals)

	MEDICATION REGIMEN		
Vital Signs	Placebo (n=124)	Epro+HCTZ 12.5mg (n=128)	Epro + HCTZ 25 mg (n=124†)
SitSBP (mmHg)			
Baseline	155.8 ± 1.4	154.1 ± 1.3	154.2 ± 1.3
Study Endpoint	150.3 ± 1.5	140.0 ± 1.4	137.9 ± 1.4
Change from Baseline	-5.5 ± 1.1	-14.0 ± 1.1	-16.3 ± 1.1
Difference from placebo (95% CI) p-value		-8.6 (-12.3, -4.9) < 0.0001*	-10.9 (-14.6, -7.1) < 0.0001*
Difference from epro + 12.5 mg HCTZ (95% CI) p-value			-2.3 (-6.0, -1.5) 0.145
SitHR (bpm)			
Baseline	74.1 ± 0.7	74.5 ± 0.7	74.1 ± 0.8
Study Endpoint	74.1 ± 0.9	73.9 ± 0.8	72.8 ± 0.9
Change from Baseline	0.1 ± 0.7	-0.6 ± 0.6	-1.2 ± 0.6

n = number of patients with a baseline value and study endpoint value
* Indicates significance at 0.05 using modified Bonferroni procedure,
† 4 patients (#061.052.00217, #016.274.00277, #061.472.00340, and #061.573.00457) randomized to eprosartan 400 mg/ HCTZ 25 mg did not have any trough (pre-dose) vital signs taken after randomization and were not included in analysis.

The total percentages of patients who responded at endpoint were also dose related to HCTZ, being 29% in placebo group, 55.5% in eprosartan 400 mg/HCTZ 12.5 mg once/day group and 73.4% in the eprosartan 400 mg/HCTZ 25 mg once/day group (Table Epro-061-12), the differences between placebo and each of the active treatment groups being statistically significant (by Cochran Mantel Haenszel analysis). Here, too, in a dose related (to HCTZ) manner, the percentage of responders due to placebo effect was 29%, that due to HCTZ was 17.9% for the 12.5 mg dose and 35.8% mmHg for the 25 mg dose, leaving a meager 8.6% percentage of responders attributable to the eprosartan 400 mg once/day dose.

Analyses of subgroups showed that eprosartan 400 mg/HCTZ 25 mg once/day treatment reduced the SitDBP significantly compared to placebo for all subgroups except patients whose race was classified as "Other", and for

those patients with baseline SitDBP ≥105 mmHg. Subgroups containing larger number of patients (all subgroups except Oriental patients and patients whose race was classified as "Other") showed a dose related (to HCTZ) responder rate ranging from 13.3-43.3% in placebo group, 51.0-82.4% for eprosartan 400 mg/HCTZ 12.5 mg treatment group to 66.7-82.6% for eprosartan 400 mg/HCTZ 25 mg treatment group.

Table Epro-061-12. Number (%) of patients who responded (Patients with SitDBP < 90 mmHg, or 90-100 mmHg and decreased from baseline by at ≥ 10 mmHg) at study endpoint (Cochran Mantel Haenszel Analysis)

	MEDICATION REGIMEN					
Response	Placebo (n=124)		Epro+HCTZ 12.5mg (n=128)		Epro + HCTZ 25 mg (n=124†)	
Endpoint	No.	(%)	No.	(%)	No.	(%)
<90 mmHg	30	(24.2)	57	(44.5)	77	(62.1)
90-100 mmHg**	6	(4.8)	14	(10.9)	14	(11.3)
Total	36	(29.0)	71	(55.5)	91	(73.4)
Relative Risk (95% CI) p-value			1.59 (1.22, 2.08) < 0.001*		2.62 (1.87, 3.68) < 0.001*	
Relative Risk (95% CI) p-value					-1.66 (-1.11, 2.51) 0.003*	

n = number of patients with a baseline value and study endpoint value
* Indicates significance at 0.05 using modified Bonferroni procedure; ** The decrease must have been at least 10 mmHg from baseline.
† 4 patients (#061.052.00217, #016.274.00277, #061.472.00340, and #061.573.00457) randomized to eprosartan 400 mg/ HCTZ 25 mg did not have any trough (pre-dose) vital signs taken after randomization and were not included in analysis.

5. CONCLUSION

At the doses used, eprosartan/HCTZ combinations showed no differences from placebo in clinical and laboratory safety profiles. No excessive lowering of blood pressure and no effect on heart rate were found.

There was a dose-related (to HCTZ) statistically significant reduction in sitting diastolic blood pressure compared to placebo. However, the reduction in SitDBP attributable to eprosartan 400 mg once/day was small (2 mmHg) compared to that due to placebo effect (5.4 mmHg) and HCTZ 12.5 mg (2.4 mmHg) and 25 mg (4.8 mmHg). Secondary efficacy parameters (sitting systolic blood pressure and percentage of patients who responded at endpoint) also showed the same trend, with a reduction in sitting systolic blood pressure of 6.2 mmHg (compared to 5.5 mmHg for placebo) and a responder rate of 8.6% (compared to 29% for placebo) attributable to eprosartan 400 mg once/day. Over-enrollment of patients (124-128 patients per group rather than the required 70 patients per group) may have contributed to the finding of spurious statistical significance in the efficacy parameters between the eprosartan/HCTZ treatment groups and the placebo treatment group.

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Khin Maung U, MBBS, MMedSc, MD(NSW), MD, FACP

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS

MEDICAL OFFICER REVIEW OF CLINICAL PHARMACOLOGY

NDA #:	20-738		
DRUG NAME:	**Teveten™ (Eprosartan)** Tablets		
SPONSOR:	SmithKline Beecham Pharmaceuticals		
TYPE OF DOCUMENT:	New NDA (Clinical Pharmacology Review)		
DATE OF CORRESPONDENCE:	*11-Oct-1997*	DATE ASSIGNED:	*02-May-1997*
DATE RECEIVED:	*18-Oct-1996*	DATE COMPLETED	*07-Aug-1997*
MEDICAL OFFICER:	Khin Maung U, M.D.		

INTRODUCTION

In this clinical pharmacology review of NDA 20-738 Teveten™ (eprosartan), a summary of the clin-pharm review incorporating data from the clin-pharm trials in an integrated manner is first presented. This information may be referenced to when drafting appropriate sections of the labeling for eprosartan.

The clin-pharm review summary is followed by separate sections on review of dose-response studies and bioequivalence trials. The information in these sections would be important in the consideration of recommendations for dosing of eprosartan. The findings may be incorporated together with data from the efficacy review of eprosartan for a final dosing recommendation to go into the label.

A draft label for the clinical pharmacology, precautions and dosage and administration sections of the package insert for eprosartan follows. A brief discussion of the issues that still need to be considered because valid inferences could not be made is outlined.

A listing of clinical pharmacology trials is given in Table 1 (mainly pharmacodynamic or PD trials) and Table 2 (mainly pharmacokinetic or PK trials). Seven clinical pharmacology trials contained both PD and PK information, and they are presented in both tables. During the month of July (about 3 weeks before this review was completed), the sponsor submitted two more trials for review (Study #051 and Study #061). Study #051 contained PD data related to change in left ventricular mass index following treatment with eprosartan or enalapril, and it is reviewed under PD clinical pharmacology trials. Study #061 contained efficacy and safety data related to use of eprosartan with HCTZ; it is also reviewed under PD clinical pharmacology trials.

After the two summary tables, a list of clinical pharmacology trial protocols is presented in serial order of the protocol numbers.

This list is followed by a detailed review of each clinical pharmacology trial presenting more complete information regarding study design, patient population, statistical assumptions used for sample size, primary and secondary endpoints, safety data related to clinical, laboratory and ECGs parameters, and detailed PD and/or PK results.

CLINICAL PHARMACOLOGY REVIEW OF NDA 20-738 (EPROSARTAN) SUMMARY

CLINICAL PHARMACOLOGY

Mechanism of Action
Eprosartan is claimed to block the binding to angiotensin II to the AT_1 receptor in tissues (e.g., vascular smooth muscle and adrenal gland).

There was no partial agonist activity on effective renal plasma flow (ERPF) as measured by CL_{PAH} following a single oral dose of eprosartan 350 mg which increased ERPF at 1 hour (by 27.5%) and 4 hours (by 13.6%) under salt replete conditions (Protocol #006).

The angiotensin II blocking activity of eprosartan was found in healthy subjects in whom single oral doses of 200 mg (on low or high salt diet) and 400 mg (Protocol #043, Part 1 B and Part 2) and of 350 mg eprosartan (Protocol #006 Parts 1, 2 and 3) blocked the vasoconstricting effects of angiotensin II infusion on ERPF.

In healthy subjects, eprosartan reduces serum aldosterone concentrations following single oral doses of eprosartan above 10 mg (Protocol #043). A dose related reduction in serum aldosterone concentrations over the range of 10-200 mg eprosartan was observed (Protocol #006). A single oral dose of 350 mg eprosartan blunted the Angiotensin II-induced increase in serum aldosterone concentrations (Protocol #006). While low salt diet increased serum aldosterone concentrations, eprosartan (200 mg and 400 mg doses) given with low salt diet suppressed the rise in serum aldosterone concentrations due to low salt diet, and blocked the further rise in serum aldosterone concentrations induced by Angiotensin II infusion (Protocol #0043).

Plasma renin activity was increased following single oral doses of eprosartan 50 mg and above, and in subjects given 200 mg or 400 mg eprosartan with low salt diet (Protocol #043). In subjects on low salt diet receiving eprosartan 200 mg or 400 mg, the mean plasma renin activity increased which was not suppressed by infusion of angiotensin II (Protocol #043 Part 1 B and Part 2).

Pharmacokinetics
Following intravenous dosing, plasma concentrations of eprosartan were not detectable or very low in the majority of subjects given intravenous doses of 0.1 and 0.3 mg, but were measurable for 2 to 4 hours at 1, 3, and 5 mg doses, and for up to 8-10 hours following 10 and 20 mg doses of eprosartan (Protocol #004). In Table Epro-004-1, Median Cmax, AUC(0-τ) and AUC(0-∞) increased in a dose proportional manner over 1 mg to 20 mg intravenous dose range. Cmax of eprosartan (Protocol #004) and of total radioactivity (Protocol #020) were seen at 0.5 hour and declined from peak in a bi-exponential manner. Median $T_{1/2}$ for the 1 to 20 mg intravenous doses of eprosartan ranged from 1.05 to 2.34 hours.

Following oral dosing with single doses of eprosartan oral solution or eprosartan tablets, peak plasma concentrations were achieved within 1 to 2 hours (Protocol #003, #006 Part 3, and #020 with labeled eprosartan) and within 1-3 hours (Protocol #006 Part 2, and #008), respectively. Plasma concentrations were measurable for 3 to 6 hours following 1, 3, 10 mg doses, for 10-12 hours following 30, 50 and 100 mg doses (solution or tablets), and 12 to 24 hours following the 200 mg (solution or tablet) and 350 mg (tablet) doses (the values at 12 and 24 hours being < 1-5% of peak concentrations) (Protocol #003).

Cmax, AUC(0-τ) and AUC(0-∞) increased in a dose proportional manner with the oral eprosartan solution up to 200 mg (Protocol #003). With eprosartan tablets at higher doses (100, 200 and 350 mg), Cmax, AUC(0-τ) and AUC(0-∞) increased with an increase in dose but were not dose proportional (Protocol #003), with median Cmax and median AUC(0-τ) increasing approximately 10-fold over the entire 20-fold dose range (Protocol #006).

The point estimate and 90% confidence intervals of dose-normalized AUC(0-τ') and dose-normalized Cmax for the 200 mg dose were contained within the protocol-specified 20% acceptance range for equivalence (0.80, 1.25) in Table Epro-008-2. Thus, dose-proportionality was concluded for the 200 mg dose relative to the 100 mg reference dose (Protocol #008). The 90% confidence interval for the dose-normalized AUC(0-τ') for the 800 mg dose to the 100 mg reference dose, and the 90% confidence interval for the dose-normalized Cmax for the 400 mg and 800 mg doses to the 100 mg reference dose were not contained within the acceptance range (Protocol #008).

Table Epro-004-1. Pharmacokinetic values for intravenous eprosartan administered to healthy volunteers

Parameter	Cmax [ng/ml]	T1/2 [h]	AUC(0-t) [ng.h/ml]	AUC(0-∞) [ng.h/ml]
0.1 mg (n=4)				
Mean	NC	NC	NC	NC
0.3 mg (n=4)				
Mean ± SD	38.9±10.8	NC	NC	NC
Median	36.3	NC	NC	NC
1 mg (n=4)				
Mean±SD	120.7±34.5	1.23±0.53	110.3±46.7	130.7±46.1
Median	118.8	1.05	110.5	136.0
3 mg (n=4)				
Mean±SD	333.2±20.5	2.24±1.85	458.8±215.6	499.2±238.2
Median	333.2	1.45	377.3	409.4
5 mg (n=4)				
Mean±	555.6±159.0	1.79±0.60	595.1±223.5	628.8±218.2
Median	592.9	1.68	631.7	663.7
10 mg (n=4)				
Mean±	1313.2±345.2	2.10±0.40	1573.0±537.6	1602.1±531.0
Median	1173.3	2.05	1430.3	1459.1
20 mg (n=4)				
Mean±	2286.7±734.1	2.24±0.32	2448.9±895.0	2490.8±901.3
Median	2404.6	2.34	2452.7	2500.2

Table Epro-008-2. Point Estimates and 90% confidence intervals of comparisons of eprosartan doses

Parameter	Comparison	Point Estimate	90% Confidence Interval
AUC(0-τ')†	200mg : 100mg	0.93	(0.83, 1.06)
AUC(0-τ')†	400mg : 100mg	0.83	(0.73, 0.93)
AUC(0-τ')†	800mg : 100mg	0.69	(0.61, 0.78)
Cmax†	200mg : 100mg	0.85	(0.74, 0.97)
Cmax†	400mg : 100mg	0.76	(0.66, 0.87)
Cmax†	800mg : 100mg	0.55	(0.48, 0.64)
Tmax§	200mg - 100mg	0.02 h	(-0.45 h, 0.48 h)
Tmax§	400mg - 100mg	0.26 h	(-0.02 h, 0.73 h)
Tmax§	800mg - 100mg	-0.01 h	(-0.27 h, 0.49 h)

† Data presented as the ratio of the geometric means of each dose relative to the 100 mg reference dose
§ Data presented as the median difference of each dose and the 100 mg reference dose

Table Epro-008-1. Dose-normalized pharmacokinetic values for eprosartan following single oral doses

End Point	100 mg	200 mg	400 mg	800 mg
Dose-normalized AUC(0-τ') (ng.h/ml)				
Geometric Mean	12.75	11.90	10.46	8.76
Mean±	13.96±6.27	12.77±5.07	11.65±6.18	9.30±3.45
Median	11.75	11.87	10.97	8.03
Dose-normalized Cmax (ng/ml)				
Geometric Mean	3.90	3.29	2.94	2.15
Mean±	4.39±2.34	3.51±1.27	3.18±1.44	2.32±0.92
Median	3.95	3.27	3.11	2.17
AUC(0-τ) (ng.h/ml)				
Mean±	1400±637	2620±1046	4887±2525	7855±2782
Median	1175	2374	4476	6977
Dose-normalized AUC(0-τ) (ng.h/ml)				
Mean±	14.00±6.37	13.10±5.23	12.22±6.31	9.82±3.48
Median	11.75	11.87	11.19	8.72

† Tmax presented as median (range).

While the mean AUC(0-τ') and the mean Cmax increased with increasing dose over the 100-800 mg single oral dose range, the mean dose-normalized AUC(0-τ') and the mean dose-normalized Cmax (Table Epro-008-1) showed a decreasing trend with increasing dose (Protocol #008). These findings suggest saturation of absorption of eprosartan over the 100 mg to 800 mg oral dose range.

The median Tmax ranged from 1 to 1.5 hours, and is similar for both the oral solution formulation and the tablet formulation (Protocol #003). The median Tmax was 1-2 hours (Part 2) and 1.75 - 2.5 hours (Part 3) in Protocol #006, and 2.5-3 hours for the 100, 200, 400 and 800 mg doses in Protocol #008. These findings suggest that the rates of absorption of the different doses of eprosartan were similar.

Median $T_{1/2}$ for the 30, 50 and 100 mg doses of eprosartan ranged from 2.68 to 3.15 hours for eprosartan solution and 2.49 to 3.26 hours for eprosartan tablets; for 200 mg dose, the median $T_{1/2}$ was 4.51 hours for eprosartan oral solution and 3.92 for eprosartan tablets; for the 350 mg dose of eprosartan, the median $T_{1/2}$ was 5.28 hours (Protocol #003).

However, in the above studies, each subject did not receive all of the doses, and the number of subjects per dose group was small; thus, no definitive conclusions could be drawn regarding dose proportionality or the relative bioavailability of the tablet formulation.

Metabolism and elimination

Acyl glucuronidation was the only metabolic pathway found (Protocol #020). The acyl glucuronide was not detectable in plasma nor feces. This metabolite accounted for approximately 20% of the radioactivity in the urine (Protocol #020). The eprosartan acyl glucuronide is presumed to be excreted into the intestinal lumen via the bile. The major route of excretion was via the feces (61 and 90% of dose excreted after i.v. and oral administration, respectively). Urinary excretion account for 37% and 7% of dose being excreted after intravenous and oral administration, respectively (Protocol #020).

Distribution

The median steady state volume of distribution (Vss) was about 13 liters (Protocol #004) to 17 liters (Protocol #020) which approximates total extracellular water. This small steady-state volume of distribution indicates minimal tissue distribution of eprosartan and a high degree of plasma protein binding (approximately 98%).

The median plasma clearance at steady state for the 3 to 20 mg doses was approximately 7.5 L/h (Protocol #004) to 9 L/h (Protocol #020). The blood clearance of eprosartan (based on a blood-to-plasma ratio of 0.62 for eprosartan) was approximately 12 L/h (Protocol #004) to 14.7 L/h (Protocol #020). Assuming normal hepatic blood flow of 1500 ml/min and negligible renal clearance of eprosartan, the estimated hepatic extraction ratio of eprosartan is approximately 0.15 (Protocol #004) to 0.17 (Protocol #020), giving an absolute bioavailability of approximately 83% (Protocol #020) to 85% (Protocol #004) when eprosartan was administered by the intravenous route.

Bioavailability (and effect of food)

The relative bioavailability (tablet/solution) based on median AUC values was approximately 70%, 80% and 60% for the 50 mg, 100 mg dose and 200 mg doses of eprosartan, respectively (Protocol #003). Using iv data obtained in Protocol 004 with the data from this study, the absolute bioavailability of eprosartan estimated from the median AUC(0-∞) values ranges from approximately 12% to 18% for the tablet formulation and 21% to 24% for the oral solution formulation. In a study using ^{14}C-labeled eprosartan (Protocol #020), the average absolute bioavailability of eprosartan following oral administration was 14.7% (range: 8.6 to 24.0%). The reasons for low bioavailability of eprosartan were: (i) low absorption rather than extensive first pass metabolism, (ii) slow absorption of eprosartan and (iii) absorption throughout the small and large intestine (rather than fecal elimination due to poor solubility).

Peak plasma concentrations were reached earlier by about 1 hour when single oral doses of eprosartan (300 mg, 350 mg or 800 mg, in Protocols #005, 007 and 086, respectively) were given in the fasted state than when given with a high fat meal.

The AUC(0-τ) was larger by 56% and 20%, respectively, when 350 mg and 800 mg doses of eprosartan were given with a high fat meal (Protocol #007 and #086, respectively). The 95% confidence intervals for AUC(0-τ) do not include the value 1.00 indicating a food effect on AUC(0-τ). At a lower dose of 300 mg eprosartan (Protocol

#005), AUC(0-∞) was decreased (by 9.9%) in the fed state compared to the fasted state; the 95% confidence intervals for AUC(0-∞) contained the value 1.00 suggesting no food effect (Table Epro-005-2/007-3/086-2).

Cmax in the fed state was 25% lower than in the fasted state for the 300 mg dose of eprosartan (Protocol #005). Cmax was 7% less when 800 mg eprosartan was given after a high fat meal compared to the fasted condition (Protocol #086). The 95% confidence intervals for Cmax (Protocol #086) include the value 1 indicating no substantial difference produced by food. On the other hand, the Cmax was 80% higher when 350 mg (7 x 50 mg) eprosartan was given after a high fat meal compared to the fasted condition (Protocol #007). The 95% confidence intervals for Cmax do not include the value 1.00 indicating a food effect on Cmax (Protocol #007).

Table Epro-005-2/007-3/086-2. Point Estimates and 90% confidence intervals of comparisons of oral and i.v. eprosartan in fed and fasted states

Protocol #	Parameter	Comparison	Point Estimate	95% Confidence Interval
005	*AUC(0-∞)†*	B:A	0.89	(0.70, 1.13)
	Cmax†	B:A	0.75	(0.58, 0.96)
	Tmax§	B-A	1.25 h	(0.75 h, 1.75 h)
007	*AUC(0-τ)†*	B:A	1.56	(1.26, 1.93)
	Cmax†	B:A	1.80	(1.48, 2.17)
	Tmax§	B-A	0.63	(-0.75 h, 2.25 h)
086	*AUC(0-τ)†*	B:A	1.20	(1.01, 1.41)
	Cmax†	B:A	0.93	(0.77, 1.12)
	Tmax§	B-A	1.75 h	(1.00 h, 2.50 h)

† Data presented as the ratio of the geometric means for oral eprosartan in regimen B (fed) : regimen A (fasted)
§ Data presented as the median difference of oral eprosartan in regimen B (fed) - regimen A (fasted) and 95% C.I.

All of the above findings probably suggest variability of absorption when eprosartan was given with food.

The high fat meal caused a delay in Tmax of 1.25 hours for the 300 mg dose (Protocol #005), 0.63 hours for the 350 mg dose (Protocol #007) and 1.75 hours for the 800 mg dose of eprosartan (Protocol #086). The 95% confidence intervals for Tmax of the first two studies included the value zero suggesting that the rate of absorption is not different in the fed and fasted states. However, the 95% confidence interval for Tmax in Protocol #086 does not include the value zero suggesting that the rate of absorption is different in the fed and fasted states.

Overall, the results suggest that administration of eprosartan with a high fat meal:
(i) slightly delayed the rate of absorption which was not clinically significant, and
(ii) did not effect the extent of absorption (Protocol #005) or slightly increased the extent of absorption (by 56% for the 350 mg dose (Protocol #007) and 20% for the 800 mg dose (Protocol #086) of eprosartan).

It may thus be suggested that eprosartan can be given orally without regard to meal times.

Special Populations

Pediatric
The pharmacokinetics of eprosartan have not been investigated in patients < 18 years of age.

Geriatric
Following a single oral dose of 200 mg eprosartan, elderly men had peak plasma concentrations of eprosartan between 3 and 6 hours for elderly men (compared to 2 and 4 hours for young males); the plasma concentrations then declined in a multi-exponential manner. Eprosartan was highly protein bound to plasma proteins (approximately 98%) with no apparent differences in the mean fraction unbound between elderly males relative to young males. In Table Epro-025-1, total and free mean AUC(0-∞), mean Cmax, and median Tmax values in the elderly were > 2-fold larger compared to young males (Protocol #025).

Gender
In young females, peak plasma concentrations after a single oral dose of 200 mg eprosartan was reached 2 and 4 hours similar to young men. Subsequent plasma concentrations of eprosartan declined in a multi-exponential manner. In Table Epro-025-1, there were no differences in the mean fraction unbound (approximately 2%), total and unbound AUC(0-∞) or Cmax, and in Tmax or terminal half-life ($T_{1/2}$) values between young males and young females (Protocol #025).

Table Epro-025-1. Pharmacokinetics of single oral dose (200 mg) eprosartan in young males, young females and elderly males

End Point	Young Males	Young Females	Elderly Males
AUC(0-∞) (ng.h/ml)			
Geometric Mean	1828	1817	4215
Mean±	2171±1544	2322±1806	4572±1653
Median	1429	1383	4600
Cmax (ng/ml)			
Geometric Mean	418	435	828
Mean±	498±347	599±509	914±353
Median	349	323	940
Tmax (h)			
Mean±	2.75±0.46	3.52±0.76	4.89±1.25
Median	3.00	4.00	5.04
T1/2 (h)			
Mean±	2.81±0.49	3.76±2.04	6.19±1.58
Median	2.89	3.10	5.79
fu (%)			
Mean±	2.11±0.31	2.15±0.22	2.17±0.22
Free AUC(0-∞) (ng.h/ml)			
Geometric Mean	38.2	38.9	91.2
Mean±	44.7±30.5	49.7±40.5	98.5±34.6
Median	32.6	30.5	106.8
Free Cmax (ng/ml)			
Geometric Mean	8.73	9.32	17.92
Mean±	10.19±6.65	12.86±11.23	19.82±7.93
Median	7.95	7.65	19.08

In Patients with Hypertension

Table Epro-009-3/048-2. Pharmacokinetic values for eprosartan following repeat oral doses for 7 days

Protocol	Protocol #009				Protocol #048		
Endpoint	50 mg	100 mg	150 mg bid	350 mg	600 mg	800 mg	1200 mg
Cmax (ng/ml)							
Mean± S.D.	672.6± 674.9	1480.2±8 66.6	1634.9± 710.2	1818.0±76 3.4	1608± 726	2103± 1502	2961± 1432
Median	395.4	1296.9	1712.1	1627.9	1332	1748	2457
Tmax (hr)							
Mean±S.D.	1.84±0.83	1.38±0.42	1.81±1.19	1.97±1.07	2.56±1.82	1.88±1.09	2.72±1.60
Median	1.75	1.50	1.50	1.75	2.25	1.50	3.00
AUC(0-τ) (ng.h/ml)							
Mean± S..D.	2770± 2783	5768± 2792	6340± 2818	8067± 2936	9731± 4381	9521± 4975	19125± 8632
Median	1776	5298	6600	8173	9198	9165	20062
AUC(0-∞) (ng.h/ml)							
Mean± S.D.	2923± 2766	6284± 3015	–	8184± 3169	10786±4 963	10443±4 818	22423± 10749
Median	1873	5617	–	6651	10204	10246	21695
$T_{1/2}$ (h)							
Mean±S.D.	5.74±3.51	9.60+7.09	–	7.76±1.40	9.02±3.13	8.64±4.17	12.24±6.58
Median	5.37	7.73	–	7.81	7.85	8.93	9.22
Accumulation Ratio							
Geometric Mean	0.78	1.04	1.02	0.80	1.11	0.85	1.14±
Minimum	0.28	0.50	0.63	0.31	0.72	0.52	0.62
Maximum	2.46	2.44	1.63	1.51	1.68	1.93	2.50

Accumulation Ratio = {$AUC_{(0-\tau)}$ on Day 7} ÷{$AUC_{(0-\infty)}$ on Day 1}

At the doses studied (50, 100, 350 mg qd and 150 mg bid in Protocol #009, and 600, 800 and 1200 mg qd in Protocol #048), the plasma concentrations reached peak values within 1 to 3 hours. Plasma levels were < 10% of peak values after 12 hours (Protocol #009 and #048). In Table Epro-009-33/048-2, $T_{1/2}$ was longer for higher doses. being between 8.64 to 12.24 hours for the 600, 800 and 1200 mg qd doses (Protocol #048) and between 4.09 and 9.6 hours for the 50, 100, 350 mg qd doses and 150 mg bid dose (Protocol #009). Table Epro-009-33/048-2 also showed that a dose-related increase in mean Cmax, AUC(0-t) and AUC(0-∞) were found (except for AUCs for the 800 mg dose after 7 days). There was no accumulation with repeated doses (Protocol #009, #048). Steady-state appeared to be reached by Day 4 (Protocol #048).

The above pharmacokinetic data in hypertensive patients suggest that eprosartan requires bid dosing.

In Patients with Renal Insufficiency

Plasma concentrations of eprosartan reached peak values at almost the same time in volunteers with normal renal function and those with varying degrees of renal failure (Tmax = 4 hr for eprosartan 200 mg dose, Protocol #021), and in hemodialysis-dependent patients with end stage renal disease or ESRD (Tmax = 1.5 hr for eprosartan 400 mg dose, Protocol #099). Plasma concentrations of eprosartan achieved steady state levels by 6 to 7 days except in the case of subjects with severe renal function impairment (Protocol #021).

Table Epro-021-3/4. Mean (SD) and geometric mean of pharmacokinetic parameters for eprosartan and unbound eprosartan on Day 7 following repeated oral 200 mg q 12 h dosing to subjects with normal renal function and with mild, moderate and severe renal impairment

Parameter	Normal (n=7)	Mild (n=8)	Moderate (n=12)	Severe (n=3)
Eprosartan				
AUC(0-12) (ng.h/ml) Mean(SD)	2961 (1558)	2239 (867)	3711 (1772)	4597 (1423)
Geometric Mean	2661	2086	3431	4449
Cmax (ng/ml) Mean (SD)	590 (318)	536 (217)	795 (388)	888 (202)
Geometric Mean	525	494	732	873
Tmax (h)*	4.0 (2.0 - 6.0)	4.0 (3.0 - 4.0)	4.0 (3.0 - 6.0)	3.0 (0.0 - 6.0)
Unbound Eprosartan				
%fu (ex vivo)	1.40 (0.22)	1.60 (0.12)	1.60 (0.19)	2.70 (0.51)
Unbound AUC(0-12) (ng.h/ml) Mean (SD)	40.0 (18.5)	35.4 (13.2)	61.2 (35.3)	124 (50)
Geometric Mean	37.0	33.3	54.6	118.5
Unbound Cmax (ng/ml) Mean (SD)	8.18 (4.49)	8.41 (3.21)	13.2 (7.7)	23.3 (1.4)
Geometric Mean	7.29	7.88	11.64	23.27
Renal clearance (ml/min) Mean (SD)	39.2 (27.1)	45.6 (7.3)	23.1 (17.4)	2.16 (0.57)
Geometric Mean	27.97	45.06	14.20	2.12

* Tmax data presented as median (range)

While there was a high degree of variability, the mean (and geometric mean of) AUC, Cmax, unbound AUC and unbound Cmax were similar for subjects with normal renal function and those with mild renal impairment (Protocol #021). In Table Epro-021-3/4, the mean AUC, Cmax, unbound AUC and unbound Cmax increased as the severity of renal function impairment increased: AUC and Cmax were 25-35% greater in patients with moderate renal impairment, 51-55% greater in patients with severe renal impairment, and unbound AUC and unbound Cmax were respectively, 25-35% and 53-61% greater in subjects with moderate renal impairment, and 51-55% and 185-210%, respectively, greater in subjects with severe renal impairment (Protocol #021). In hemodialysis-dependent patients with end-stage renal disease the AUC was 60% greater and the unbound AUC was 73-172% greater (Protocol #099).

In all subjects, eprosartan was highly bound to plasma protein. The unbound fraction increased with worsening renal impairment (Table Epro-021-3/4), being very small (1.4-1.6%) in subjects with normal renal function or mild to moderate renal impairment and relatively larger (2.7%) in subjects with severe renal impairment (Protocol #021), and being the largest (3.02%) in hemodialysis-dependent patients with ESRD (Protocol #099).

Dialysis treatment altered the AUC, Cmax and protein binding of eprosartan (Table Epro-099-3). On dialysis day, AUC(0-τ) and Cmax were was increased by about 35% compared to non-dialysis day. The median Tmax occurred about 2.5 hours later on the dialysis day compared to non-dialysis day (Protocol #099). The post-hemodialysis percent unbound fraction on the dialysis day (2.01%) was decreased compared to pre-dialysis value (3.19%) and 7 hour post-dose on non-dialysis day (3.26%), indicating an increase in plasma protein binding immediately after dialysis (Protocol #099).

Table Epro-099-3. Mean (SD) pharmacokinetic parameters for eprosartan and unbound eprosartan following single oral 400 mg dose to hemodialysis patients (Non-Dialysis day and Dialysis day)

Parameter		Non-Dialysis Day (n=9)§	Dialysis Day (n=8)
AUC(0-τ) (ng.h/ml)	Mean (SD)	15075 (17375)	20593 (17423)
	Median	7545	13346
	Geometric Mean	9652	15352
Cmax (ng/ml)	Mean (SD)	2180 (1626)	2900 (1520)
	Median	1662	2203
	Geometric Mean	1724	2564
Tmax (h)*	Median	1.55 (1.03 - 4.02)	3.98 (1.98 - 7.50)
	Mean (SD)	2.13 (1.00)	4.27 (1.64)
%fu (3h)	Mean (SD)	2.81 (0.83)	3.19 (0.78)
	Median	2.54	3.26
%fu (7 h)	Mean (SD)	3.26 (0.72)	2.01 (0.43)
	Median	3.05	1.90
CL_{hd} (ml/min)	Mean (SD)	---	11.22 (7.10)
	Median	---	9.95

* Tmax data presented as median (range)
§ Subject #002 did not have a reportable %fu value at 7 hour sample time-point on the Non-Dialysis Day

The mean renal clearance and excretion of eprosartan in urine decreased as renal function impairment becomes more severe (Table Epro-021-3/4), being, respectively 95% and 90% lower in subjects with severe renal impairment (Protocol #021). In hemodialysis-dependent patients with ESRD, CL_{hd} of eprosartan, determined by dialysate measurement, was 11.22 ml/min. Eprosartan, being highly protein bound, is not cleared by hemodialysis, the contribution of CL_{hd} to systemic clearance being small (about 10%).

The above findings may be considered within the context of two studies where eprosartan at a dose of 1200 mg/day for a week was well tolerated without any increase in adverse events, and Cmax and AUC(0-τ) that were, respectively, 3 and 4 times greater than that observed in the present study. Thus, no dose adjustments may be required when eprosartan is administered to patients with mild, moderate or severe renal impairment.

In Patients with Hepatic Insufficiency

In a study of a single 100 mg oral dose of eprosartan in 8 male subjects with hepatic insufficiency (documented by liver biopsy, liver/spleen scan or clinical laboratory tests, with serum albumin 2.6-4.0 g/dl and prothrombin time ≥1.2 times the upper limit of the laboratory reference range; 1 patient had advanced, 5 had moderate and 2 had minimal hepatic insufficiency by Child's Classification) and 8 healthy men (Table Epro-022-2/3), eprosartan AUC(0-τ) increased by about 40% without concomitant increase in Cmax, and the estimated $T_{1/2}$ was similar for both groups of patients (Protocol #022). There was no relationship between plasma protein binding of eprosartan and serum albumin concentrations. The results suggested that no dose adjustments is required when eprosartan is administered to patients with hepatic disease.

Table Epro-022-2/3. Mean (SD) and geometric mean of pharmacokinetic parameters for eprosartan and unbound eprosartan following single oral 100 mg dosing to subjects with normal hepatic function and with hepatic insufficiency

Parameter		Hepatic (n=8)	Healthy (n=8)
Eprosartan			
AUC(0-τ) (ng.h/ml)	Mean (SD)	2610 (1624)	1616 (379)
	Geometric Mean	2225	1570
Cmax (ng/ml)	Mean (SD)	486 (243)	428 (128)
	Geometric Mean	436	413
Tmax (h)*		6.00 (2.00 - 6.00)	4.00 (3.00 - 6.00)
$T_{1/2},\lambda_1$ (h)		2.45 (0.66)	2.08 (0.92)
Unbound Eprosartan			
Unbound AUC(0-τ) (ng.h/ml)	Mean (SD)	52.6 (43.2)	28.5 (7.2)
	Geometric Mean	42.3	27.7
Unbound Cmax (ng/ml)	Mean (SD)	9.51 (5.93)	7.62 (4.51)
	Geometric Mean	8.28	7.26

* Tmax data presented as median (range)

Pharmacodynamic and Clinical Effects

Effect on Renal Hemodynamics (ERPF and GFR)

In healthy subjects, Eprosartan 300 mg twice a day for 7 days (Protocol #024) increased the ERPF as measured by CL_{PAH}. In salt restricted individuals, a dose-related increase in ERPF was found (Protocol #043), with the maximum increase in CL_{PAH} being observed at 100 mg eprosartan (31.7%±13.1%). The effect plateaued at higher doses (increase in CL_{PAH} being 25.3±7.5% and 17.4%±9.6% with eprosartan 200 mg, and 24.5%±16.1% and 20.2%±8.7% with eprosartan 400 mg). The peak CL_{PAH} occurred approximately 2 - 3 hours post-dose. Eprosartan did not produce an increase in glomerular filtration rate (GFR) as measured by CL_{IN} (Protocol #043 and #069).

In patients with mild to moderate hypertension, ERPF and GFR were not increased by eprosartan (Protocol #026). There were no apparent changes in mean serum aldosterone concentration nor in plasma renin activity following eprosartan treatment compared to placebo (Protocol #026).

In subjects with varying renal insufficiency, ERPF and GFR were not increased nor reduced by eprosartan. The study (Protocol #044) was ended prior to meeting the target enrollment of 9 subjects per renal group. Because of the small sample sizes for normal and severe renal groups, and imbalance in treatment sequences within each group, valid inferences could not be made.

Effect on Urinary Electrolyte Excretion

In healthy subjects on low salt diet, eprosartan showed a mild natriuretic effect, the mean 24-hour urinary Na^+ excretion being increased by 17.7 mEq/day (Protocol #043). Following a single oral dose of eprosartan 400 mg (Protocol #043), the 24-hour urinary excretion of sodium was statistically significantly increased (30.19 mEq/day, 95% CI: 25.02, 35.37 mEq/day) compared to placebo (18.77 mEq/day, 95% CI: 13.62, 23.92 mEq/day).

In patients with essential hypertension, there were no changes in fractional excretion and urinary excretion rates of Na^+ and K^+ after treatment with eprosartan (Protocol #026).

In patients with chronic renal failure, while the fractional excretion and urinary excretion rates of Na^+ and K^+ increased with more severe stages of renal failure, no changes in these parameters were found after treatment with eprosartan (Protocol #044).

Effect on Blood Pressure in Patients with Hypertension (and dosing requirements)

Once/day dosing:

Table Epro-009-4/048-4. Change (placebo subtracted) in cuff and ambulatory systolic and diastolic blood pressure following repeat oral doses of eprosartan for 7 days

Study	Protocol #009				Protocol #048		
Time	50 mg	100 mg	150mg bid	350 mg	600 mg	800 mg	1200 mg
Systolic Cuff Blood Pressure (compared to placebo)							
0h	-3.75	0.08	-3.17	-5.08	1.67	-4.25	5.08
3h	-3.25	-4.75	-8.00	-3.50	0.00	-1.50	-8.25
12h	0.25	-3.50	-7.50	-6.25	--	--	--
24h	2.00	-2.83	-0.25	-4.67	-7.08	-5.92	-7.50
Diastolic Cuff Blood Pressure (compared to placebo)							
0h	-3.08	0.75	-2.67	-2.33	0.83	-0.42	2.83
3h	2.25	-2.75	-8.25	-6.00	-0.25	-3.00	-2.50
12h	-1.75	0.75	-3.50	-3.75	--	--	--
24h	-0.42	0.17	0.75	-2.25	-2.67	0.17	-1.92
Ambulatory Blood Pressure Monitoring (Systolic) (compared to placebo)							
0-12h	-18.22	-18.25	-8.47	-14.31	-1.820	1.595	-8.622
12-24h	-7.41	-2.68	-5.02	-18.21	-1.674	-3.908	-7.304
0-24h	-15.70	-11.99	-7.14	-16.05	-1.849	-0.524	-8.366
Ambulatory Blood Pressure Monitoring (Diastolic) (compared to placebo)							
0-12h	-7.70	-9.07	-4.57	-5.67	-2.816	-0.965	-6.049
12-24h	-0.42	-2.15	-5.61	-7.78	-0.800	-2.989	-5.069
0-24h	-5.92	-6.38	-5.13	-6.36	-1.699	-1.841	-5.864

In Table Epro-009-4/048-4, after repeated dosing of 50, 100, and 350 mg once/day and 150 mg bid of eprosartan, the diastolic cuff blood pressure was reduced (≥ 3 mmHg) at 3 to 12 hours post-dose for doses of eprosartan 100 mg and above (Protocol #009). Ambulatory blood pressure monitoring and averaged mean arterial pressure did not show dose-dependent lowering of blood pressure.

At repeated dosing of 600, 800, and 1200 mg once/day, the diastolic cuff blood pressure was reduced (inconsistently) at 3 hours post-dose (Table Epro-009-4/048-4). Cuff blood pressure, ambulatory blood pressure monitoring and averaged mean arterial pressure did not show dose-dependent lowering of blood pressure.

Table Epro-061-10/11. Mean (±SE) trough sitting diastolic and systolic blood pressure, and heart rate at baseline and study endpoint, and mean change from baseline at study endpoint (95% Bonferroni confidence intervals)

	MEDICATION REGIMEN		
SitDBP (mmHg)	**Placebo (n=124)**	**Epro+HCTZ 12.5mg (n=128)**	**Epro + HCTZ 25 mg (n=124†)**
Baseline	101.0 ± 0.3	101.3 ± 0.4	99.8 ± 0.3
Study Endpoint	95.6 ± 0.8	91.5 ± 0.7	87.6 ± 0.7
Change from Baseline	-5.4 ± 0.8	-9.8 ± 0.7	-12.2 ± 0.6
Difference from placebo (95% CI) p-value		-4.4 (-6.7, -2.1) < 0.0001*	-6.9 (-9.1, -4.6) < 0.0001*
Difference from epro + 12.5 mg HCTZ (95% CI) p-value			-2.5 (-4.7, -0.2) 0.0095*
SitSBP (mmHg)			
Baseline	155.8 ± 1.4	154.1 ± 1.3	154.2 ± 1.3
Study Endpoint	150.3 ± 1.5	140.0 ± 1.4	137.9 ± 1.4
Change from Baseline	-5.5 ± 1.1	-14.0 ± 1.1	-16.3 ± 1.1
Difference from placebo (95% CI) p-value		-8.6 (-12.3, -4.9) < 0.0001*	-10.9 (-14.6, -7.1) < 0.0001*
Difference from epro + 12.5 mg HCTZ (95% CI) p-value			-2.3 (-6.0, -1.5) 0.145
SitHR (bpm)			
Baseline	74.1 ± 0.7	74.5 ± 0.7	74.1 ± 0.8
Study Endpoint	74.1 ± 0.9	73.9 ± 0.8	72.8 ± 0.9
Change from Baseline	0.1 ± 0.7	-0.6 ± 0.6	-1.2 ± 0.6

n = number of patients with a baseline value and study endpoint value
* Indicates significance at 0.05 using modified Bonferroni procedure
† 4 patients (#061.052.00217, #016.274.00277, #061.472.00340, and #061.573.00457) randomized to eprosartan 400 mg/ HCTZ 25 mg did not have any trough (pre-dose) vital signs taken after randomization and were not included in analysis.

In Table-061-10/11, when 400 mg eprosartan once/day was given together with HCTZ, there was a dose-related (to HCTZ) statistically significant reduction in sitting diastolic blood pressure compared to placebo (Table Epro-061-10/11). The reduction in SitDBP attributable to eprosartan 400 mg once/day was small (2 mmHg) compared to that due to placebo effect (5.4 mmHg), HCTZ 12.5 mg (2.4 mmHg) and HCTZ 25 mg (4.8 mmHg). Secondary efficacy parameters (sitting systolic blood pressure and percentage of patients who responded at endpoint) also showed the same trend, with a reduction in sitting systolic blood pressure of 6.2 mmHg (compared to 5.5 mmHg for placebo) and a responder rate of 8.6% (compared to 29% for placebo) attributable to eprosartan 400 mg once/day. It is likely that over-enrollment of patients (124-128 patients per group rather than the required 70 patients per group) may have contributed to the finding of spurious statistical significance in the efficacy parameters between the eprosartan/HCTZ treatment groups and the placebo treatment group.

These findings suggests that at the doses studied (up to 1200 mg/day) using diastolic cuff blood pressure, eprosartan requires bid dosing or requires the addition of HCTZ to maintain a sustained reduction in blood pressure.

Twice/day dosing:
Table Epro-051-13 showed that in hypertensive patients with left ventricular hypertrophy, similar decreases in sDBP and sSBP from baseline were found at titration, maintenance and study endpoints with eprosartan 200 mg bid

titrated up to 400 mg bid, or enalapril 10 mg qd titrated up to 40 mg qd, the treatments being given for a total duration of 26 weeks. At these bid dose regimens of eprosartan, the proportion of responders (sDBP decreased to <90 mmHg or 90-100 mmHg and decrease from baseline by ≥10 mmHg) was greater in the eprosartan regimen (12.8%) compared to enalapril regimen (12.0%) at both titration and study endpoints (Protocol #051).

Table Epro-051-13

Trough sDBP, sSBP and sitting Heart Rate (mean ± SEM) at baseline (b/l) and change from baseline at titration, maintenance and study endpoints

sDBP (mmHg)	Eprosartan	Enalapril
Baseline	(n=31)	(n=35)
Mean ± SEM	99.9±1.0	101.3±0.7
Titration endpoint	(n=31)	(n=35)
Mean ± SEM	83.8±1.6	88.1±1.7
Change from b/l	(n=31)	(n=35)
Mean ± SEM	-16.1±1.3	-13.1±1.7
Maintenance endpoint	(n=29)	(n=28)
Mean ± SEM	83.0±1.8	84.2±1.2
Change from b/l	(n=29)	(n=28)
Mean ± SEM	-16.1±1.6	-17.0±1.1
Study endpoint	(n=31)	(n=35)
Mean ± SEM	83.6±1.9	87.4±1.6
Change from b/l	(n=31)	(n=35)
Mean ± SEM	-16.3±1.7	-13.8±1.5
sSBP (mmHg)		
Baseline	(n=31)	(n=35)
Mean ± SEM	166.6±2.0	165.3±2.0
Titration endpoint	(n=31)	(n=35)
Mean ± SEM	147.2±2.6	149.2±2.9
Change from b/l	(n=31)	(n=35)
Mean ± SEM	-19.4±2.4	-16.1±2.7
Maintenance endpoint	(n=29)	(n=28)
Mean ± SEM	147.7±3.1	141.2±2.6
Change from b/l	(n=29)	(n=28)
Mean ± SEM	-18.8±3.1	-22.9±2.4
Study endpoint	(n=31)	(n=35)
Mean ± SEM	147.7±3.0	146.1±2.9
Change from b/l	(n = 31)	(n = 35)
Mean ± SEM	-18.9±2.9	-19.3±2.6
Sitting Heart Rate (bpm)		
Baseline	(n=31)	(n=35)
Mean ± SEM	74.6±1.3	74.5±1.8
Titration endpoint	(n=31)	(n=35)
Mean ± SEM	70.8±1.4	73.8±2.0
Change from b/l	(n=31)	(n=35)
Mean ± SEM	-3.8±1.3	-0.7±1.7
Maintenance endpoint	(n=29)	(n=28)
Mean ± SEM	72.1±1.4	71.6±1.8
Change from b/l	(n=29)	(n=28)
Mean ± SEM	-2.4±1.2	-2.9±1.7
Study endpoint	(n=31)	(n=35)
Mean ± SEM	72.0±1.3	72.5±1.9
Change from b/l	(n=31)	(n=35)
Mean ± SEM	-2.6±1.1	-1.9±1.8

The findings suggest overall that eprosartan should be prescribed in doses of **200 mg to 400 mg twice/day.**

Effect on Heart Rate

There was no change in heart rate reported for the eprosartan-treated patients in any of the clin-pharm trials reviewed.

Effect on Left Ventricular Hypertrophy in Patients with Hypertension

In patients with hypertension and pre-existing left ventricular hypertrophy, left ventricular mass index (LVMI) was similar to baseline in the eprosartan regimen (mean change being -1.5 g/m^2) and decreased in the enalapril regimen (-7.6 g/m^2) at study endpoint (Protocol #051). At month 6, a decrease in LVMI from baseline was found in both medication regimens, being larger for enalapril (-11.9 g/m^2) compared to eprosartan (-3.6 g/m^2). The difference between medication regimens in change of LVMI from baseline was not statistically significant at either time point.

Table Epro-051-11

LVMI (g/m^2) (mean ± SEM) at baseline and change from baseline at month 6 and study endpoint

LVMI (g/m^2)	Eprosartan	Enalapril
Baseline	(n=13)	(n=15)
Mean ± SEM	126.5± 8.4	123.7± 5.9
Month 6	(n = 9)	(n= 8)
Mean ± SEM	123.6± 12.7	103.3± 7.5
Month 6 change	(n = 9)	(n= 8)
Mean ± SEM	-3.6 ± 7.6	-11.9± 4.1
Study endpoint	(n=11)	(n=15)
Mean ± SEM	122.7± 10.6	116.5± 6.7
Study endpoint change	(n=11)	(n=14)
Mean ± SEM	-1.5± 6.4	-7.6± 5.4

Eprosartan, compared to enalapril, caused a greater decrease in peak systolic wall stress (PSWS) and increase in isovolumic relaxation time at both month 6 and study endpoint from baseline. LV end diastolic volume was found to decrease more in the enalapril regimen compared to eprosartan at both month 6 and study endpoint. None of these differences between the two treatment regimens was statistically significant (Protocol #051) which may be due to lack of power, having a total of only 25 patients with evaluable echocardiographic data rather than the total of 50 patients (25 patients per group) required to provide 80% power to detect a rather large change in LVMI of 27 g/m^2.

Effect on Urinary Uric Acid Excretion

Studies of the effect of eprosartan on uric acid excretion by fractional excretion of urinary uric acid (Fe_{UA}), urinary excretion rate of uric acid, and U_{UA}/U_{CR} ratio showed that eprosartan does not have a uricosuric effect based on lack of changes in Fe_{UA} and U_{UA}/U_{CR} ratio. This finding holds true for all of the population groups studied: healthy subjects (Protocol #069, #094 and #095), patients with essential hypertension (Protocol #026) and patients with renal impairment (Protocol #044).

Effect on Proteinuria in Patients with Type II Diabetes Mellitus

While urinary protein in diabetic (NIDDM) patients on placebo increased from baseline by 34%, the urinary protein in those on eprosartan decreased by 1% at Week 6 (Protocol #090), the differences being not statistically significant (Table Epro-090-4/5). In a subset of patients who had proteinuria > 1000 mg/24 hr, a statistically significant reduction (P = 0.0254) in urinary protein was observed in patients on eprosartan (by 34%) compared to an increase in proteinuria by 22% in patients receiving placebo.

Urinary albumin was reduced in patients on eprosartan (by about 5%) in contrast to increased (by 30 %) urinary albumin in patients on placebo, but the differences were not statistically significant (P = 0.0827).

Table Epro-090-4/5. Percentage change from baseline in urinary protein and urinary albumin at Week 6

	All Patients (Proteinuria)		High Proteinuria Pts		All Patients (Albuminuria)	
Parameter	*Placebo*	*Eprosartan*	*Placebo*	*Eprosartan*	*Placebo*	*Eprosartan*
N	40	35	17	9	39	33
Mean	33.8	-1.1	22.2	-34.1	30.0	-4.7
SE	15.7	18.8	13.3	21.1	16.7	20.1
P value	0.0597		0.0254		0.0827	

PRECAUTIONS

General

Impaired Renal Function

The mean AUC and Cmax, the unbound fraction, total and unbound plasma concentrations, and unbound Cmax and unbound AUC, all increased as the severity of renal function impairment increased. The mean renal clearance and excretion of eprosartan in urine decreased as renal function impairment becomes more severe, being, respectively 95% and 90% lower in subjects with severe renal impairment (Protocol #021).

Dialysis treatment increases the AUC, Cmax, Tmax and protein binding (and thus, reduces the free or unbound fraction) of eprosartan. Eprosartan, being highly protein bound, is not cleared by hemodialysis, the contribution of CL_{hd} to systemic clearance being small (about 10%) (Protocol #099).

While no dose adjustments may be required when eprosartan is administered to patients with mild, moderate or severe renal impairment, care should be exercised (since plasma concentrations of eprosartan and its blood pressure lowering effects are not proportionally related)

Impaired Hepatic Function
A small proportion of eprosartan undergoes metabolism by acyl glucuronidation, and this eprosartan acyl glucuronide is excreted into the intestinal lumen via the bile (Protocol #020). A study of a single 100 mg oral dose of eprosartan in 8 male subjects with hepatic insufficiency showed that eprosartan AUC(0-τ) increased by about 40% without concomitant increase in Cmax (Protocol #022). There was no relationship between plasma protein binding of eprosartan and serum albumin concentrations. While the results suggested that no dose adjustments is required when eprosartan is administered to patients with hepatic disease, care should be exercised in administering eprosartan to patients with hepatic disease and/or biliary obstructive disorders.

Information to Patients

Pregnancy
No information is found in the clin-pharm trials reviewed.

Drug Interactions

Digoxin
Eprosartan had no effect on single oral-dose pharmacokinetics of digoxin in healthy subjects (Protocol #023). AUC(0-τ), Cmax and Tmax were similar for eprosartan and digoxin compared to digoxin alone (Table Epro-023-1).

Using an equivalence-type approach, the 90% confidence intervals for the ratios of the geometric means for digoxin with eprosartan relative to digoxin alone for AUC(0-τ), AUC(0-∞), and Cmax (Table Epro-023-2) were completely contained within the range [0.70, 1.43], and AUC(0-τ) and Cmax also met the more stringent 90% confidence interval criterion of [0.80, 1.25].

Table Epro-023-2. Point Estimates and 95% confidence intervals of comparisons of digoxin and digoxin plus steady-state eprosartan

Parameter	Comparison	Point Estimate	95% Confidence Interval
AUC(0-τ)†	B:A	0.99	[0.90, 1.09]
Cmax†	B:A	1.00	[0.86, 1.17]
AUC(0-∞)†	B:A	1.01	[0.81, 1.26]
Tmax (h)§	B-A	0.25	[-0.25, 0.50]
T1/2 (h)*	B-A	5.95	[-4.38, 16.28]

† Data presented as the ratio of the geometric means for digoxin with eprosartan (Regimen B) relative to digoxin alone (Regimen A)
§ Data presented as the median difference in Tmax for digoxin with eprosartan (Regimen B) relative to digoxin alone (Regimen A)
* Data presented as the mean difference in $T_{1/2}$ for digoxin with eprosartan (Regimen B) relative to digoxin alone (Regimen A)

Warfarin
Table Epro-027-1. Mean INR

Comparison	Warfarin + eprosartan (n = 11)	Warfarin + placebo (n = 7)
Baseline INR		
Mean	1.48	1.41
Median	1.47	1.48
S.D.	0.079	0.198
Day 22 INR		
Mean	1.44	1.31
Median	1.39	1.27
S.D.	0.256	0.181

Eprosartan and warfarin at steady-state concentrations in healthy volunteers were not associated with any interaction as measured by the INR (Protocol #027). The mean INR for subjects given warfarin plus eprosartan (1.44) was slightly higher than those given warfarin plus placebo (1.31) but the differences were not statistically significant (Table Epro-027-1). The mean difference in INR for the two blinded study groups was 0.0678 (Table Epro-027-2). The approximation ratio between warfarin plus eprosartan versus warfarin plus placebo and its associated 90% confidence intervals fall within the 25% acceptance range.

Table Epro-027-2. Mean difference in INR (point estimates) and confidence intervals

Comparison	Point Estimate	95% C.I.
{Eprosartan + warfarin} - {placebo + warfarin}	0.0678	(-0.113, 0.248)
{Eprosartan + warfarin} - {placebo + warfarin}, excluding Subject #020	0.0343	(-0.105, 0.173)

Glyburide

Eprosartan had no effect on the 24-hour plasma glucose concentrations in diabetic patients stabilized on glyburide therapy (Protocol #028). The average mean plasma glucose concentrations on Day 0 and Day 7 were similar between groups Table Epro-028-1). The Point Estimates on Day 0 and Day 7 were 0.97 and 0.96 respectively, and the 90% confidence intervals were within the range of 0.70 to 1.30 supporting equivalence (Table Epro-028-1).

Table Epro-028-1. Average mean (s.d.) plasma glucose concentration

Day	n	Eprosartan	Placebo
Day 0 (baseline)	12	199 (63.7)	206 (67.1)
Day 7 (post-dose)	12	203 (65.1)	212 (52.0)

Table Epro-028-2. Point Estimates and 95% confidence intervals for mean plasma glucose concentrations

Comparison	Point Estimate†	90% Confidence Interval
Day 0 (baseline)	0.97	(0.83, 1.10)
Day 7 (post-dose)	0.96	(0.90, 1.01)

†Point estimate: expressed as a ratio of the mean response for glyburide + eprosartan to glyburide + placebo

In all of the above, the effect s of digoxin, warfarin or glyburide on the pharmacokinetics of eprosartan were not studied.

Ranitidine

Table Epro-029-1. Pharmacokinetics of eprosartan following single oral dose without and with ranitidine

End Point	Eprosartan	Eprosartan + Ranitidine	Point estimate (95% C.I.)
AUC(0-τ) (ng.h/ml)			
Geometric Mean	7190	6382	0.89 (0.77, 1.03)
Mean (SD)	8042 (4128)	7504 (4635)	
Median	6597	6283	
Cmax (ng/ml)			
Geometric Mean	1905	1772	0.93 (0.81, 1.07)
Mean	2260 (1465)	2019 (1173)	
Median	1755	1556	
Tmax (hr)			
Mean	1.60 (0.71)	1.83 (1.29)	
Median	1.49	1.50	
Ae (mg)			
Mean	12.86 (5.74)	11.19 (6.93)	
Median	12.05	9.64	
CLr (ml/min)			
Geometric Mean	26.5 (17.44)	25.4 (11.86)	0.96 (0.64, 1.43)
Mean	31.15	27.25	
Median	24.20	24.02	

The pharmacokinetics of a single dose of eprosartan was not altered by the concomitant administration of ranitidine (Protocol 029). Cmax and AUC(0-τ) were, on average, approximately 7% and 11% lower, respectively for eprosartan plus ranitidine than for eprosartan alone; the 95% confidence intervals for Cmax and AUC(0-τ) include the value 1 indicating no substantial differences between regimens (Table Epro-029-1). The renal clearance of eprosartan (CLr) was approximately 4% lower in eprosartan plus ranitidine regimen than for eprosartan alone; the 95% confidence interval of CLr include the value 1 indicating no substantial difference between regimens (Table Epro-029-1).

CRP 450 Interactions

Eprosartan does not undergo oxidative metabolism and its single oral dose and repeat oral dose pharmacokinetcs were not affected by concomitant administration of steady state fluconazole, a CYP2C9 inhibitor (Protocol #094) or ketoconazole, a CYP3A4 inhibitor (Protocol #095).

Fluconazole

The AUC(0-τ) for eprosartan increased by 4% following administration of eprosartan with fluconazole, and Cmax decreased by 11%; these changes were within the 95% confidence intervals (Table Epro-094-5), and suggest no substantial alteration in pharmacokinetics of eprosartan when fluconazole was administered.

Table Epro-094-5. Point Estimates and 95% confidence intervals of eprosartan singly and together with fluconazole

Parameter	Comparison	Point Estimate	95% Confidence Interval
Eprosartan			
AUC(0-τ)†	Day 20 : Day 10	1.04	0.87, 1.25
Cmax†	Day 20 : Day 10	0.89	0.67, 1.19
Tmax§	Day 20 : Day 10	0.00 h	-0.52, 0.50 h

Ketoconazole

AUC(0-τ) and Cmax for eprosartan were 3% and 20% lower, respectively, after administration of ketoconazole compared with eprosartan alone; these changes were within the 95% confidence intervals (Table Epro-095-5), and suggest no substantial alteration in pharmacokinetics of eprosartan when ketoconazole was added.

Table Epro-095-5. Point Estimates and 95% confidence intervals of eprosartan singly and together with ketoconazole

Parameter	Comparison	Point Estimate	95% Confidence Interval
Eprosartan			
AUC(0-τ)†	Day 10 : Day 5	0.97	0.74, 1.28
Cmax†	Day 10 : Day 5	0.80	0.59, 1.08
Tmax§	Day 10 : Day 5	0.25 h	-0.50 h, 1.25 h

Nursing Mothers

It is not known whether eprosartan is excreted in human milk.

Pediatric Use

Safety and effectiveness in pediatric patients have not been studied.

Geriatric Use

Following a single oral dose of 200 mg eprosartan, elderly men had peak plasma concentrations of eprosartan between 3 and 6 hours for elderly men (compared to 2 and 4 hours for young males); the plasma concentrations then declined in a multi-exponential manner. Eprosartan was highly protein bound to plasma proteins (approximately 98%) with no apparent differences in the mean fraction unbound between elderly males relative to young males. Total and free mean AUC(0-∞), mean Cmax, and median Tmax values in the elderly were > 2-fold larger compared to young males (Protocol #025).

DOSE-RESPONSE AND DOSING INTERVAL (Pharmacokinetic and Pharmacodynamic Considerations)

For making recommendations for dosing of eprosartan, a compilation of data from clinical pharmacology trials that studied oral (single or repeat) doses of eprosartan is made. The following relationships are considered:

(i) relationship of dose to pharmacokinetic parameters (AUC(0-τ) and Cmax),
(ii) relationship of dose to pharmacodynamic parameters (change in cuff blood pressure and change in ambulatory blood pressure), and
(iii) interrelationships between dose, plasma concentrations and the changes in cuff and ambulatory systolic and diastolic blood pressures.

In studies using intravenous dosing (Protocol #004), median Cmax, AUC(0-τ) and AUC(0-∞) increased in a dose proportional manner over the 1 to 20 mg intravenous dose range. The issue of dose proportionality arises because of the low bioavailability of the drug following oral administration (14.7%, range: 8.6 to 24.0%; Protocol #020).

Relationship of dose to pharmacokinetic parameters

In Table DR-1, Cmax, AUC(0-τ) and AUC(0-∞) increased in a dose proportional manner with the oral eprosartan solution up to 200 mg (Protocol #003).

With eprosartan tablets at higher doses (100, 200 and 350 mg), Cmax, AUC(0-τ) and AUC(0-∞) increased with an increase in dose but were not dose proportional (Protocol #003). The median Cmax and median AUC(0-τ) increasing approximately 10-fold over the entire 20-fold dose range (Protocol #006). Also, for the same dose use, e.g., 100 mg, AUC and Cmax obtained in different clinical trials varied widely (e.g., 2354, 1182, 3242, 1396 and 5768 for AUC in Protocols #003, #006 (Pt 2), #006 (Pt 3), #008 and #009, respectively, and 1007, 461.6, 566.2, 439, and 1480 for Cmax in Protocols #003, #006 (Pt 2), #006 (Pt 3), #008 and #009, respectively).

The dose-normalized AUC(0-τ') and dose-normalized Cmax for the 200 mg dose were contained within the protocol-specified 20% acceptance range for equivalence (0.80, 1.25). Thus, dose-proportionality was concluded for the 200 mg dose relative to the 100 mg reference dose (Protocol #008).

However, the 90% confidence interval for the dose-normalized AUC(0-τ') for the 800 mg dose to the 100 mg reference dose, and the 90% confidence interval for the dose-normalized Cmax for the 400 mg and 800 mg doses to the 100 mg reference dose were not contained within the acceptance range (Protocol #008).

While the mean AUC(0-τ) and the mean Cmax increased with increasing dose over the 100-800 mg single oral dose range, the mean dose-normalized AUC(0-τ) and the mean dose-normalized Cmax showed a decreasing trend with increasing dose (Protocols #006 Parts 2 and 3, #008), suggesting saturation of absorption of eprosartan over the 100 mg to 800 mg oral dose range.

The median Tmax ranged from 1 to 1.5 hours, and is similar for both the oral solution formulation and the tablet formulation (Protocol #003). The median Tmax was 1-2 hours (Part 2) and 1.75 - 2.5 hours (Part 3) in Protocol #006, and 2.5-3 hours for the 100, 200, 400 and 800 mg doses in Protocol #008. These findings suggest that the rates of absorption of the different doses of eprosartan were similar.

In patients with hypertension at the doses used (50, 100, 350 mg qd and 150 mg bid in Protocol #009, and 600, 800 and 1200 mg qd in Protocol #048), a dose-related increase in mean Cmax, AUC(0-t) and AUC(0-∞) were found (except for AUCs for the 800 mg dose after 7 days). In hypertensive patients, too, the dose-normalized AUC(0-τ) and the dose-normalized Cmax decreased as the dose was increased, suggesting saturation of absorption of eprosartan over the dose of 100 mg. There was no accumulation with repeated doses (Protocol #009, #048). Steady-state appears to be reached by Day 4 (Protocol, #048).

The use of different lots of eprosartan in these trials may be the cause of the variations in pharmacokinetic findings:

Protocols #	Lot numbers
003, 006 and 009	U-92054 (10 mg) and U-92055 (50 mg),
008	U-94191 (100 mg) and U-94190 (200 mg)
048	U-93235 (100 mg)

(The next section on bioequivalence discusses further on the tablets used in the clinical trials and the wet granulation capsules to be used commercially.

Table DR-1. Relationship of dose to pharmacokinetic parameters

Dose (mg)	N	AUC(0-τ) *(ng.h/ml)*	Dose-normalized AUC(0-τ) *(ng.h/ml)*	Cmax *(ng/ml)*	Dose-normalized Cmax *(ng/ml)*	Tmax *(h)*
Protocol #003 (Oral eprosartan solution)						
1	6	66.4	66.4	29.3	29.3	1.50
3	4	94.0	31.3	45.4	15.1	1.25
10	5	253.5	25.4	99.7	10.0	1.50
30	4	1091.7	36.4	396.3	13.2	1.02
50	4	1399.2	28.0	578.5	11.6	1.25
100	7	2502.4	25.0	979.2	9.8	1.00
200	6	7021.4	35.1	3040.2	15.2	1.00
Protocol #003 (Eprosartan tablets)						
30	2	1230	41.0	436	14.5	1.50
50	4	1000	20.0	458	9.2	1.00
100	6	2354	23.5	1007	10.1	1.00
200	6	3950	19.8	1181	5.9	1.00
350	3	5880	16.8	1317	3.8	1.50
Protocol #006 (Part 2)						
10	8	286	28.6	94.8	9.5	1.50
30	8	590	19.7	221.5	7.4	1.25
50	8	873	17.5	273.4	5.5	1.00
70	8	1165	16.6	462.2	6.6	1.00
100	8	1182	11.8	461.6	4.6	1.00
200	8	2658	13.3	818.9	4.1	2.00
Protocol #006 (Part 3)						
50	4	1305	16.1	365.6	7.3	1.75
100	4	3242	32.4	566.2	5.7	2.00
350	4	7983	22.8	1195.2	3.4	2.50
Protocol #008						
100	35	1396	14.0	439	4.4	2.58
200		2553	12.8	702	3.5	3.02
400		4661	11.7	1273	3.2	3.02
800		7443	9.3	1857	2.3	3.00
Protocol #009† (in patients with hypertension)						
50	8	2770	55.4	673	13.5	1.75
100	8	5768	57.7	1480	14.8	1.50
150 bid	8	6340	21.1	1635	5.5	1.50
350	8	8067	23.0	1818	5.2	1.75
Protocol #048† (in patients with hypertension)						
600	8	9731	16.2	1608	2.7	2.25
800	8	9521	11.9	2103	2.6	1.50
1200	8	19125	15.9	2961	2.5	3.00

† Values were after 7 days of oral administration of eprosartan

Relationship of dose to pharmacodynamic parameters (reduction in blood pressure)

At single and repeated dosing of 50, 100, and 350 mg once/day and 150 mg bid of eprosartan, the diastolic cuff blood pressure was reduced (≥ 3 mmHg) at 3 to 12 hours post-dose for doses of eprosartan 100 mg and above (Protocol #009). Dose-related responses was found in the systolic cuff blood pressure 3 and 12 hours post-dose, and diastolic cuff blood pressure 3-hours post-dose (Protocol #009) up to 150 mg bid dose (Table DR-2). Ambulatory blood pressure monitoring and averaged mean arterial pressure did not show dose-dependent lowering of blood pressure.

At single and repeated dosing of 600, 800, and 1200 mg once/day, cuff blood pressure, ambulatory blood pressure monitoring and averaged mean arterial pressure did not show dose-dependent lowering of blood pressure (Table DR-2). If a fall in diastolic cuff blood pressure by ≥ 3 mmHg is taken as an acceptable response to treatment, then this response is observed (albeit inconsistently) at 3 hours after dosing.

These findings suggest that at the doses studied (up to 1200 mg/day) using diastolic cuff blood pressure, eprosartan requires bid dosing.

Table DR-2. Relationship of dose to reduction in blood pressure in patients with hypertension

Study #	Dose	Time-point	Change in Cuff Blood Pressure		Time-period	Change in Ambulatory Blood Pressure	
	(mg)	*(hour)*	*Systolic (mmHg)*	*Diastolic (mmHg)*	*(hour)*	*Systolic (mmHg)*	*Diastolic (mmHg)*
009	50	3	-3.25	+2.25	0-12	-18.22	-7.70
	100	3	-4.75	-2.75	0-12	-18.25	-9.07
	150x2	3	-8.00	-8.25	0-12	-8.47	-4.57
	350	3	-3.50	-6.00	0-12	-14.31	-5.67
	50	12	+0.25	-1.75	0-24	-15.70	-5.92
	100	12	-3.50	+0.75	0-24	-11.99	-6.38
	150x2	12	-7.50	-3.50	0-24	-7.14	-5.18
	350	12	-6.25	-3.75	0-24	-16.1	-6.36
048	600	3	0	-0.25	0-12	-1.82	-2.82
	800	3	-1.50	-3.00	0-12	+1.60	-0.97
	1200	3	-8.25	-2.5	0-12	-8.62	-6.05
	600	24	-7.08	-2.67	0-24	-1.85	-1.70
	800	24	-5.92	+0.17	0-24	-0.52	1.84
	1200	24	-7.50	-1.92	0-24	-8.37	-5.87

Interrelationship between dose, plasma concentrations and change in blood pressure

At repeat (one week) doses of 50, 100 and 350 mg qd and 150 mg bid, the 3-hour and 12-hour plasma levels of eprosartan increased with increasing dose (Table DR-3, Protocol #009), though the increase in plasma concentrations were not dose proportional (for a 7-fold increase in dose, the plasma concentrations showed only an increase by less than 2 1/2 fold). The plasma concentrations at 3- or 12-hour time-points do not correlate with changes in the systolic or diastolic blood pressure by cuff or ambulatory measurements.

At repeat doses of 600, 800 and 1200 mg once/day, also, the 3-hour plasma levels of eprosartan increased with increasing dose (Table DR-3, Protocol #048); the increase in plasma concentrations were not dose proportional (for a 2-fold increase in dose, the plasma concentrations showed an increase by 2 1/2 fold at 3 hours). The plasma concentrations at 3- or 12-hour time-points do not correlate proportionally with changes in the systolic or diastolic blood pressure by cuff or ambulatory measurements.

Table DR-3 Interrelationship between eprosartan dose, pharmacokinetic parameters and change in blood pressure

Study #	Dose	3-hr plasma concentration	12-hr plasma concentration	Change in Cuff Blood Pressure		Change in Ambulatory Blood Pressure	
	(mg)	*(ng/ml)*	*(ng/ml)*	*Systolic (mmHg)*	*Diastolic (mmHg)*	*Systolic (mmHg)*	*Diastolic (mmHg)*
009	50	513.8	48.3	-3.25	+2.25	-18.22	-7.70
	100	844.4	53.2	-4.75	-2.75	-18.25	-9.07
	150x2	991.0	74.5	-8.00	-8.25	-8.47	-4.57
	350	1147.8	109.9	-3.50	-6.00	-14.31	-5.67
048	600	917.8	219.9	0	-0.25	-1.82	-2.82
	800	1596.3	163.6	-1.50	-3.00	+1.60	-0.97
	1200	2359.3	478.8	-8.25	-2.5	-8.62	-6.05

Once/day versus twice/day dose of eprosartan

In the clinical pharmacology trials reviewed, the following observations were made:

Once/day dosing: Three clinical trials using once/day dosing of eprosartan (Protocol #009, #048 and #061) at different dose levels (50-350 mg in Protocol #009; 600, 800 and 1200 mg in Protocol #048; and 400 mg eprosartan with HCTZ (12.5 mg or 25 mg) in Protocol #061) all showed consistently that effective blood pressure reduction (by ≥ 3 mmHg sitting DBP) occurred only at 3 and 12 hours post dose.

Twice/day dosing: Eprosartan, at doses of 200 mg bid titrated up to 400 mg bid administered for a total duration of 26 weeks (Protocol #051), produced clinically significant reductions in sitting diastolic blood pressure (by 16.1 to 16.3 mmHg) from baseline.

The findings suggest overall that eprosartan should be prescribed in doses of **200 mg to 400 mg twice/day.**

Dose of eprosartan in patients with disease

Dose of eprosartan in patients with renal disease

AUC, Cmax, the unbound fraction, unbound AUC and unbound Cmax of eprosartan were similar for subjects with normal renal function and those with mild renal impairment (Protocol #021). As the severity of renal function impairment increased, AUC and Cmax, unbound Cmax and unbound AUC, and the unbound fraction also increased (Protocol #021), being the largest in hemodialysis-dependent patients with end stage renal disease (Protocol #099).

Dialysis treatment increased the AUC(0-τ) and Cmax by about 35% compared to the non-dialysis day and decreased the percent unbound fraction. Eprosartan, being highly protein bound, was not cleared by hemodialysis, the contribution of CL_{hd} to systemic clearance being small (about 10%).

In two studies where eprosartan was administered at a dose of 1200 mg/day for a week, subjects had Cmax and AUC(0-τ) that were, respectively, 3 and 4 times greater than that observed in the hemodialysis-dependent patients study, and they tolerated the drug without any increase in adverse events. Thus, no dose adjustments are required when eprosartan is administered to patients with mild, moderate or severe renal impairment, or with end-stage renal disease requiring hemodialysis.

Dose of eprosartan in patients with hepatic disease

In a study of a single 100 mg oral dose of eprosartan in 8 male subjects with hepatic insufficiency and 8 healthy men, eprosartan AUC(0-τ) increased by about 40% without concomitant increase in Cmax, and the estimated $T_{1/2}$ was similar for both groups of patients.

No dose adjustment is required when eprosartan is administered to patients with hepatic impairment.

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PHARMACOKINETICS OF EPROSARTAN IN BIOEQUIVALENCE STUDIES

Five clinical pharmacology trials were carried out (Protocol #018, #034, #035, #089 and #092) to compare the bioequivalence of the new commercial tablet ( ) formulation of eprosartan at different doses (100, 200, 300 and 400 mg) with the old tablets that were used in the clinical trials.

All five clinical trials were randomized, open-label and period-balanced, cross over studies. In four, single oral doses of eprosartan (100 mg, 300 mg (two trials) and 400 mg were studied; the remaining clinical trial studied repeat doses of 200 mg twice/day for 7 doses was studied. In two trials, there were 3 arms each, and in the other 3 trials, there were two arms each. The characteristics of these bioequivalence trials are given in Table BE-1.

Table BE-1 Bioequivalence clinical pharmacology trials

Study #	Design, Patient population	Treatment groups	Lot #	Primary Endpoint	Secondary Endpoint
018	ol, co, sd in HMV	Eprosartan 100 mg (50 mg x 2) wgf Eprosartan 100 mg (100 mg x 1) wgf Eprosartan 100 mg (50 mg x 2) dcf	U-93180 U-93174 U-93008	AUC(0-τ) and Cmax	Tmax and $T_{1/2}$
034	ol, co, rd in HMV	Eprosartan (new) 200 mg bid x 7 doses Eprosartan (old) 100mg x2 bid x7doses	U-94175 U-94068	AUC(0-τ) and Cmax	Tmax
035	ol, co, sd, in HMV	Eprosartan (new) 400 mg Eprosartan (old) 100 mg x 4 tabs Eprosartan (old) 200 mg x 2 tabs	U-95111 U-93235 U-94190	AUC(0-τ) and Cmax	AUC(0-τ') and Tmax
089	ol, co, sd, in HMV	Eprosartan (new) 300 mg Eprosartan (old) 100 mg x 3 tabs	U-95110 U-94068	AUC(0-τ) and Cmax	Tmax
092	ol, co, sd, in HMV	Eprosartan (new) 300 mg tab Eprosartan (old) 100mg x1 plus) Eprosartan (old) 200mg x1)	U-95110 U-94191 U-94190	AUC(0-τ) and Cmax	Tmax

ol = open-label; co = crossover; sd = single dose; rd = repeat dose; HMV = healthy male volunteers

Study Procedures

Eligible subjects were administered a single oral dose of eprosartan of the assigned formulation following a standard breakfast (except study #034 where subjects took the assigned formulation twice/day for 7 doses). Blood samples for pharmacokinetic analysis were obtained pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours following dosing.

Concentration-time data analysis was performed using a non-compartmental pharmacokinetic analysis program to obtain Cmax, Tmax, the apparent terminal elimination rate constant (λ), $T_{1/2}$, and AUC(0-τ).

Endpoints

AUC(0-∞) and Cmax were primary endpoints, and Tmax was the secondary endpoint. Bioequivalence was demonstrated when the 90% confidence intervals for the ratios of test : reference for *ln*-transformed AUC(0-τ) and *ln*-transformed Cmax were contained within the range (0.80, 1.25), representing a symmetric 20% range on the *ln* scale.

Pharmacokinetic Results

In Table BE-2, AUC(0-τ), Cmax and Tmax values were generally comparable between the test (new) formulations intended for commercial use and the reference (old) formulation that had been used in the clinical trials, suggesting that the rate and extent of absorption of eprosartan appeared to be similar between the new commercial formulations and the old formulation used in the clinical trials.

The values of the point estimates for AUC(0-τ) and Cmax also were around 1 (Tables BE-3 and BE-4) except that the point estimates of AUC(0-τ) for the new 400 mg formulation (Protocol #035) and the new 300 mg formulation (Protocol #089) were 1.16 and 1.15, respectively, and the point estimates of Cmax for the new 400 mg formulation (Protocol #035) and the new 300 mg formulation (Protocol #089) were 1.30 and 1.31, respectively.

Table BE-2 Pharmacokinetics of eprosartan in bioequivalence clinical pharmacology trials

Study #	Treatment groups	N	AUC(0-τ) (ng.h/ml)†	Cmax (ng/ml)†	Tmax (h)§	T1/2 (h)§
018	Eprosartan 100 mg (50 mg x 2) wgf	24	1368	390	3.00	1.74
	Eprosartan 100 mg (100 mg x 1) wgf		1382	354	4.00	7.98
	Eprosartan 100 mg (50 mg x 2) dcf		1445	379	3.00	1.91
034	Eprosartan (new) 200 mg bid x 7 doses	32	2468	684	2.62	NC
	Eprosartan (old) 100mg x2 bid x7doses		2927	793	2.74	NC
035	Eprosartan (new) 400 mg	64	4426	1078	2.98	NC
	Eprosartan (old) 100 mg x 4 tabs		3824	837	3.01	NC
	Eprosartan (old) 200 mg x 2 tabs		5412	1340	2.98	NC
089	Eprosartan (new) 300 mg	48	3610	1028	1.00	NC
	Eprosartan (old) 100 mg x 3 tabs		3152	784	1.55	NC
092	Eprosartan (new) 300 mg tab	48	3331	1087	1.00	NC
	Eprosartan (old) 100mg x1 + 200mg x1		3217	1037	1.00	NC

† geometric mean; § median; NC = not calculated

Table BE-3 Point estimates and 90% C.I. of AUC of eprosartan in bioequivalence clinical pharmacology trials

Study #	Treatment groups	Group	AUC Point Estimates	AUC 90% C.I.	Conclusion*
018	Eprosartan 100 mg (50 mg x 2) wgf	A	A:C = 1.04	(0.86, 1.27)	Not
	Eprosartan 100 mg (100 mg x 1) wgf	B	B:C = 1.03	(0.84, 1.26)	bioequivalent
	Eprosartan 100 mg (50 mg x 2) dcf	C			
034	Eprosartan (new) 200 mg bid x 7 doses	A	A:B = 0.91	(0.84, 0.98)	AUC is
	Eprosartan (old) 100mg x2 bid x7doses	B			bioequivalent
035	Eprosartan (new) 400 mg	A	A:B = 1.16	(1.09, 1.24)	Not
	Eprosartan (old) 100 mg x 4 tabs	B	A:C = 0.83	(0.78, 0.88)	bioequivalent
	Eprosartan (old) 200 mg x 2 tabs	C			
089	Eprosartan (new) 300 mg	A	A:B = 1.15	(1.02, 1.29)	Not
	Eprosartan (old) 100 mg x 3 tabs	B			bioequivalent
092	Eprosartan (new) 300 mg tab	A	A:B = 1.04	(0.84, 1.28)	Not
	Eprosartan (old) 100mg x1 + 200mg x1	B			bioequivalent

*Bioequivalence = when 90% CI for ratios of test: reference for *ln* transformed AUC are contained within the range (0.80, 1.25)

Table BE-4 Point estimates and 90% C.I. of Cmax of eprosartan in bioequivalence clinical pharmacology trials

Study #	Treatment groups	Group	Cmax Point Estimates	AUC 90% C.I.	Conclusion*
018	Eprosartan 100 mg (50 mg x 2) wgf	A	A:C = 1.04	(0.80, 1.34)	Not
	Eprosartan 100 mg (100 mg x 1) wgf	B	B:C = 0.94	(0.73, 1.22)	bioequivalent
	Eprosartan 100 mg (50 mg x 2) dcf	C			
034	Eprosartan (new) 200 mg bid x 7 doses	A	A:B = 0.86	(0.78, 0.95)	Not
	Eprosartan (old) 100mg x2 bid x7doses	B			bioequivalent
035	Eprosartan (new) 400 mg	A	A:B = 1.30	(1.19, 1.42)	Not
	Eprosartan (old) 100 mg x 4 tabs	B	A:C = 0.82	(0.75, 0.89)	bioequivalent
	Eprosartan (old) 200 mg x 2 tabs	C			
089	Eprosartan (new) 300 mg	A	A:B = 1.31	(1.11, 1.55)	Not
	Eprosartan (old) 100 mg x 3 tabs	B			bioequivalent
092	Eprosartan (new) 300 mg tab	A	A:B = 1.05	(0.86, 1.27)	Not
	Eprosartan (old) 100mg x1 + 200mg x1	B			bioequivalent

*Bioequivalence = when 90% CI for ratios of test: reference for *ln* transformed Cmax are contained within the range (0.80, 1.25)

However, in ALL of the above studies, the 90% confidence intervals for the ratios of test : reference for *ln*-transformed AUC(0-τ) and *ln*-transformed Cmax were <u>not</u> contained within the range (0.80, 1.25). Thus, based on the analysis of the primary endpoints, the new (commercial) formulations of 100 mg, 200 mg, 300 mg and 400 mg eprosartan can <u>not</u> be considered bioequivalent to the reference formulations that were used in the clinical trials.

CONCLUSION

Five clinical pharmacology trials were carried out (Protocol #018, #034, #035, #089 and #092) to compare the bioequivalence of the new commercial tablet) formulation of eprosartan at different doses (100, 200, 300 and 400 mg) with the old) tablets that were used in the clinical trials. In all instances, the 90% confidence intervals for the 90% confidence intervals for the ratios of test : reference for *ln*-transformed AUC(0-τ) and *ln*-transformed Cmax were <u>not</u> contained within the range (0.80, 1.25). Based on this analysis of AUC(0-τ) and Cmax, the new (commercial) formulations of 100 mg, 200 mg, 300 mg and 400 mg eprosartan are not bioequivalent to the reference formulations that were used in the clinical trials

RECOMMENDATION FOR LABELING OF EPROSARTAN

Mechanism of Action
Eprosartan is claimed to block the binding to angiotensin II to the AT_1 receptor in tissues (e.g., vascular smooth muscle and adrenal gland). There was no partial agonist activity on effective renal plasma flow (ERPF) as measured by CL_{PAH}. The angiotensin II blocking activity of eprosartan was found in healthy subjects in whom single oral doses of 200 mg (on low or high salt diet), 400 mg and 350 mg eprosartan blocked the vasoconstricting effects of angiotensin II infusion on ERPF.

In healthy subjects, eprosartan reduces serum aldosterone concentrations following single oral doses of eprosartan above 10 mg. A dose related reduction in serum aldosterone concentrations over the range of 10-200 mg eprosartan was observed. A single oral dose of 350 mg eprosartan blunted the Angiotensin II-induced increase in serum aldosterone concentrations. While low salt diet increased serum aldosterone concentrations, eprosartan (200 mg and 400 mg doses) given with low salt diet suppressed the rise in serum aldosterone concentrations due to low salt diet, and blocked the further rise in serum aldosterone concentrations induced by Angiotensin II infusion.

Plasma renin activity was increased following single oral doses of eprosartan 50 mg and above, and in subjects given 200 mg or 400 mg eprosartan with low salt diet. In subjects on low salt diet receiving eprosartan 200 mg or 400 mg, the mean plasma renin activity increased which was not suppressed by infusion of angiotensin II.

Pharmacokinetics
Following intravenous dosing, plasma concentrations of eprosartan were not detectable or very low in the majority of subjects given intravenous doses of 0.1 and 0.3 mg, but were measurable for 2 to 4 hours at 1, 3, and 5 mg doses, and for up to 8-10 hours following 10 and 20 mg doses of eprosartan. Median Cmax and AUC increased in a dose proportional manner over the 1 mg to 20 mg intravenous dose range. Cmax of eprosartan and of total radioactivity were seen at 0.5 hour and declined from peak in a bi-exponential manner. Median $T_{1/2}$ for the 1 to 20 mg intravenous doses of eprosartan ranged from 1.05 to 2.34 hours.

Following oral dosing with single doses of eprosartan oral solution or eprosartan tablets, peak plasma concentrations were achieved within 1 to 3 hours. Plasma concentrations were measurable for 3 to 6 hours following 1, 3, 10 mg doses, for 10-12 hours following 30, 50 and 100 mg doses (solution or tablets), and 12 to 24 hours following the 200 mg (solution or tablet) and 350 mg (tablet) doses (the values at 12 and 24 hours being < 1-5% of peak concentrations).

Cmax and AUC increased in a dose proportional manner with the oral eprosartan solution up to 200 mg. With eprosartan tablets at higher doses (100-800 mg), Cmax and AUC increased with an increase in dose but were not dose proportional. The mean dose-normalized AUC and the mean dose-normalized Cmax showed a decreasing trend with increasing dose, suggesting saturation of absorption of eprosartan over the 100 mg to 800 mg oral dose range.

The dose-normalized AUC and dose-normalized Cmax for the 200 mg dose were contained within the protocol-specified 20% acceptance range for equivalence (0.80, 1.25). Thus, dose-proportionality was concluded for the 200 mg dose relative to the 100 mg reference dose. The 90% confidence interval for the dose-normalized AUC for the 800 mg dose to the 100 mg reference dose, and the 90% confidence interval for the dose-normalized Cmax for the 400 mg and 800 mg doses to the 100 mg reference dose were not contained within the acceptance range.

The median Tmax ranged from 1 to 3 hours for the dose range 50-800 mg. Median $T_{1/2}$ for the 30, 50 and 100 mg doses of eprosartan ranged from 2.49 to 3.26 hours. For the 200 mg dose, the median $T_{1/2}$ was 3.92 hours and for the 350 mg dose of eprosartan, the median $T_{1/2}$ was 5.28 hours.

Metabolism and elimination
Acyl glucuronidation was the only metabolic pathway found. The acyl glucuronide was not detectable in plasma nor feces. This metabolite accounted for approximately 20% of the radioactivity in the urine. The eprosartan acyl glucuronide is presumed to be excreted into the intestinal lumen via the bile. The major route of excretion was via the feces (61 and 90% of dose excreted after i.v. and oral administration, respectively). Urinary excretion account for 37% and 7% of dose being excreted after intravenous and oral administration, respectively.

Distribution
The median steady state volume of distribution (Vss) was about 13 liters to 17 liters which approximates total extracellular water. This small steady-state volume of distribution indicates minimal tissue distribution of eprosartan and a high degree of plasma protein binding (approximately 98%).

The median plasma clearance at steady state for the 3 to 20 mg doses was approximately 7.5 L/h to 9 L/h. The blood clearance of eprosartan (based on a blood-to-plasma ratio of 0.62 for eprosartan) was approximately 12 L/h to 14.7 L/h. Assuming normal hepatic blood flow of 1500 ml/min and negligible renal clearance of eprosartan, the estimated hepatic extraction ratio of eprosartan is approximately 0.15 to 0.17, giving an absolute bioavailability of approximately 83% to 85% when eprosartan was administered by the intravenous route.

Bioavailability
The relative bioavailability based on median AUC values was approximately 70%, 80% and 60% for the 50 mg, 100 mg dose and 200 mg doses of eprosartan, respectively. Using iv data from another study, the absolute bioavailability of eprosartan estimated from the median AUC values ranges from approximately 12% to 18% for the tablet formulation. In a study using ^{14}C-labeled eprosartan, the average absolute bioavailability of eprosartan following oral administration was 14.7% (range: 8.6 to 24.0%). The reasons for low bioavailability of eprosartan were: (i) low absorption rather than extensive first pass metabolism, (ii) slow absorption of eprosartan and (iii) absorption throughout the small and large intestine (rather than fecal elimination due to poor solubility).

Effect of food
Peak plasma concentrations were reached earlier by about 1 hour when single oral doses of eprosartan (300 mg, 350 mg or 800 mg) were given in the fasted state than when given with a high fat meal.

The AUC was larger by 56% and 20%, respectively, when 350 mg and 800 mg doses of eprosartan were given with a high fat meal. The 95% confidence intervals for AUC do not include the value 1.00 indicating a food effect on AUC. At a lower dose of 300 mg eprosartan, AUC was decreased (by 9.9%) in the fed state compared to the fasted state; the 95% confidence intervals for AUC contained the value 1.00 suggesting no food effect.

Cmax in the fed state was 25% lower than in the fasted state for the 300 mg dose of eprosartan. Cmax was 7% less when 800 mg eprosartan was given after a high fat meal compared to the fasted condition. The 95% confidence intervals for Cmax include the value 1 indicating no substantial difference produced by food. On the other hand, the Cmax was 80% higher when 350 mg eprosartan was given after a high fat meal compared to the fasted condition. The 95% confidence intervals for Cmax do not include the value 1.00 indicating a food effect on Cmax.

The high fat meal caused a delay in Tmax of 1.25 hours for the 300 mg dose, 0.63 hours for the 350 mg dose and 1.75 hours for the 800 mg dose of eprosartan. The 95% confidence intervals for Tmax of the first two studies included the value zero suggesting that the rate of absorption is not different in the fed and fasted states. However, the 95% confidence interval for Tmax in the last study does not include the value zero suggesting that the rate of absorption is different in the fed and fasted states.

All of the above findings probably suggest variability of absorption when eprosartan was given with food. Overall, the results suggest that administration of eprosartan with a high fat meal:
(i) slightly delayed the rate of absorption which was not clinically significant, and
(ii) did not effect the extent of absorption or slightly increased the extent of absorption (by 56% for the 350 mg dose and 20% for the 800 mg dose of eprosartan).

It may thus be suggested that eprosartan can be given orally without regard to meal times.

Special Populations

Pediatric
The pharmacokinetics of eprosartan have not been investigated in patients < 18 years of age.

Geriatric
Following a single oral dose of 200 mg eprosartan, elderly men had peak plasma concentrations of eprosartan between 3 and 6 hours for elderly men (compared to 2 and 4 hours for young males); the plasma concentrations then

declined in a multi-exponential manner. Eprosartan was highly protein bound to plasma proteins (approximately 98%) with no apparent differences in the mean fraction unbound between elderly males relative to young males. Total and free mean AUC, mean Cmax, and median Tmax values in the elderly were > 2-fold larger compared to young males.

Gender
In young females, peak plasma concentrations after a single oral dose of 200 mg eprosartan was reached 2 and 4 hours similar to young men. Subsequent plasma concentrations of eprosartan declined in a multi-exponential manner. There were no differences in the mean fraction unbound (approximately 2%), total and unbound AUC or Cmax, and in Tmax or terminal half-life ($T_{1/2}$) values between young males and young females.

In Patients with Hypertension
At the doses studied (50, 100, 350 mg qd, 150 mg bid, 600, 800 and 1200 mg qd), the plasma concentrations reached peak values within 1 to 3 hours. Plasma levels were < 10% of peak values after 12 hours. $T_{1/2}$ was longer for higher doses, being between 8.64 to 12.24 hours for the 600, 800 and 1200 mg qd doses and between 4.09 and 9.6 hours for the 50, 100, 350 mg qd doses and 150 mg bid dose. A dose-related increase in mean Cmax and AUC were found (except for AUCs for the 800 mg dose after 7 days). There was no accumulation with repeated doses. Steady-state appeared to be reached by Day 4.

The above pharmacokinetic data in hypertensive patients suggest that eprosartan requires bid dosing.

In Patients with Renal Insufficiency
Plasma concentrations of eprosartan reached peak values at almost the same time in volunteers with normal renal function and those with varying degrees of renal failure (Tmax = 4 hr for eprosartan 200 mg dose), and in hemodialysis-dependent patients with end stage renal disease or ESRD (Tmax = 1.5 hr for eprosartan 400 mg dose). Plasma concentrations of eprosartan achieved steady state levels by 6 to 7 days except in the case of subjects with severe renal function impairment.

While there was a high degree of variability, the means AUC, Cmax, unbound fraction, and unbound AUC and unbound Cmax were similar for subjects with normal renal function and those with mild renal impairment. They increased as the severity of renal function impairment increased, being highest in hemodialysis-dependent patients with ESRD.

Dialysis treatment altered the AUC, Cmax and protein binding of eprosartan. On dialysis day, AUC and Cmax were was increased by about 35% compared to non-dialysis day. The median Tmax occurred about 2.5 hours later on the dialysis day compared to non-dialysis day.

The mean renal clearance and excretion of eprosartan in urine decreased as renal function impairment becomes more severe, being, respectively 95% and 90% lower in subjects with severe renal impairment. In hemodialysis-dependent patients with ESRD, CL_{hd} of eprosartan, determined by dialysate measurement, was 11.22 ml/min. Eprosartan, being highly protein bound, is not cleared by hemodialysis, the contribution of CL_{hd} to systemic clearance being small (about 10%).

In Patients with Hepatic Insufficiency
In a study of a single 100 mg oral dose of eprosartan in 8 male subjects with hepatic and 8 healthy men, eprosartan AUC increased by about 40% without concomitant increase in Cmax, and the estimated $T_{1/2}$ was similar for both groups of patients. There was no relationship between plasma protein binding of eprosartan and serum albumin concentrations. The results suggested that no dose adjustments is required when eprosartan is administered to patients with hepatic disease.

Pharmacodynamic and Clinical Effects

Effect on Renal Hemodynamics (ERPF and GFR)
In healthy subjects, Eprosartan 300 mg twice a day for 7 days increased the ERPF as measured by CL_{PAH}. In salt restricted individuals, a dose-related increase in ERPF was found, with the maximum increase in CL_{PAH} being observed at 100 mg eprosartan (31.7%±13.1%). The effect plateaued at higher doses (increase in CL_{PAH} being 25.3±7.5% and 17.4%±9.6% with eprosartan 200 mg, and 24.5%±16.1% and 20.2%±8.7% with eprosartan 400 mg). The peak CL_{PAH} occurred approximately 2 - 3 hours post-dose. Eprosartan did not produce an increase in glomerular filtration rate (GFR) as measured by CL_{IN}.

In patients with mild to moderate hypertension, ERPF and GFR were not increased by eprosartan. There were no apparent changes in mean serum aldosterone concentration nor in plasma renin activity following eprosartan treatment compared to placebo.

In subjects with varying renal insufficiency, ERPF and GFR were not increased nor reduced by eprosartan. The study was ended prior to meeting the target enrollment of 9 subjects per renal group.

Effect on Urinary Electrolyte Excretion
In healthy subjects on low salt diet, eprosartan showed a mild natriuretic effect, the mean 24-hour urinary Na^+ excretion being increased by 17.7 mEq/day. Following a single oral dose of eprosartan 400 mg, the 24-hour urinary excretion of sodium was statistically significantly increased (30.19 mEq/day, 95% CI: 25.02, 35.37 mEq/day) compared to placebo (18.77 mEq/day, 95% CI: 13.62, 23.92 mEq/day).

In patients with essential hypertension, there were no changes in fractional excretion and urinary excretion rates of Na^+ and K^+ after treatment with eprosartan.

In patients with chronic renal failure, while the fractional excretion and urinary excretion rates of Na^+ and K^+ increased with more severe stages of renal failure, no changes in these parameters were found after treatment with eprosartan.

Effect on Blood Pressure in Patients with Hypertension (and dosing requirements)
Once/day dosing:
At single and repeated dosing of 50, 100, and 350 mg once/day and 150 mg bid of eprosartan, the diastolic cuff blood pressure was reduced (≥ 3 mmHg) at 3 to 12 hours post-dose for doses of eprosartan 100 mg and above. Ambulatory blood pressure monitoring and averaged mean arterial pressure did not show dose-dependent lowering of blood pressure.

At single and repeated dosing of 600, 800, and 1200 mg once/day, the diastolic cuff blood pressure was reduced (inconsistently) at 3 hours post-dose. Cuff blood pressure, ambulatory blood pressure monitoring and averaged mean arterial pressure did not show dose-dependent lowering of blood pressure.

When 400 mg eprosartan once/day was given together with HCTZ, there was a dose-related (to HCTZ) statistically significant reduction in sitting diastolic blood pressure compared to placebo. The reduction in SitDBP attributable to eprosartan 400 mg once/day was small (2 mmHg) compared to that due to placebo effect (5.4 mmHg), HCTZ 12.5 mg (2.4 mmHg) and HCTZ 25 mg (4.8 mmHg). Secondary efficacy parameters (sitting systolic blood pressure and percentage of patients who responded at endpoint) also showed the same trend, with a reduction in sitting systolic blood pressure of 6.2 mmHg (compared to 5.5 mmHg for placebo) and a responder rate of 8.6% (compared to 29% for placebo) attributable to eprosartan 400 mg once/day. It is likely that over-enrollment of patients (124-128 patients per group rather than the required 70 patients per group) may have contributed to the finding of spurious statistical significance in the efficacy parameters between the eprosartan/HCTZ treatment groups and the placebo treatment group.

Twice/day dosing:
In hypertensive patients with left ventricular hypertrophy, similar decreases in sDBP and sSBP from baseline were found at titration, maintenance and study endpoints with eprosartan 200 mg bid titrated up to 400 mg bid, or enalapril 10 mg qd titrated up to 40 mg qd, the treatments lasting for a total duration of 26 weeks. At these bid dose regimens of eprosartan, the proportion of responders (sDBP decreased to <90 mmHg or 90-100 mmHg and decrease from baseline by ≥10 mmHg) was greater in the eprosartan regimen (12.8%) compared to enalapril regimen (12.0%) at both titration and study endpoints.

The findings suggest overall that eprosartan should be prescribed in doses of **200 mg to 400 mg twice/day.**

Effect on Heart Rate
There was no change in heart rate reported for the eprosartan-treated patients in the clin-pharm trials reviewed.

Effect on Left Ventricular Hypertrophy in Patients with Hypertension
In patients with hypertension and pre-existing left ventricular hypertrophy, left ventricular mass index (LVMI) was similar to baseline in the eprosartan regimen (mean change being -1.5 g/m^2) and decreased in the enalapril regimen (-7.6 g/m^2) at study endpoint. At month 6, a decrease in LVMI from baseline was found in both medication

regimens, being larger for enalapril (-11.9 g/m^2) compared to eprosartan (-3.6 g/m^2). The difference between medication regimens in change of LVMI from baseline was not statistically significant at either time point.

Eprosartan, compared to enalapril, caused a greater decrease in peak systolic wall stress (PSWS) and increase in isovolumic relaxation time at both month 6 and study endpoint from baseline. LV end diastolic volume was found to decrease more in the enalapril regimen compared to eprosartan at both month 6 and study endpoint. None of these differences between the two treatment regimens was statistically significant.

Effect on Urinary Uric Acid Excretion
Studies of the effect of eprosartan on uric acid excretion by fractional excretion of urinary uric acid (Fe_{UA}), urinary excretion rate of uric acid, and U_{UA}/U_{CR} ratio showed that eprosartan does not have a uricosuric effect based on lack of changes in Fe_{UA} and U_{UA}/U_{CR} ratio. This finding holds true for all of the population groups studied: healthy subjects, patients with essential hypertension and patients with renal impairment.

Effect on Proteinuria in Patients with Type II Diabetes Mellitus
While urinary protein in diabetic (NIDDM) patients on placebo increased from baseline by 34%, the urinary protein in those on eprosartan decreased by 1% at Week 6, the differences being not statistically significant. In a subset of patients who had proteinuria > 1000 mg/24 hr, a statistically significant reduction (P = 0.0254) in urinary protein was observed in patients on eprosartan (by 34%) compared to an increase in proteinuria by 22% in patients receiving placebo.

Urinary albumin was reduced in patients on eprosartan (by about 5%) in contrast to increased (by 30 %) urinary albumin in patients on placebo, but the differences were not statistically significant (P = 0.0827).

PRECAUTIONS

General

Impaired Renal Function
The mean AUC and Cmax, the unbound fraction, total and unbound plasma concentrations, and unbound Cmax and unbound AUC, all increased as the severity of renal function impairment increased. The mean renal clearance and excretion of eprosartan in urine decreased as renal function impairment becomes more severe, being, respectively 95% and 90% lower in subjects with severe renal impairment.

Dialysis treatment increases the AUC, Cmax, Tmax and protein binding (and thus, reduces the free or unbound fraction) of eprosartan. Eprosartan, being highly protein bound, is not cleared by hemodialysis, the contribution of CL_{hd} to systemic clearance being small (about 10%).

While no dose adjustments may be required when eprosartan is administered to patients with mild, moderate or severe renal impairment, care should be exercised (since plasma concentrations of eprosartan and its blood pressure lowering effects are not proportionally related).

Impaired Hepatic Function
A small proportion of eprosartan undergoes metabolism by acyl glucuronidation, and this eprosartan acyl glucuronide is excreted into the intestinal lumen via the bile. A study of a single 100 mg oral dose of eprosartan in 8 male subjects with hepatic insufficiency showed that eprosartan AUC increased by about 40% without concomitant increase in Cmax. There was no relationship between plasma protein binding of eprosartan and serum albumin concentrations. While the results suggested that no dose adjustments is required when eprosartan is administered to patients with hepatic disease, care should be exercised in administering eprosartan to patients with hepatic disease and/or biliary obstructive disorders.

Information to Patients

Drug Interactions
Eprosartan had no effect on single oral-dose pharmacokinetics of digoxin in healthy subjects. Eprosartan and warfarin at steady-state concentrations in healthy volunteers were not associated with any interaction as measured by

the INR. Eprosartan had no effect on the 24-hour plasma glucose concentrations in diabetic patients stabilized on glyburide therapy. In all of the above, the effect s of digoxin, warfarin or glyburide on the pharmacokinetics of eprosartan were not studied.

The pharmacokinetics of a single dose of eprosartan was not altered by the concomitant administration of ranitidine.

CRP 450 Interactions
Eprosartan does not undergo oxidative metabolism and its single oral dose and repeat oral dose pharmacokinetcs were not affected by concomitant administration of steady state fluconazole, a CYP2C9 inhibitor or ketoconazole, a CYP3A4 inhibitor.

Nursing Mothers
It is not known whether eprosartan is excreted in human milk.

Pediatric Use
Safety and effectiveness in pediatric patients have not been studied.

Geriatric Use
Following a single oral dose of 200 mg eprosartan, elderly men had peak plasma concentrations of eprosartan between 3 and 6 hours for elderly men (compared to 2 and 4 hours for young males); the plasma concentrations then declined in a multi-exponential manner. Eprosartan was highly protein bound to plasma proteins (approximately 98%) with no apparent differences in the mean fraction unbound between elderly males relative to young males. Total and free mean AUC(0-∞), mean Cmax, and median Tmax values in the elderly were > 2-fold larger compared to young males.

DOSAGE AND ADMINISTRATION

The recommended dose of eprosartan is 200 mg twice/day. The dose may be titrated to 400 mg twice/day. (Other dosage information to be added, based on findings in efficacy review.)

Eprosartan may be administered with or without food.

No initial dosage adjustment is required for elderly patients, for patients with mild renal impairment or for patients with mild to moderate hepatic impairment. In patients with moderate to severe renal impairment and severe hepatic impairment, care should be exercised. In hemodialysis-dependent patients with end-stage renal disease, eprosartan is not cleared by hemodialysis.

Eprosartan may be administered with hydrochlorothiazide.

The following and other sections of the package will need to be written based on Efficacy, Safety, Biopharm and Chemistry Reviews:-

1. ADVERSE REACTIONS
2. Clinical Laboratory Test Findings
3. OVERDOSAGE
4. Carcinogenesis, Mutagenesis, Impairment of Fertility
5. Pregnancy
6. Pregnancy Categories C
7. Description
8. Indications
9. Contraindications
10. WARNINGS
11. Fetal/Neonatal Morbidity and Mortality
12. Hypotension in Volume- and/or Salt-Depleted Patients

NDA #:	20-738		
DRUG NAME:	**Teveten™ (Eprosartan)** Tablets		
SPONSOR:	SmithKline Beecham Pharmaceuticals		
TYPE OF DOCUMENT:	New NDA (Clinical Pharmacology Review)		
DATE OF CORRESPONDENCE:	*11-Oct-1997*		
DATE RECEIVED:	*18-Oct-1996*	DATE ASSIGNED:	*02-May-1997*
MEDICAL OFFICER:	Khin Maung U, M.D.	DATE COMPLETED	*07-Aug-1997*

Issues in the clin-pharm review of NDA 20-738 Teveten™ (Eprosartan) Tablets that made drawing valid inferences difficult are as follows:

(1) **Bioequivalence**

In five clin-pharm trials (Protocols #018, #034, #035, #089, #092) involving substantial numbers of subjects to determine bioequivalence of the commercial (wet granulation) formulation to the (direct compressed) formulation used in the clinical trials, bioequivalence was demonstrated for none of the commercial formulations. This is worrisome. It remains to be seen if the pivotal clinical trials were carried out with the commercial formulations, and a reproducible dose-response is observed across different clinical trials.

(2) **Dose-Response**

The pharmacokinetic (AUC, Cmax) studies showed a dose-proportional response up to a single oral dose of 200 mg eprosartan. The pharmacokinetics were not dose-proportional at higher doses with the eprosartan tablets used, although a dose-related response was present. The peak plasma concentrations also were not dose-proportional. The effect on blood pressure also was not dose-related in the clin-pharm trials reviewed. With this lack of relationship of dose to pharmacokinetics/plasma concentration and, subsequently, to blood pressure reduction response, it is difficult to rationalize a dosing regimen for eprosartan based on the clin-pharm trials data alone. Data from efficacy review of pivotal clinical trials may be more useful.

Also, the same dose used in different clinical trials produced rather different pharmacokinetics or blood pressure effects. One reason for this lack of dose-response relationship may be due to lack of bioequivalence (above) of the different eprosartan formulations used in these studies.

(3) **Dose in disease states**

While the sponsor suggested that dose adjustment is not necessary for chronic renal insufficiency or hepatic insufficiency, the number of patients that have been exposed to eprosartan is very small. Also, the pharmacokinetics increased with an increase in the severity of renal failure. The fact that plasma levels do not correlate with clinical (blood pressure lowering) response obviates the usefulness of adjusting dose based on plasma levels (such as for digoxin) in these patients with renal or hepatic insufficiency. A worrisome finding is the fact that eprosartan is not cleared by hemodialysis. More experience in these situations is needed, and careful and close observation of patients with renal or hepatic insufficiency should be made when eprosartan is prescribed for these patients.

(4) **Inadequate/inappropriate sample sizes**

Apart from the small number of patients with renal and hepatic insufficiency in the studies mentioned above, inadequate sample size did not allow definitive inferences to be made with regard to response of left ventricular hypertrophy to long term (6 month) treatment with eprosartan.

On the other hand, the clinical trial of eprosartan with HCTZ enrolled more patients than are necessary, giving a statistically significant response in endpoint parameters which may or may not be the true response.

(5) **Drug Interactions**

In drug interactions with digoxin, warfarin and glyburide, the effect of these drugs on the pharmacokinetics of eprosartan have not been studied. Thus, when eprosartan is used with these drugs, its effects and adverse experiences will need to be observed carefully.

Use of eprosartan with ß-blockers such as atenolol has not been studied. From the clin-pharm review, it is not known whether eprosartan could be administered with other antihypertensive agents.

The clinical trial of eprosartan with HCTZ indicated that the blood pressure lowering effects of HCTZ exceeded that of eprosartan.

(6) **General**

In patients in whom renal function may depend on the activity of the renin-angiotensin-aldosterone system (such as patients with severe congestive heart failure), treatment with ACE inhibitors and angiotensin receptor antagonists have been associated with oliguria and/or progressive azotemia, and, in rare instances, acute renal failure and/or death. Eprosartan should thus be used with care in such situations.

In studies of ACE inhibitors with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. While a trial of valsartan for 4 days in 12 patients with unilateral renal artery stenosis reported no "significant" increases in serum creatinine or blood urea nitrogen, the effect of eprosartan is not really known.

It is not known from the clin-pharm studies whether there is any relationship of effect to race. ACE-inhibitors have generally been found to be less effective in low-renin hypertensives (frequently blacks) than in high-renin hypertensives (frequently whites).

8/7/97

Khin Maung U, MBBS, MMedSc, MD(NSW), MD, FACP

cc: orig.
HFD-110
HFD-110 / CSO / C. Ganley (Secondary Reviewer) / K.M.U

NDA #: 20-738

DRUG NAME: **Teveten™ (Eprosartan) Tablets**

Table 1. ***Clinical Pharmacology Trials (PD mainly)***

Study # & PK/PD	Design, Patient population	Treatment groups	N	Primary Endpoint	Secondary Endpoint
006; PD & PK	db, pc, co, sd, HMV: Pt 1 Part 2 Part 3	Eprosartan (dose-rising) vs placebo Eprosartan 10, 30, 50, 70, 100, 200 mg Eprosartan 50, 100, 300 mg	8 each 8 each 4 each	ERPF (CL_{PAH})	Ur Elec excr & $Fe_{Na,K,Cl}$ Plasma cortisol and aldosterone levels
009; PD & PK	db, pc, co, sc, rd, mild to moderate HTN†	Eprosartan 50, 100, 150, 350 mg qd vs placebo	32	Plasma conc; safety	av sDBP; av sSBP; MAP; pulse rate
024; PD	ol, co, rd, HMV	SB203220 600 mg qd x 8d + Captopril 25 mg d8 Eprosartan 300 mg bid x 7d + Captopril 25 mg d8 Captopril 250 mg bid x 7d + eprosartan 300 mg d8 Placebo	14	ERPF (CL_{PAH})	GFR (CL_{IN})
026; PD	db, pc, co, rd, in mild to moderate HTN†	Eprosartan 300 mg bid x 28 d Placebo x 29 d	14 14	ERPF (CL_{PAH}) GFR (CL_{IN})	Safety labs, Urine Elec. excr. & $Fe_{Na,K,Cl}$ Filtration fraction (CL_{IN}/ CL_{PAH}), CL_{CR}/ CL_{IN}, UUA/UCr
027; PK & PD	db, pc, pg, rd, in HMV	Eprosartan 300 mg bid+Warfarin x 7 d Placebo bid + Warfarin x 7d	11 7	INR on Day 22	PK studies, if INR not in ±25% equivalence range
028; PK & PD	db, pc, co, rd, in patients with NIDDM on glyburide	Eprosartan 200 mg bid x 7 d Placebo x 7 d (Both above getting glyburide 1.25 to 5 mg qd x 7 d before and during study)	12 12	Mean 24-h plasma glucose conc. on Day 0 and Day 7	PK studies, if mean plasma glucose conc. not in ±30% equivalence range
043; PD	Pt I: ol, co, sd, Pt II: db, pc, co, sd in HMV	Pt IA: eprosartan dose-rising Pt IB: eprosartan + low salt, eprosartan + salt loading, and placebo + low salt Pt II: eprosartan 400 mg, captopril 25 mg, placebo	9 each 6 each 14 each	ERPF (CL_{PAH})	GFR (CL_{IN}), serum aldosterone, plasma renin activity, blood pressure, Ur Elec. excr
044; PD	db, pc, co, rd, in healthy volunteers and patients with renal insufficiency	Eprosartan 300 mg bid x 6d + eprosartan 300 mg d7 Captopril 25 mg bid x 6d + eprosartan 300 mg d7 Placebo x 6 d + eprosartan 300 mg d7	31 33 31	ERPF (CL_{PAH}) GFR (CL_{IN})	Safety labs, Urine Elec. excr. & $Fe_{Na,K,Cl}$ Filtration fraction (CL_{IN}/ CL_{PAH}), CL_{CR}/ CL_{IN}, UUA/UCr
048; PK & PD	db, pc, co, rd, dose-rising, in mild to moderate HTN†	Eprosartan 600, 800, 1200 mg vs placebo	24	Plasma conc; safety	av sDBP; av sSBP; pulse rate, ambulatory BP
051; PD	db, ac, mc, pg, rd, in essential HTN† + LVH§	Eprosartan 200 → 400 mg bid Enalapril 10 → 40 mg qd	11 14	change in LVMI from baseline	EF, PSWS, LVEDV, LVESV, LVDD, LVFS, Peak E/A, Peak E deceln., Isovolumic relaxation, PWT, sDBP, sSBP, sHR, Responders
061; efficacy	db, pc, pg, mc, rd, in mild to moderate HTN†	Eprosartan 400 mg + HCTZ 12.5mg qd Eprosartan 400 mg + HCTZ 25 mg qd Placebo	128 124 124	mean change in sDBP from baseline	sSBP, sHR, Responders
069; PD	ol, co, sd in HMV	Eprosartan 400 mg Losartan 50 mg	12 12	ERPF (CL_{PAH}), Fe_{UA}, UUA/UCr, safety	GFR (CL_{IN}), $Fe_{Na,K,Cl}$, Plasma renin activity & aldosterone levels, CL_{CR}/ CL_{IN},
090; PD	db, pg, rd, in patients with NIDDM and average urine protein ≥300 & ≤3000 g/24h	Eprosartan 300 mg bid Placebo	34 41	% change in 24 h urine protein at Week 6	Urine albumin Urine creatinine
094; PD & PK	ol, pc, pg, rd, in HMV	Eprosartan 200 mg bid ± fluconazole 200 mg qd Losartan 100 mg qd ± fluconazole 200 mg qd Placebo	14 16 14	Undisso & total urine UA, serum UA, UUA/UCr, Urine creatinine	PK = AUC(0-τ), Cmax
095; PD & PK	ol, pc, pg, rd, in HMV	Eprosartan 200 mg bid ± ketoconazole 200 mg qd Losartan 100 mg qd ± ketoconazole 200 mg qd Placebo	13 14 15	Undisso & total urine UA, serum UA, UUA/UCr, Urine creatinine	PK = AUC(0-τ), Cmax

db = double blind; ol = open-label; pc = placebo-controlled; ac = active controlled; co = crossover; pg = parallel group; sd = single dose; rd = repeat dose; HMV = healthy male volunteers; mc = multicenter; sc = single center;
av = average; sDBP = sitting diastolic blood pressure; sSBP = sitting systolic blood pressure; MAP = mean arterial pressure; sHR = sitting heart rate;
† sDBP ≥ 95 mmHg and ≤ 114 mmHg; § LVMI ≥ 110 g/m^2 in males and ≥ 90 g/m^2 in females.

Table 2. ***Clinical Pharmacology Trials (PK mainly)***

Study # & PK/PD	Design, Patient population	Treatment groups	N	Primary Endpoint	Secondary Endpoint
003; PK	sb, pc, sd, in HMV	Eprosartan solution 1, 3, 10, 30, 50, 100, 200, 350, 500 mg or Placebo	4 - 7 in each	AUC(0-τ) and Cmax	Tmax and safety data
004; PK	sb, pc, sd, intravenous dose in HMV	Eprosartan 0.1, 0.3, 1, 3, 5, 10, 20, 35, 50 mg or Placebo	12 each	AUC(0-τ), AUC(0-∞), Cmax	Tmax, CL, Vss, safety data
005; PK	ol, co, sd, in HMV	Eprosartan 300mg po to fasted subjects Eprosartan 300 mg po to fed subjects Eprosartan 20 mg iv to fasted subjects	17 17 17	AUC(0-τ) and Cmax	Tmax and safety data
006; PD & PK	db, pc, co, sd, HMV: Pt 1 Part 2 Part 3	Eprosartan (dose-rising) vs Placebo Eprosartan 10, 30, 50, 70, 100, 200 mg Eprosartan 50, 100, 300 mg	8 each 8 each 4 each	ERPF (CL_{PAH})	Ur Elec excr & $Fe_{Na,K,Cl}$ Plasma cortisol and aldosterone levels
007; PK	ol, co, sd, in HMV	Eprosartan 350mg po to fasted subjects Eprosartan 350 mg po to fed subjects	12 12	AUC(0-τ) and Cmax	Tmax and safety data
008; PK	ol, co, sd, in HMV	Eprosartan 100, 200, 400 and 800 mg	23	AUC(0-τ) & Cmax	Tmax
009; PD & PK	db, pc, co, sc, rd, mild to moderate HTN†	Eprosartan 50, 100, 150, 350 mg qd vs Placebo	32	Plasma conc.; safety	av. sDBP; av. sSBP; MAP; pulse rate
018; PK	ol, co, sd in HMV	Eprosartan 100 mg (50 mg x 2) wgf Eprosartan 100 mg (100 mg x 1) wgf Eprosartan 100 mg (50 mg x 2) dcf	24	AUC(0-τ) and Cmax	Tmax, $T_{1/2}$, and safety data
020; PK	ol, co, sd (iv oral) in HMV	Eprosartan 20 mg iv Eprosartan 100 mg oral	3 4	Metabolic study	
021; PK	ol, pg, rd in chronic renal insufficiency	Eprosartan 200 mg bid with food x 7 d to normal renal function, mild renal insufficiency, moderate renal insufficiency and severe renal insufficiency	 7 8 13 3	%fu, AUC(0-12), Cmax, unbound AUC(0-12) and Cmax, CLr/CLCr, Tmax	safety data
022; PK	ol, pg, sd in HMV & patients with hepatic insufficiency	Eprosartan 100 mg to HMV and patients with hepatic insufficiency	8 each	AUC(0-τ)	Cmax, Tmax, plasma protein binding
23; PK	ol, co, rd, in HMV	Digoxin 0.6 mg Eprosartan 200 mg bid x 7 d + digoxin 0.6 mg on d4	12	AUC(0-τ) for digoxin	Cmax, Tmax, $T_{1/2}$, AUC(0-∞)
025; PK	ol, pg, sd, rd, in young men, young women, elderly men	Eprosartan 200 mg in young men Eprosartan 200 mg in young women Eprosartan 200 mg in elderly men	8 8 8	AUC(0-∞) and Cmax	Safety data
027; PK & PD	db, pc, pg, rd in HMV	Eprosartan 300 mg bid+Warfarin x 7 d Placebo bid + Warfarin x 7 d	11 7	INR on Day 22	PK studies, if INR not in ±25% equivalence range
028; PK & PD	db, pc, co, rd, in patients with NIDDM on glyburide	Eprosartan 200 mg bid x 7 d Placebo x 7 d (Both above & getting glyburide 1.25 to 5 mg qd x 7 d before and during study)	12 12	Mean 24-h plasma glucose conc. on Day 0 and Day 7	PK studies, if mean plasma glucose conc. not in ±30% equivalence range
029; PK	ol, co, sd in HMV	Eprosartan 400 mg Ranitidine 150 mg bid x 3 d, Eprosartan 400 mg + ranitidine 150 mg on Day 4	17 16	AUC(0-τ) and Cmax	CLr (renal clearance of eprosartan)
034; PK	ol, co, rd in HMV	Eprosartan (new) 200 mg bid x 7 doses Eprosartan (old) 100mg x2 bid x7doses	32	AUC(0-τ) and Cmax	Tmax
035; PK	ol, co, sd, in HMV	Eprosartan (new) 400 mg Eprosartan (old) 100 mg x 4 tabs Eprosartan (old) 200 mg x 2 tabs	64	AUC(0-τ) and Cmax in ±20% equivalence range	AUC(0-τ) and T max
048; PK & PD	db, pc, co, rd, dose-rising, in mild to moderate HTN†	Eprosartan 600, 800, 1200 mg vs placebo	24	Plasma conc; safety	av. sDBP; av. sSBP; pulse rate, ambulatory BP
086; PK	ol, co, sd, in HMV	Eprosartan 800mg po to fasted subjects Eprosartan 800 mg po to fed subjects	20 20	AUC(0-τ) and Cmax	Tmax and safety data
089; PK	ol, co, sd, in HMV	Eprosartan (new) 300 mg Eprosartan (old) 100 mg x 3 tabs	48	AUC(0-τ) and Cmax	Tmax
092; PK	ol, co, sd, in HMV	Eprosartan (new) 300 mg tab Eprosartan (old) 100mg x1 + 200mg x1	48	AUC(0-τ) and Cmax	Tmax
094; PD & PK	ol, pc, pg, rd, in HMV	Eprosartan 200 mg bid)±(fluconazole Losartan 100 mg qd) (200mg qd Placebo	14 16 14	urine UA, serum UA, UUA/UCr, Urine creatinine	PK = AUC(0-τ), Cmax
095; PD & PK	ol, pc, pg, rd, in HMV	Eprosartan 200mg bid)±(ketoconazole Losartan 100 mg qd) (200 mg qd Placebo	13 14 15	urine UA, serum UA, UUA/UCr, Urine creatinine	PK = AUC(0-τ), Cmax
99; PK	ol, pg, sd in hemodialysis-dependent patients & controls	Eprosartan 400 mg (on a dialysis day and on a non-dialysis day) and controls	8, 9 10	AUC(0-τ) and Cmax	%fu, Tmax, unbound Cmax, unbound AUC(0-τ)

PD = pharmacodynamic study; PK = pharmacokinetic study; DI = drug interaction study; db = double blind; sb = single blind; ol = open-label; pc = placebo-controlled; ac = active controlled; co = crossover; pg = parallel group; sd = single dose; rd = repeat dose; HMV = healthy male volunteers; mc = multicenter; sc = single center; av. = average; sDBP = sitting diastolic blood pressure; sSBP = sitting systolic blood pressure; MAP = mean arterial pressure; sHR = sitting heart rate; † sDBP ≥ 95 mmHg and ≤ 114 mmHg; § LVMI ≥ 110 g/m^2 in males and ≥ 90 g/m^2 in female.

LIST OF CLINICAL PHARMACOLOGY TRIALS REVIEWED

1. Protocol 003: A dose rising study to assess the safety and preliminary pharmacokinetics of single oral doses of SK&F 108566 in healthy male volunteers

2. Protocol 004: A dose rising study to assess the safety and preliminary pharmacokinetics of single intravenous doses of SK&F 108566 in healthy male volunteers

3. Protocol 005: A study of the absolute bioavailability and effect of food on the final commercial formulation of eprosartan in healthy male volunteers

4. Protocol 006: A dose-response study to assess the pharmacokinetics and pharmacodynamics of single oral doses of SK&F 108566 in healthy male volunteers

5. Protocol 007: Investigation of the effect of food on the pharmacokinetics of SK&F-108566 in healthy male volunteers

6. Protocol 008: A dose proportionality study of the final commercial formulation of eprosartan in healthy male volunteers

7. Protocol 009: A study of the safety, pharmacokinetics and preliminary efficacy of repeated oral doses of SK&F 108566 in patients with mild to moderate essential hypertension

8. Protocol 018: Comparison of the bioavailability of the original tablet formulation and a new intermediate release tablet formulation of SK&F 108566 in healthy male volunteers

9. Protocol 020: A study to determine the balance/excretion, pharmacokinetics and biotransformation of eprosartan (SK&F 108566) given as a single oral (100 mg) and single intravenous (20 mg) doses on separate occasions to healthy male adult subjects

10. Protocol 021: A study of the pharmacokinetics of multiple oral doses of SK&F 108566 in subjects with renal insufficiency

11. Protocol 022: A study of the effect of hepatic disease on the pharmacokinetics of a single oral dose of SK&F 108566

12. Protocol 023: Investigation of the effect of repeated oral doses of SK&F 108566 on the single dose pharmacokinetics of orally administered digoxin in healthy male volunteers

13. Protocol 024: A comparison of the renal hemodynamic effects of SB 203220, Eprosartan and Captopril in healthy male volunteers

14. Protocol 025: A study to evaluate the effect of age and gender on the pharmacokinetics of SK&F 108566 in healthy volunteers

15. Protocol 026: A study to determine the effect of SK&F 108566 on the renal hemodynamics of patients with mild to moderate essential hypertension

16. Protocol 027: A study to determine the effect of SK&F 108566 on the anticoagulant effect of Warfarin

17. Protocol 028: A study to determine the safety and effect of eprosartan on the pharmacodynamics and pharmacokinetics of glyburide in diabetic patients at steady state

18. Protocol 029: A study to evaluate the effect of ranitidine on the pharmacokinetics of eprosartan in healthy young male volunteers

19. Protocol 034: A replicate design study to evaluate the bioequivalence of the clinical trials formulation and the proposed commercial tablet formulation of SK&F 108566 in healthy male volunteers

20. Protocol 035: A study to evaluate the bioequivalence of the clinical trials formulations and the proposed 400 mg commercial tablet formulation of eprosartan in healthy male volunteers

21. Protocol 043: Renal response to an angiotensin II antagonist, SK&F 108566, in healthy volunteers

22. Protocol 044: Effects of SK&F 108566 vs captopril on renal hemodynamics in healthy volunteers and in patients with varying degrees of renal insufficiency

23. Protocol 048: Investigation of the safety, pharmacokinetics of single and repeated oral doses of SK&F 108566 (600 mg/day, 800 mg/day and 1200 mg/day) in patients with mild to moderate essential hypertension

24. Protocol 051: A 6-month, double-blind, double dummy, parallel, multicentre study of the action of SK&F 108566 in comparison with enalapril on left ventricular hypertrophy in patients with essential hypertension (DBP ≥95 and ≤114 mmHg)

25. Protocol 061: An 8-week, double-blind, double-dummy, placebo-controlled, parallel group, multicenter comparison of regimens of oral SK&F 108566 and hydrochlorothiazide given in combination in patients with mild to moderate essential hypertension (DBP ≥ 95 & ≤ 114 mmHg)

26. Protocol 069: A study of the renal hemodynamic effects of Eprosartan and Losartan in normal healthy male volunteers

27. Protocol 086: A study of the effect of food on eprosartan pharmacokinetics in healthy male volunteers

28. Protocol 089: A study to evaluate the bioequivalence of the 100 mg clinical trials tablet and the proposed 300 mg commercial tablet formulation of eprosartan in healthy male volunteers

29. Protocol 090: A six-week, double-blind study to compare the effects of eprosartan and placebo on proteinuria in patients with Type II diabetes mellitus

30. Protocol 092: A study to evaluate the bioequivalence of the proposed 300 mg commercial tablet formulation versus the clinical trials tablet and of eprosartan in healthy male volunteers

31. Protocol 094: An investigation of the effects of fluconazole on the pharmacokinetics, urine uric acid excretion, safety and tolerability of eprosartan and losartan in healthy male volunteers

32. Protocol 095: An investigation of the effects of ketoconazole on the pharmacokinetics, urine uric acid excretion, safety and tolerability of eprosartan and losartan in healthy male volunteers

33. Protocol 099: An evaluation of the pharmacokinetics of a single oral dose of eprosartan in hemodialysis-dependent patients with end stage renal disease compared to volunteers with normal renal function

Protocol 003: **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol 1.105)*

DATE OF CORRESPONDENCE: *11-Oct-1996*
DATE RECEIVED: *18-Oct-1996*
DATE ASSIGNED: *26-Jun-1997*
DATE COMPLETED *26-Jun-1997*

03.1 STUDY PROTOCOL

03.1.1 Title

A dose rising study to assess the safety and preliminary pharmacokinetics of single oral doses of SK&F 108566 in healthy male volunteers

03.1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. This study evaluates the safety and pharmacokinetics of eprosartan, an A-II AT_1 receptor antagonist, in single oral doses.

03.1.3 Objectives

1. To evaluate the single dose safety and tolerability of SK&F 108566 oral solution over the dose range of 1 to 500 mg, and
2. To obtain preliminary pharmacokinetic data for SK&F 108566 in humans.

03.1.4 Study design

The study was a single-blind, placebo-controlled, oral dose rising study. Subjects were to participate in 4 study sessions which were separated by at least one week. During each study period, subjects received, by random allocation, 100 ml of placebo oral solution (Lot# U-92009) or SK&F 108566 oral solution (Lot# U-92010) in one of the following single oral doses under single-blind conditions: 1, 3, 10, 30, 50, 100, 200, 350, or 500 mg. Active doses of SK&F 108566 were given in ascending order, the maximum dose being limited to 200 mg for the oral solution, and in some subjects oral tablets {30 (3 x 10 mg tablets, Lot# U-92054), 50 (Lot# U-92055), 100 (2 x 50 mg tablets), 200 (4 x 50 mg tablets) and 350 mg (7 x 50 mg tablets)} were substituted for the oral solution, being administered with 100 ml water. No subject proceeded to a higher dose until the lower doses had been safely (based on clinical grounds) administered and their effects observed in at least 3 subjects.

03.1.5 Protocol Amendments

Preliminary plasma concentration data which became available during the study suggested that Cmax values following doses > 200 mg of SK&F 108566 oral solution would exceed plasma concentration (approximately 2000 ng/ml) evaluated during animal toxicology studies. Therefore, the dose of the oral solution was limited to a maximum of 200 mg, and subjects who were scheduled to receive 350 or 500 mg doses of the oral solution were reassigned to receive the tablet formulation (30 to 350 mg). Thus, a protocol amendment was made to study SK&F 108566 oral tablets (10 mg and 50 mg) in addition to the oral solution specified on the protocol, and allow the substitution of oral tablets for oral solution in up to six additional subjects.

03.1.6 Population enrolled/analyzed

21 healthy, non-smoking, adult male volunteers 18-50 years of age, weight > 50 kg and within 10% of ideal weight (based on height), and a negative urine drug screen within 30 days were enrolled.

Compliance: Subjects took study medication in the clinical pharmacology unit under nursing supervision.

Pre-study screening: The screening visit (30 days prior to start of the study) included a complete medical and medication history, physical examination, and 12-lead ECG. Blood (15 ml) and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, urinalysis and drug screen). Subjects were not permitted to take any prescription or non-prescription medications 2 week prior to and during the study, and alcohol, tobacco and caffeine within 24 hours prior to and during each pharmacokinetic study session.

03.1.7 Study procedures

Subjects report to the clinical pharmacology unit between 7-8 a.m. after a 10-hour overnight fast. Baseline symptoms and signs were recorded at the first session and blood and urine samples obtained for clinical laboratory studies. A 12-lead ECG was obtained prior to dosing, and a single-led ECG was monitored continuously for 8 hours after dosing, with 15-second printouts produced at hourly intervals during the first 4 hours of monitoring, and then at the end of the 8-hour period. Supine blood pressure and pulse rate were recorded at times -15, -10, -5, 0 (predose), 5, 10, 15, 30 and 45 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12 and 24 hours following administration of study medication. Sitting and standing blood pressure and pulse rate were recorded at 1, 2 and 3

hours after dosing following measurement of supine vital signs. Subjects remained recumbent for 4 hours following dosing except to void and during blood pressure measurements. From 4 to 8 hours post dose, subjects were allowed to sit in bed while undergoing continuous single lead ECG monitoring. After 8 hours, subjects were allowed to ambulate in the clinical pharmacology unit at will.

Subjects remained in the clinical pharmacology unit for 24 hours after dosing. Water, soft drinks without caffeine or fruit juices (except grapefruit juice) were permitted *ad lib* 5 hours after dosing, and lunch and dinner were given at 5 and 10 hours post dose, respectively. Blood samples (5 ml) for pharmacokinetic analysis were drawn at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours following dosing. Blood (15 ml) and urine samples were collected at 24 hours after dosing to repeat safety clinical laboratory tests. A brief physical examination and 12-lead ECG were performed at 24 hours. Subjects were discharged after collection of the last blood and urine sample. Subjects returned 1 week following the last administration of the study medication for safety laboratory tests.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

03.1.8 **Pharmacokinetic procedures:**
Blood samples collected in heparinized tubes and chilled on ice were centrifuged at 4°C, and plasma was transferred to polypropylene containers and frozen at -20°C to be assayed within 2 months. Plasma concentrations of eprosartan were determined by reverse phase HPLC with UV detection. The lower limit of quantification (LLQ) in plasma was 10 ng/ml for a 0.5 ml aliquot. Urine was collected and pooled for the interval 0-24 hours after administration of study medication, and immediately frozen and stored at -20°C to be used later for exploratory biotransformation work. (N.B. The urine specimens were inadvertently discarded by the laboratory.)

Concentration-time data analysis was performed using a non-compartmental pharmacokinetic analysis program to obtain the maximum observed plasma concentration (Cmax) and time at which Cmax occurred (Tmax), the apparent terminal elimination rate constant (λ), AUC(0-τ), $T_{1/2}$, and AUC(0-∞).

03.1.9 **Endpoints:**
Although not defined by protocol at this stage in the development program for eprosartan, AUC(0-τ) and Cmax were presumed to be the primary endpoints. Tmax and safety data were presumed to be the secondary endpoints.

03.1.10 **Sample size:**
The numbers of subjects in study groups were based on feasibility. No statistical power calculations were done.

03.1.11 **Investigator , Center and Study Dates:**
Bernard Ilson, MD, SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center, Philadelphia, USA. Dates: 03-Jun-1992 to 05-Oct-1992.

03.2. **STUDY POPULATION**

03.2.1 **Subject disposition:**
21 healthy male volunteers, 20-42 (mean = 28) years of age, weighing 66.0 to 89.5 (mean = 76.2) kg, and 166-191 (mean = 177) cm tall, were randomized. 90% were Caucasian, 5% were African-American, and 5% were Asian.

03.2.2 **Withdrawals:**
Subject #366 (after SK&F oral solution 10 mg), Subject #377 (after SK&F oral solution 1 mg and placebo solution) and Subject #380 (placebo) were withdrawn because of adverse experiences.

03.2.3 **Protocol violations:**
Subject 371 was treated with amoxicillin for seven days for an upper respiratory tract infection. His final study session was delayed until 19 days after this antibiotic therapy had been completed.

03.3 **SAFETY RESULTS**

03.3.1 **General considerations:**
Subject #377 had premature ventricular contractions noted on ECG monitor prior to initial dosing. A total of 20 adverse experiences (AEs) were reported for 11 subjects, viz., 13 AEs in 9 subjects on SK&F 108566 and 7 AEs in 4 subjects given placebo.

03.3.2 **Deaths:** There were no deaths during this study.

03.3.3 **Withdrawals:** Three subjects were withdrawn from the study because of AEs. Subject #366 reported a vasovagal episode about 1 hour after SK&F oral solution 10 mg. Subject #377 had an increase in frequency of pre-existing premature ventricular contractions after dosing with SK&F oral solution 1 mg and again after placebo solution. Subject #380 had an episode of ventricular ectopy about 3 hours after a dose of placebo.

03.3.4 **Serious, Non-fatal Adverse Events:** There was no non-fatal adverse experience during this study.

03.3.5 **Adverse Events:** No dose-related AEs were noted following administration of SK&F oral solution or tablets. Apart from the upper respiratory infection in Subject #371 that was treated with a 7-day course of amoxicillin, all other AEs resolved without treatment.

Placebo (7 AEs):	Subject #368 reported nausea and vomiting, #377 had frontal headache and premature ventricular contractions were noted on ECG monitor, #380 had premature ventricular contractions and an episode of idioventricular rhythm noted on ECG monitor, and #530 reported lightheadedness;
1 mg SK&F oral solution (3 AEs):	Subject #359 reported slight nausea, #377 had premature ventricular contractions were noted on ECG monitor, and reported throat tightness;
10 mg SK&F oral solution (1 AE):	Subject #366 reported a vasovagal syncope (associated with phlebotomy);
30 mg SK&F oral solution (2 AEs):	Subject #359 reported nausea, #381 reported contact dermatitis;
50 mg SK&F tablets (1 AE):	Subject #368 reported ecchymosis in left scapular area;
100 mg SK&F tablets (3 AEs):	Subject #371 reported respiratory infection (cough, sneezing, increased pressure, left face tenderness and nasal discharge), #534 reported slight frontal headache and slight discomfort at the side of right eye.
100 mg SK&F oral solution (2 AEs):	Subject #372 reported lower abdominal cramping and diarrhea;
200 mg SK&F oral solution (1 AE):	Subject #360 reported pain in left antecubital area radiating to left shoulder

03.3.6 **Laboratory findings, ECGs, Vital signs**

No patient in this study exhibited abnormal heart rates or orthostatic changes in blood pressure.

12 subjects had change in supine systolic blood pressure by > 30 mmHg from baseline or supine diastolic blood pressure by > 20 mmHg from baseline. Of these, Subject #366 had a vasovagal episode following phlebotomy about 1 hour after 10 mg SK&F oral solution; he recovered fully within minutes of the episode. The remaining subjects were: #360 (200 mg SK&F oral solution), #361 (placebo and 30 mg SK&F solution), #368 (50 mg SK&F solution), #372 (3 mg SK&F solution), #373 (placebo, 10 and 50 mg SK&F solution), #376 (placebo), #380 (placebo, 1 mg SK&F solution), #381 (placebo), #529 (200 mg SK&F tablet), #531 (200 mg SK&F solution) and #534 (100 mg SK&F solution and tablet, 350 mg tablet). The changes in blood pressure were not sustained, were asymptomatic, were not associated with changes in heart rate, and did not appear to be dose-related.

Screening ECGs were normal apart from Subject #377 who had pre-existing PVCs noted on monitor prior to dosing. He had an increase in frequency of pre-existing PVCs noted on monitor at 5 to 8 hours after administration of both placebo and 1 mg of SK&F oral solution. Subject #380 had an episode of ventricular ectopy about 3 hours after a dose of placebo. These two subjects were withdrawn from the study.

Elevations of ALT, AST and/or CPK of more than twice the upper limit of the laboratory reference range subsequent to screening laboratory tests were noted for 5 subjects (#360, #371, #376, #381 and #534). In all subjects, these values returned towards baseline values within the reference range about 3 to 6 days later. Other isolated laboratory abnormalities noted were: Subject #359 (hematocrit = 35.4% 7 days after placebo), #371 (3+ urine hemoglobin 7 days after 10 mg oral SK&F solution), #381 (urine pH of 8.0, 24 hours after 1 mg SK&F solution), and #532 (WBC 13/hpf in urine 7 days after 200 mg SK&F tablets).

03.4 PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS

03.4.1 Solution Formulation

Following single doses of eprosartan oral solution, the mean plasma concentration-time profiles were in general similar for different doses with peak plasma concentrations of eprosartan observed at about 1 to 2 hours (Table Epro-003-1). Plasma concentrations declined from the peak rapidly, being measurable for 3 to 6 hours following 1, 3, 10 mg doses, for 10-12 hours following 30, 50 and 100 mg doses, and up to 24 hours following the 200 mg dose (the values at 12 and 24 hours being commonly < 1% of peak concentrations).

Table Epro-003-1. Pharmacokinetic values for SK&F 10866 oral solution administered to healthy volunteers

Parameter	Cmax (ng/ml)	Tmax (h)	AUC(0-t) (ng.h/ml)	AUC(0-∞) (ng.h/ml)	$T_{1/2}$ (h)
1 mg (n=6)					
Mean	29.3	1.42	66.4	NC	NC
Median	28.9	1.50	56.1	NC	NC
S.D.	6.1	0.38	25.6	NC	NC
3 mg (n=4)					
Mean	45.4	1.63	94.0	NC	NC
Median	45.5	1.25	95.6	NC	NC
S.D.	12.	0.95	21.9	NC	NC
10 mg (n=5)					
Mean	99.7	1.43	253.5	NC	NC
Median	94.4	1.50	219.1	NC	NC
S.D.	37.2	0.44	135.0	NC	NC
30 mg (n=4)					
Mean	396.3	1.26	1091.7	1164	3.31
Median	295.6	1.02	989.2	1035	3.15
S.D.	258.1	0.50	368.1	411	0.95
50 mg (n=4)					
Mean	578.5	1.25	1399.2	1511	3.07
Median	658.5	1.25	1417.4	1475	2.68
S.D.	203.7	0.29	656.5	754	1.33
100 mg (n=7)					
Mean	979.2	1.00	2502.4	2634	3.75
Median	1038.8	1.00	2700.9	2826	2.98
S.D.	458.7	0.29	1257.5	1317	2.06
200 mg (n=6)					
Mean	3040.0	1.00	7021.4	7174	4.88
Median	2713.1	1.00	5210.3	5332	4.51
S.D.	1111.0	0	3253.2	3272	2.56

NC = Not calculated

Cmax, AUC(0-τ) and AUC(0-∞) increased in a dose proportional manner. The range of individual values was less than 4-fold (with the exception of one subject, #371 at 100 mg dose). Median $T_{1/2}$ for the 30, 50 and 100 mg doses of SK&F 108566 ranged from 2.68 to 3.15 hours, and after 200 mg dose, the median $T_{1/2}$ was 4.51 hours. Since each subject did not receive all of the doses administered, and the number of subjects per dose group was small, no definitive conclusions could be drawn regarding dose proportionality.

03.4.2 **Tablet Formulation**

Following single doses of eprosartan tablets, the mean plasma concentration-time profiles were in general similar for different doses with peak plasma concentrations of eprosartan observed at about 1 to 2 hours (Table Epro-003-2). Plasma concentrations were measurable for 10-12 hours following 30, 50 and 100 mg doses, and for 12-24 hours following the 200 and 350 mg doses (the values at 12 and 24 hours being < 5% to < 1% of peak concentrations).

The median Cmax, AUC(0-τ) and AUC(0-∞) were higher for the 30 mg dose as compared to the 50 mg dose (Table Epro-003-2). However, only 2 and 4 subjects, respectively, were studied at these doses. Three 10 mg tablets were used for the 30 mg dose while 50 mg tablets were used for the other doses and differences in tablet solubility could also have contributed to this finding.

At higher doses (100, 200 and 350 mg), Cmax, AUC(0-τ) and AUC(0-∞) did not increase in a dose proportional manner. The median Cmax remained around 1000 ng/dl. The increase in the median AUC(0-τ) and AUC(0-∞) was less than dose proportional at the highest doses. The median Tmax ranged from 1 to 1.5 hours, and is similar to that observed with the oral solution formulation. Median $T_{1/2}$ ranged from 2.49 to 3.26 hours following 30, 50 and 100 mg doses, and 3.92 and 5.28 hours after the 200 mg and 350 mg doses, respectively. Since each subject did not receive all of the doses administered, and the number of subjects per dose group was small, no definitive conclusions could be drawn regarding dose proportionality or the relative bioavailability of the tablet formulation.

Also, in subjects who received 350 mg dose as tablets, the plasma concentration-time profiles plateaued at 2 to 4 hours post-dose (which was not found with the solution formulation), suggesting that the absorption of SK&F 108566 becomes saturated when administered as tablets at doses greater than 100 mg, which the sponsor attributed

to be due to the poor solubility characteristics of SK&F 108566. The relative bioavailability (tablet/solution) based on median AUC values was approximately 70% for the 50 mg dose, 80% for the 100 mg dose, and 60% for the 200 mg dose of SK&F 108566. Using intravenous data obtained in Protocol 004 with the data from this study, the absolute bioavailability of SK&F estimated from the median AUC(0-∞) values ranges from approximately 12% to 18% for the tablet formulation and 21% to 24% for the oral solution formulation.

Table Epro-003-2. Pharmacokinetic values for SK&F 10866 tablets administered to healthy volunteers

Parameter	Cmax (ng/ml)	Tmax (h)	AUC(0-t) (ng.h/ml)	AUC(0-∞) (ng.h/ml)	$T_{1/2}$ (h)
30 mg (n=2)					
Mean	435.6	1.50	1229.8	1308	3.26
Median	435.6	1.50	1229.8	1308	3.26
S.D.	86.1	0.71	163.7	146	0.01
50 mg (n=4)					
Mean	457.9	1.25	1000.0	1048	2.57
Median	356.8	1.00	961.3	993	2.49
S.D.	287.8	0.50	443.2	471	0.67
100 mg (n=6)					
Mean	1007.1	1.08	2354.2	2493	3.83
Median	856.5	1.00	2194.8	2280	3.20
S.D.	465.6	0.49	1246.1	1313	1.89
200 mg (n=6)					
Mean	1181.0	1.33	3950.4	4087	4.51
Median	1021.1	1.00	2954.0	3086	3.92
S.D.	525.2	0.82	2294.7	2301	2.49
350 mg (n=3)					
Mean	1316.8	2.17	5880.4	5986	5.54
Median	1076.0	1.50	4975.3	5071	5.28
S.D.	453.8	1.61	1619.6	1589	1.25

03.5 CONCLUSION

Single oral doses of eprosartan up to 350 mg given to healthy volunteers were not associated with serious adverse experiences in this study. No dose related increase in adverse experience was observed.

Following single doses of eprosartan oral solution peak plasma concentrations of eprosartan were observed at about 1 to 2 hours. Cmax, AUC(0-τ) and AUC(0-∞) increased in a dose proportional manner. Median $T_{1/2}$ for the 30, 50 and 100 mg doses of SK&F 108566 ranged from 2.68 to 3.15 hours, and after 200 mg dose, the median $T_{1/2}$ was 4.51 hours. Since each subject did not receive all of the doses administered, and the number of subjects per dose group was small, no definitive conclusions could be drawn regarding dose proportionality.

Peak plasma concentrations were observed at about 1 to 2 hours. Plasma concentrations were measurable for 10-12 hours following 30, 50 and 100 mg doses, and for 12-24 hours following the 200 and 350 mg doses (the values at 12 and 24 hours being < 5%, and more commonly < 1% of peak concentrations). The median Cmax, AUC(0-τ) and AUC(0-∞) were higher for the 30 mg dose as compared to the 50 mg dose. However, only 2 and 4 subjects, respectively, were studied at these doses. Three 10 mg tablets were used for the 30 mg dose while 50 mg tablets were used for the other doses, and differences in tablet solubility could also have contributed to this finding.

At higher doses (100, 200 and 350 mg), Cmax, AUC(0-τ) and AUC(0-∞) did not increase in a dose proportional manner. The median Cmax remained around 1000 ng/dl. The median Tmax ranged from 1 to 1.5 hours, and is similar to that observed with the oral solution formulation. Median $T_{1/2}$ ranged from 2.49 to 3.26 hours following 30, 50 and 100 mg doses of SK&F 108566 tablets, and 3.92 and 5.28 hours after the 200 mg and 350 mg doses, respectively. Since each subject did not receive all of the doses, and the number of subjects per dose was small, no definitive conclusions could be drawn regarding dose proportionality or relative bioavailability of tablet the formulation.

The relative bioavailability (tablet/solution) based on median AUC values was approximately 70% for the 50 mg dose, 80% for the 100 mg dose, and 60% for the 200 mg dose of eprosartan. Combining intravenous data from Protocol 004 with data from this study, the absolute bioavailability of eprosartan estimated from the median AUC(0-∞) values ranges from 12% to 18% for the tablet formulation and 21% to 24% for the oral solution formulation.