CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20738

PHARMACOLOGY REVIEW(S)

D. Wallace

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REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

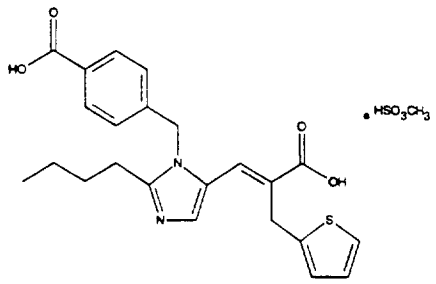
Anthony G. Proakis, Ph.D.
7/29/97

ORIGINAL SUBMISSION DATE: 10/11/96
CENTER RECEIPT DATE: 10/11/96
REVIEWER RECEIPT DATE: 10/21/96

PRODUCT: TEVETEN Tablets (Eprosartan mesylate, SKF 108566-J)

SPONSOR: SmithKline Beecham Pharmaceuticals
1250 South Collegeville Road, UP4455
P.O. Box 5089
Collegeville, PA 19426-0989
(610) 917-7249

CHEMISTRY: Eprosartan mesylate is described as (E)-2-butyl-1-(p-carboxybenzyl)-α-2-thienylimidazole-5-acrylic acid monomethanesulfonate. Its molecular weight is 520.63 and its empirical formula is $C_{23}H_{24}N_2O_4S.CH_4O_3S$.



PHARMACOLOGICAL CLASS: Angiotensin II Receptor Antagonist

PROPOSED INDICATION: Treatment of hypertension.

FORMULATION AND ROUTE OF ADMINISTRATION: TEVETEN is formulated in tablets for oral use containing eprosartan mesylate equivalent to 300 or 400 mg eprosartan /tablet; excipients include lactose monohydrate NF, microcrystalline cellulose NF, pregelatinized starch NF, croscarmellose sodium NF, magnesium stearate NF, polyethylene glycol NF, hydroxypropyl methylcellulose USP, titanium oxide USP and purified water USP. Tablets may also contain one or more of the following agents: iron oxide black, iron oxide red, iron oxide yellow, polysorbate 80.

PROPOSED DOSAGE REGIMEN: The recommended starting dose is 400 mg once daily and may be increased to a maximum of 800 mg daily.

IND UNDER WHICH CLINICAL TRIALS WERE CONDUCTED: #

TABLE OF CONTENTS [1]

[1]Note: This review does not address the mutagenicity and carcinogenicity studies conducted with eprosartan mesylate. The results and adequacy of those studies are addressed in a separate review by Dr. John Koerner.

INTRODUCTION

The renin-angiotensin system plays an important role in the regulation of blood pressure and fluid and electrolyte balance. The active hormone of this system is angiotensin II (AII). It is one of the most potent vasoconstrictor agents known. Blockade of the renin-angiotensin system, as observed with angiotensin converting enzyme (ACE) inhibitors, has proved to be effective in the treatment of hypertension and congestive heart failure.

The ACE inhibitors, though efficacious, are not specific for the angiotensin converting enzyme. These drugs also interfere with the inactivation of bradykinin, enkephalins and other biologically active peptides. Angiotensin II receptor antagonists evolved from attempts to identify agents which possessed greater specificity against the functional effects of angiotensin II.

Angiotensin II binding sites are present in various tissues including rat and rabbit adrenal cortex and adrenal medulla, rat and human uterus, rat brain and aorta, bovine cerebellum and human renal artery. Recent studies indicate that AII receptors are not homogeneous but exist in two interconvertible forms. The receptor subtypes (AT-1 and AT-2) have differential tissue distribution and functional responses. Physiologically important actions of AII, such as vascular smooth muscle contraction, aldosterone release and stimulation of renal sodium reabsorption are mediated through activation of AT-1 receptors. The AT-2 receptor is widely distributed in fetal tissues. In adult animals, some tissues contain primarily either AT-1 receptors (e.g. vascular tissue) or AT-2 receptors (e.g. brain), whereas other tissues contain the receptor subtypes in similar amounts. No functional role for AT-2 receptors has been unequivocally defined.

Eprosartan is a non-peptide compound which selectively antagonizes angiotensin II at AT-1 receptors *in vitro* and antagonizes the functional effects of angiotensin II *in vivo*.

APPEARS THIS WAY
ON ORIGINAL

PHARMACODYNAMICS

Effects Related to Proposed Therapeutic Indication

Antihypertensive Effects in Renin-Dependent Hypertensive Rats and Dogs

Antihypertensive efficacy of eprosartan was assessed in conscious renin-dependent hypertensive rats and dogs. Renin-dependent hypertension was induced by surgical partial ligation of the left renal artery followed by a post surgical recovery period of 7-10 days in rats and 4 weeks in dogs. Pretreatment mean blood pressures in rats were between 150 and 160 mmHg. Intraduodenal administration of eprosartan (1 to 10 mg/kg) caused a dose-dependent decrease in mean arterial blood pressure from control values (Fig. 1). At the 10 mg/kg dose the antihypertensive effect was maintained for at least 90 min. The reduction of blood pressure following intraduodenal administration of 10 mg eprosartan/kg to rats was associated with a significant decrease in total peripheral resistance, increased heart rate and increased cardiac output (Fig. 2).

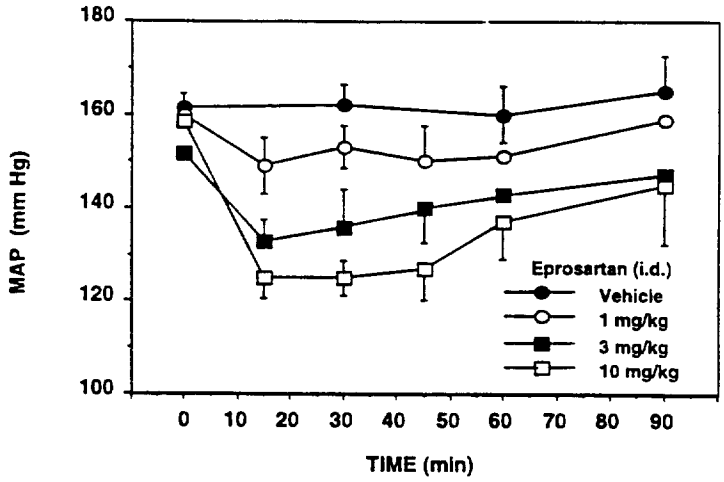


Fig. 1. Antihypertensive activity of eprosartan in conscious renin-dependent hypertensive rats (4-4-5 rats/dose group)

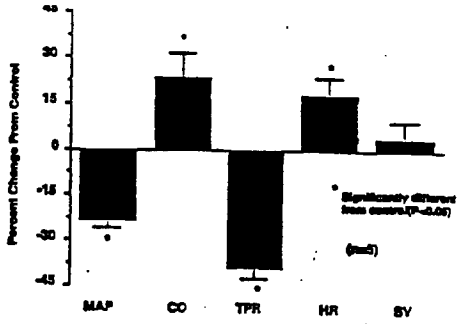


Fig. 2. Effect of eprosartan (10 mg/kg ID) on mean arterial pressure (MAP), cardiac output (CO), total peripheral resistance (TPR), heart rate (HR) and stroke volume (SV) in conscious renin-dependent hypertensive rats.

Antihypertensive activity was also assessed in conscious renin-dependent hypertensive rats following a 3-day continuous intraduodenal infusion (via indwelling intraduodenal catheters) of 25 µg eprosartan/min. Mean arterial blood pressure was significantly lower than vehicle control levels during the drug infusion period and the antihypertensive effect was sustained for at least 18 hours following cessation of the infusion (Fig. 3).

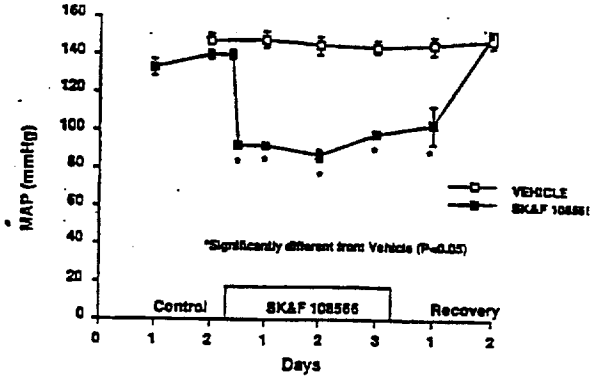


Fig. 3. Effect of 3-day infusion of eprosartan (25 ug/min ID) on mean arterial blood pressure in conscious renin-dependent hypertensive rats (n=3).

Administration of a single oral dose of eprosartan (10 mg/kg) to renin-dependent hypertensive dogs decreased mean arterial blood pressure from an average of 156 mmHg to 120 mmHg. The maximum antihypertensive effect of eprosartan occurred within the first hour following oral administration and persisted for at least 12 hours (Fig. 4).

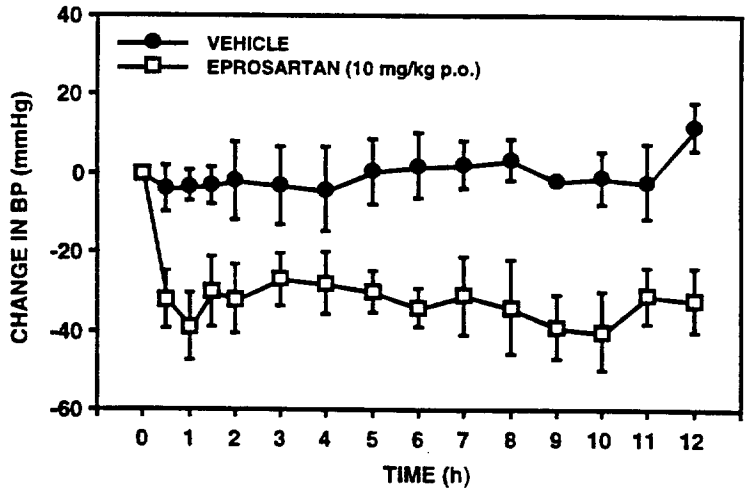


Fig. 4. Time course of antihypertensive activity of eprosartan (1 mg/kg PO) in conscious renin-dependent hypertensive dogs (n=5-7 dogs/treatment group).

Antihypertensive Effects of Eprosartan in Hydrochlorothiazide-Treated Spontaneously Hypertensive Rats

Eprosartan was assessed for antihypertensive activity in conscious spontaneously hypertensive rats before and after treatment with the diuretic, hydrochlorothiazide. A bolus dose of 10 mg eprosartan/kg administered intravenously had no effect on blood pressure in spontaneously hypertensive rats. However, 18 to 20 hours following treatment of these same rats with fluid deprivation and the diuretic, hydrochlorothiazide (10 mg/kg IV), eprosartan (10 mg/kg IV) significantly decreased mean arterial blood pressure by an average of 37 mmHg (Fig. 5).

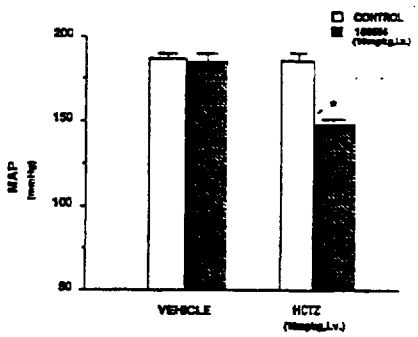


Fig. 5. Effect of eprosartan on mean arterial pressure (MAP) after vehicle or hydrochlorothiazide (10 mg/kg IV) treatment in spontaneously hypertensive rats.

In Vitro Evidence of Angiotensin II Antagonist Activity

The affinity and selectivity of eprosartan for the angiotensin II AT-1 receptor was demonstrated using radioligand binding studies in a number of tissues including membranes prepared from human liver and adrenal cortex. Eprosartan displaced [I^{125}] angiotensin II bound to membranes from glomerulus, tubule, outer medulla and cortex of rat kidney; rat mesenteric artery; human adrenal cortex and liver, tissues that are rich in AT-1 receptors, with IC_{50} values ranging from 1.5 to 9.2 nM (Table 1). The displacement curves were monophasic in nature, suggesting that the AII receptors in these tissues were predominately of the AT-1 subtype. Eprosartan, at concentrations up to 10μM, did not displace [I^{125}] angiotensin II bound to bovine cerebellar membranes, a tissue rich in AT-2 subtype receptors. Furthermore, eprosartan did not displace binding to vasopressin, endothelin, calcitonin gene-related peptide or alpha-2 adrenergic receptors.

Table 1. Radioligand Binding Studies with Eprosartan

Receptor	Tissue	IC50 (nM)*
Angiotensin II ([^{125}I]-AII)	Rat mesenteric artery	1.5±0.2
	Rat adrenal cortex	9.2±2.4
	Rat renal glomerulus	9.1±0.8
	Rat renal tubule	6.6±1.8
	Rat renal outer medulla	5.6±0.4
	Human liver	1.7
	Human adrenal cortex	3.9
	Human AT1 clone	1.4
	Bovine cerebellum (AT2)	>10000
Alpha-2 adrenoceptor ([^{3}H]-Rauwolscine)	Rat renal cortex	>1000
Vasopressin ([^{3}H]-Vasopressin)	Rat liver	>1000
Endothelin ([^{125}I]-Endothelin)	Rat kidney cortex	>1000
	Rat brain	>1000
	Rat mesenteric artery	>1000
CGRP ([^{125}I]-CGRP)	Rat liver	>1000

*IC50= Concentration (nM) of eprosartan needed to displace 50% of the indicated radioligand.

In isolated rabbit aortic rings, eprosartan produced parallel rightward shifts in the concentration-response curves to angiotensin II without affecting the maximum response (Fig.6). Schild analysis of the data yielded an apparent dissociation constant, K_b, of 0.37nM and a slope of 0.96, indicative of competitive antagonism. Eprosartan (10 μM) did not significantly affect the contractile response to norepinephrine, endothelin-1 or KCl, demonstrating that eprosartan is a selective antagonist of angiotensin II at vascular AII receptors. Similar effects of eprosartan on angiotensin II-induced contractions were observed in rabbit renal efferent arterioles (K_b = 2.7 nM).

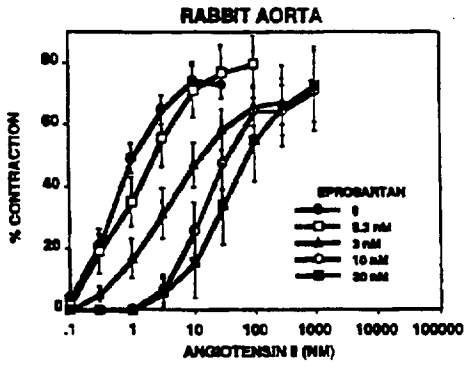


Fig. 6. Inhibition of angiotensin II-induced contraction of rabbit aorta by eprosartan (n= 6-23 tissues/conc)

Angiotensin II elicited a concentration-dependent increase in calcium levels in cultures of rat aortic smooth muscle. Eprosartan (1 nM to 10 μM) caused a concentration-dependent inhibition of angiotensin II-induced Ca^{++} mobilization, suggesting an AT-1 receptor mediated event.

Angiotensin II exerts a direct effect on the proximal renal tubule to promote sodium and fluid absorption. Angiotensin II (10 pM) increased fluid absorption by 61% in isolated perfused proximal tubules from rabbit kidney. In the presence of eprosartan (0.1 μM), angiotensin II had no significant effect on fluid absorption.

Eprosartan at a concentration of 1 μM had no effect on rabbit lung ACE activity. In all of the above studies, eprosartan was devoid of angiotensin II agonist activity.

Antagonism of Angiotensin II -Induced Pressor Responses in Rats

The ability of eprosartan to antagonize angiotensin II-induced pressor responses was measured in conscious male Sprague-Dawley rats following intraduodenal (i.d.), intragastric (i.g.) or intravenous (i.v.) administration.

Eprosartan had no effect on baseline pressure at the highest i.v. dose given, 1 mg/kg. Single bolus i.v. doses of 0.01, 0.03 and 0.3 mg eprosartan/kg administered five minutes before cumulative doses of angiotensin II (10-3000 ng/kg, i.v.) produced dose-dependent, parallel, rightward shifts in the angiotensin II dose-response curve, a response indicative of competitive antagonism (Fig. 7). Similarly, single bolus i.v. injections of 0.1 to 1.0 mg eprosartan/kg elicited dose-dependent inhibition of the pressor response to a single dose of angiotensin II (250 ng/kg, i.v.). The dose of eprosartan needed to inhibit the response to angiotensin II by 50% was 0.08 mg/kg.

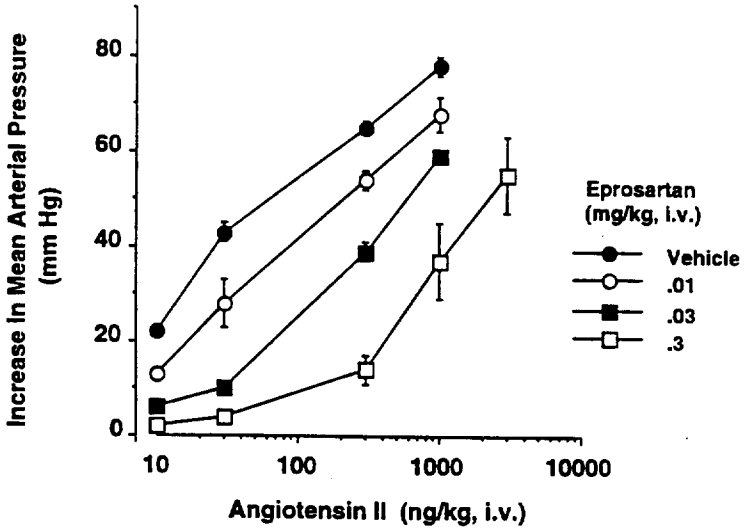


Fig. 7. Effect of eprosartan on the pressor response to angiotensin II in conscious male normotensive rats (n=4 rats/treatment group)

When administered via a duodenal catheter, eprosartan at doses of 3, 5.5 and 10 mg/kg caused a dose-related inhibition of the pressor response to angiotensin II (Fig. 8) with an ID50 of 5.5 mg/kg. Maximal inhibition occurred at 10-15 minutes post dosing and at the highest dose tested, 10 mg/kg. significant inhibition was still observed at 3 hours following drug administration. Virtually identical results in terms of potency (ID50 = 6 mg/kg) and duration of action were obtained when eprosartan was given to rats via a stomach catheter.

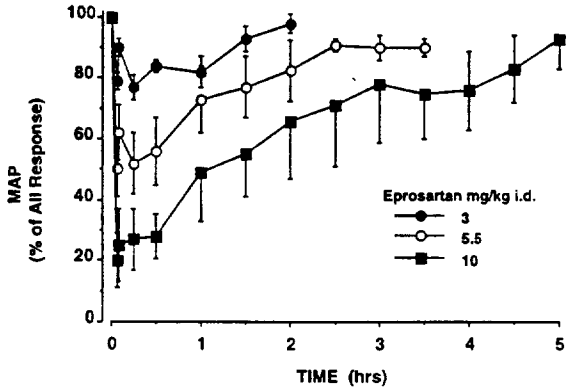


Fig. 8. Pressor responses to repeated angiotensin II injections (250 ng/kg, i.v.) before and after intraduodenal administration of eprosartan (n=3-5 rats/treatment group).

Eprosartan had no effect on the pressor responses to norepinephrine or vasopressin in conscious normotensive rats (Fig. 9). For example, 30 minutes following a dose of 10 mg/kg, i.d. eprosartan, the pressor response to angiotensin II (250 ng/kg, i.v.) was inhibited by 62% ($p<0.05$), while the responses to equipressor doses of norepinephrine (400 ng/kg, i.v.) or vasopressin (100 ng/kg, i.v.) were unaffected.

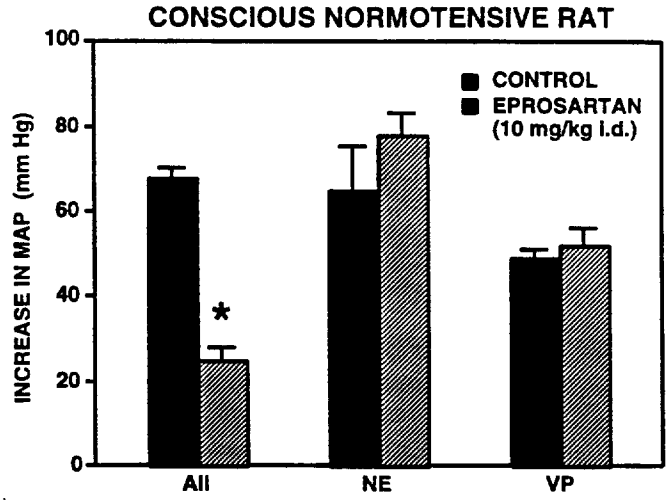


Fig. 9. Pressor responses to angiotensin (AII, 250 ng/kg, i.v.), norepinephrine (NE, 400 ng/kg, i.v.) and vasopressin (VP, 100 ng/kg, i.v.) Before (control) and 30 min after eprosartan (10 mg/kg, i.d.). * Significantly different from control ($p<0.05$) (n=3).

Antagonism of Angiotensin II -Induced Pressor Responses in Dogs

Acute i.v. infusion of angiotensin I at a rate of 100 ng/kg/min increased mean arterial pressure from 100 mmHg to approximately 160 mmHg in conscious normotensive dogs. Subsequent i.v. administration of eprosartan (0.1 to 3 mg/kg) resulted in a dose-dependent decrease in blood pressure. At the highest dose tested (3 mg/kg, i.v.), blood pressure decreased to normotensive levels (approximately 100 mmHg), and the response was maintained for at least 4 hours. Oral administration of eprosartan (1 to 10 mg/kg) also resulted in dose-dependent decreases in blood pressure which were maintained for at least 6 hours (Fig. 10). No significant reflex tachycardia was associated with eprosartan treatment. When eprosartan (10 mg/kg, p.o.) was administered 12 hours prior to initiation of the angiotensin I infusion, antihypertensive effects of eprosartan were still evident between 13-15 hours post-dosing (Fig. 10).

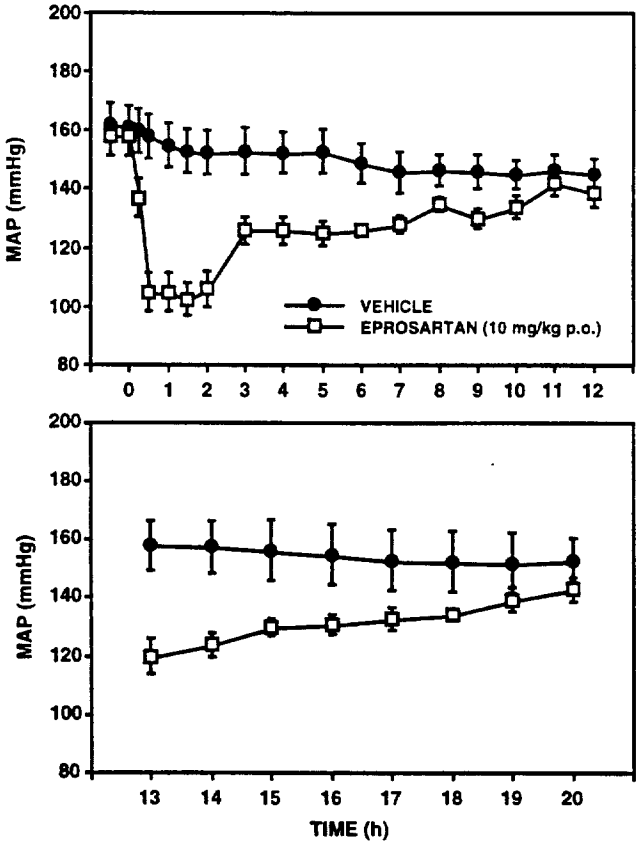


Fig. 10.: Duration of antihypertensive activity of eprosartan (10 mg/kg, p.o.) in angiotensin I-infused dogs. Angiotensin I was infused for either 1 hour prior to and for 12 hours following administration of eprosartan (top panel) or from between 12-20 hours following eprosartan dosing (lower panel). n=3-4 animals.

Other Pharmacologic Effects

Effects on Cardiovascular Reflexes

Eprosartan was studied in renin-dependent hypertensive rats to determine its effects on the orthostatatic reflex. Rats were anesthetized and once blood pressure had stabilized eprosartan (10 mg/kg, i.d.), prazosin (0.3 mg/kg, i.d.) or vehicle was administered. The rats were then subjected to a 90° vertical tilt for 60 seconds and changes in blood pressure were monitored continuously. In vehicle-treated rats, there was an initial steep fall in blood pressure upon tilting followed by a rapid return to control blood pressure within 20-30 seconds. Prazosin, an alpha-adrenoceptor antagonist known to interfere with cardiovascular reflexes, lowered blood pressure from 148 mm Hg to 120 mm Hg and during the tilt maneuver blood pressure failed to recover. Eprosartan treatment lowered blood pressure to 110 mm Hg and in these rats the orthostatic reflex remained intact with blood pressure returning to pre-tilt levels in 20-30 seconds (Fig. 11).

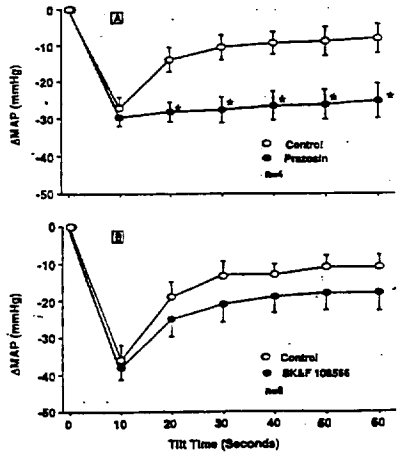


Fig. 11. Effect of eprosartan (10 mg/kg ID) or prazosin (0.3 mg/kg ID) on tilt-induced blood pressure changes in renin-dependent hypertensive rats.

Effects on Renal Function

High affinity angiotensin II receptors are associated with distinct renal structures such as the glomerulus, microvessels and proximal tubule, structures that modulate renal blood flow, glomerular filtration rate and proximal tubule water and electrolyte transport. In adult mammals, these receptors appear to be predominantly, if not exclusively, of the AT_1 subtype. The receptor binding activity of eprosartan to rat kidney tissues was examined. Eprosartan completely displaced ^{125}I-angiotensin II bound to membranes prepared from rat glomeruli, cortical tubules and outer medulla, with IC_{50} values ranging from 5.6 to 9.1 nM (Fig. 12). Furthermore, and in agreement with the binding studies, eprosartan attenuates, in a concentration-dependent manner (IC_{50} = 30 nM), angiotensin II (100 nM)-induced inhibition of cAMP formation in the glomerulus.

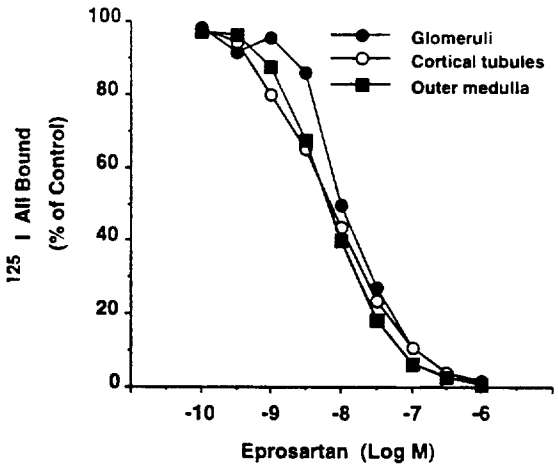


Fig. 12. Displacement of ^{125}I-angiotensin II by eprosartan in membranes prepared from rat renal glomeruli, cortical tubules and outer medulla. n=3-4 membrane preparations.

Eprosartan was tested for contractile effects on rabbit renal efferent arterioles, structures which are major sites of resistance to blood flow in the kidney and are important determinants of glomerular capillary pressure and hence glomerular filtration rate. In rabbit efferent arterioles, eprosartan (10 nM and 1 uM) displaced the angiotensin II concentration-response curve to the right in a parallel manner without affecting the maximal contractile response to the peptide (Fig 13). The apparent dissociation constant (KB) derived from these experiments was 2.7 nM.

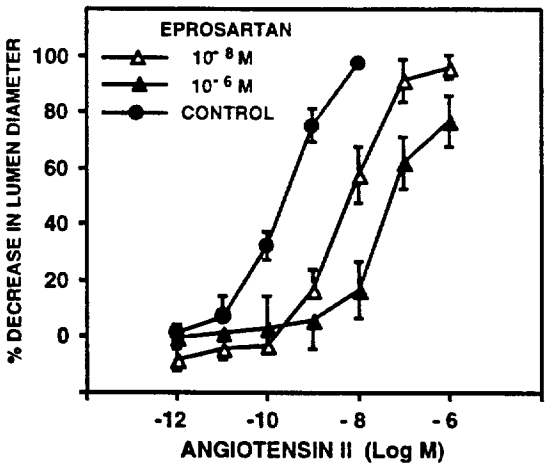


Fig. 13. Contractile response to angiotensin II in rabbit renal efferent arterioles in the absence (control) and presence of 10 nM or 1 uM eprosartan. n=4-6 experiments.

In isolated perfused rabbit proximal tubules, angiotensin II (10 pM) increased fluid absorption (a measure of sodium absorption) by 68%. In tubules pretreated with eprosartan (1 uM) the stimulation of fluid absorption by angiotensin II was totally inhibited and not different from control conditions (Fig. 14).

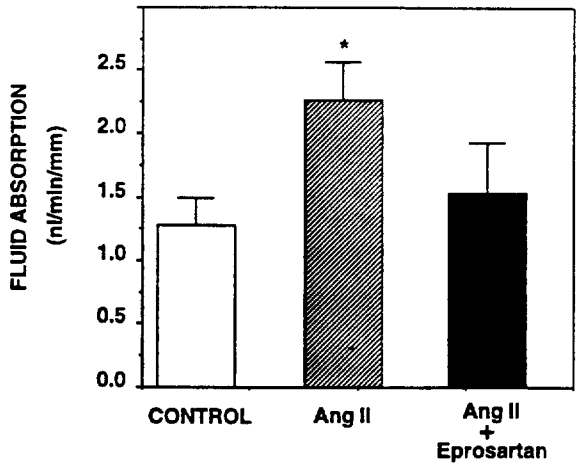


Fig. 14. Effect of eprosartan (1 uM) on angiotensin II (10 pM)-induced increases in fluid absorption in isolated perfused rabbit proximal convoluted tubule (n=4 experiments); *p<0.04 versus control.

Experiments were conducted to compare the effects of losartan and eprosartan on uric acid uptake into rat proximal tubule brush border membrane vesicles. Rats, like humans, possess a brush border membrane urate/anion exchanger which represents the first and rate limiting step in the renal reabsorption of urate and is likely the site at which uricosuric drugs act. The results of these experiments revealed that losartan inhibited urate transport in a competitive manner with an IC50 of 9.5 uM (23). Eprosartan also inhibited urate uptake but was some six-fold less potent (IC50 = 60 uM) (Fig. 15).

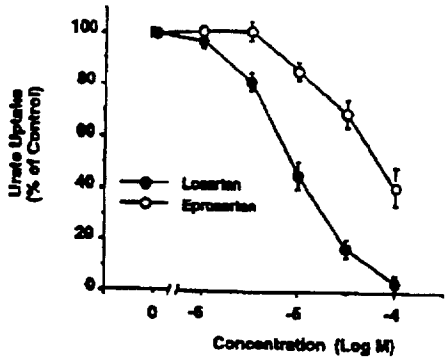


Fig. 15. Inhibition of urate uptake in rat renal brush border membranes by losartan and eprosartan. n=4-7 preparations.

Eprosartan was evaluated for effects on glycine-induced glomerular hyperfiltration in rats. In conscious normotensive rats, glycine infusion (3.7 mg/min, i.v.) increased glomerular filtration rate (GFR) by 27% (from 1.09 ± 0.53 to 1.38 ± 0.08 ml/min/100 g body weight), renal plasma flow (RPF) by 22% (2.96 ± 0.30 to 3.61 ± 0.32 ml/min/100 g) and significantly decreased renal vascular resistance (RVR) by 22% (25.4 ± 2.9 to 20.8 ± 2.5 mm Hg/(ml/min/100 g). At a dose of eprosartan (30 ug/kg.min, i.v.) that blocked the pressor response to exogenous angiotensin II but had no effect

on baseline GFR or RPF, glycine infusion had no significant effect on GFR, RPF or RVR. These studies demonstrate that eprosartan can block amino acid-induced hyperfiltration which may be an important factor in the progression of renal disease.

Cough-Inducing Activity in Dogs

Experiments were conducted to compare the incidence of cough in dogs receiving eprosartan or the ACE inhibitors, captopril and enalapril. Equipotent doses of eprosartan (3 mg/kg, p.o.), captopril (1 mg/kg, p.o.) and enalapril (1 mg/kg, p.o.) were chosen based on comparable inhibition of angiotensin I-induced increases in blood pressure. Thirty-seven male mongrel dogs were tested for coughing responses to captopril over a 4 hour period following drug administration. Four of the 37 dogs coughed in response to captopril, an incidence rate (11%) similar to that observed in humans. These 4 dogs were then retested with captopril, enalapril and eprosartan allowing at least 1 week drug wash-out between compound administration. In these dogs, captopril and enalapril induced 39 ± 14 and 34 ± 11 coughs, respectively, over the 4 hours following drug administration. However, over this same time period, only 1.5 ± 1.2 coughs were recorded following eprosartan dosing.

Safety Pharmacology

Acute Effects of Eprosartan on Cardiovascular Function in Rats

The acute effects of single intragastric doses (0, 10, 100 or 1000 mg/kg) of eprosartan on cardiovascular function were evaluated in male Sprague-Dawley rats (5/dose group) with chronically-implanted gastric catheters. Blood pressure. heart rate and dP/dt (measured from implanted femoral artery catheters) were continuously monitored for 30 min prior to and for 6 hours following administration of eprosartan or drug vehicle (1% carboxymethylcellulose); these parameters were measured approximately 24 hours after dosing to assess longer term effects. Body weight and clinical signs o were noted prior to and up to 24 hours after dosing.

There were no deaths, clinical signs of toxicity or effects on body weight associated with eprosartan treatment. Drug treatment caused no statistically significant effects on mean arterial blood pressure, heart rate or dP/dt.

Acute Effects of Eprosartan on Renal Function in Rats

The acute effects of single intragastric doses (0, 10, 100 or 1000 mg/kg) of eprosartan on renal function were evaluated in male Sprague-Dawley rats (10 rats/dose group) with chronically-implanted gastric catheters. Urine samples were collected at 2, 4, 8 and 24 hours after dosing for measurement of urine excretion rate, osmolarity and urine excretion of sodium, potassium, chloride, creatinine and urea. Body weights and clinical signs were recorded prior to and up to 24 hours after dosing. Furosemide (20 mg/kg) was used as the positive control.

There were no deaths, clinical sign of toxicity, effects on body weight or renal excretory parameters associated with eprosartan treatment. The positive control, furosemide, increased urine, sodium, potassium and chloride excretion at within 2 hours and decreased urea nitrogen excretion at 8 hours after dosing.

Acute Effects of Eprosartan on Respiratory Function

The acute effects of single doses (0, 10, 100 or 1000 mg/kg) of eprosartan on respiratory function were evaluated in male Sprague-Dawley rats (6/dose group) following oral (gavage) administration. Ventilatory parameters (tidal volume, respiratory rate, minute volume, peak expiratory flow, mean inspiratory flow and fractional inspiratory time) were measured in conscious, restrained rats prior to and at 1, 2, 4 and 24 hours after dosing. Pulmonary mechanics (total lung capacity, inspiratory capacity, forced vital capacity, forced expiratory flow, quasistatic lung compliance and functional residual capacity) were evaluated in anesthetized/paralyzed rats at 2 hours post dosing. Functional residual capacity was measured in anesthetized, spontaneously breathing rats. Control rats received an aqueous solution of 1% carboxymethylcellulose.

Single oral doses of 10, 100 or 1000 mg eprosartan/kg had no effect on ventilatory parameters in conscious, restrained rats. Doses of 10 and 100 mg eprosartan/kg had no effect on the mechanical properties of the lung. A dose of 1000 mg eprosartan/kg was associated with a statistically significant ($p<0.05$) reduction (-34%) from control functional residual capacity (FRC) at 2 hours after dosing. Other mechanical properties of the lung were unaffected. Because the effect on FRC was not associated with any evidence of pulmonary dysfunction, the sponsor placed minimal toxicological relevance to this effect.

Acute Effects of Eprosartan on Cardiovascular and Renal Function in Dogs

The acute effects of single doses (0, 10 or 1000 mg/kg) of eprosartan on cardiovascular and renal functions were evaluated in conscious male Beagle dogs (4/dose group) following oral (capsule) administration. Urine was collected, using a renal clearance protocol, prior to and at 12 consecutive 20-min intervals following eprosartan or placebo administration for determination of renal function (glomerular filtration rate, effective renal plasma flow rate, filtration fraction, renal blood flow, urine flow rate , serum and urine osmolarity, urine pH, absolute and fractional excretion of urinary electrolytes and urinary Na/K ratio). Blood pressure, heart rate lead II ECG, hematocrit and rectal temperature were determined during each renal clearance period.

There were no drug-related effects on blood pressure, heart rate, ECG or on renal hemodynamic or excretory functions in male Beagle dogs following oral doses of 10 or 1000 mg eprosartan/kg.

DRUG DISPOSITION

Absorption and Pharmacokinetics

Oral Absorption of Eprosartan in Male Rats (Rpt. # BP-1006/SK&F 108566)

This GLP study was conducted by the Drug Metabolism and Pharmacokinetics Dept., SmithKline Beecham Pharmaceuticals, King of Prussia, PA between 3/10/92 and 7/21/92.

[^{14}C]-Eprosartan was dissolved in 5% sodium bicarbonate solution and administered orally as a single oral (gavage) dose of 100 mg/kg to 2 male Sprague-Dawley bile duct-cannulated rats. Bile, urine and feces were collected from the rats at appropriate intervals over a 48-hour period following oral dosing. Bile, feces and urine samples were analyzed for radioactivity liquid scintillation spectrometry.

Following single oral administration of 100 mg [^{14}C]-eprosartan/kg to bile duct-cannulated male rats, the majority of radioactivity (average of 88%) was excreted in the feces. Minor amounts of radioactivity , corresponding to an average of 7.5% and 0.4% of the radioactive dose were excreted in the bile and urine respectively. The total average 48-hr recovery of the radiolabel in the 2 rats was 97%. Based on the average recoveries of the administered dose in the bile and urine, it was estimated that about 8% of drug-related material was absorbed following oral administration of 100 mg [^{14}C]-eprosartan/kg solution.

Table 2. Recovery of Radioactivity

Sample (0-48 hr)	% of Radioactive Dose	
	Rat #1	Rat #2
Bile	6.34	8.56
Urine	0.39	0.36
Feces	91.1	85.2
GI Tract Carcass Cage Rinse	0.078 0.008 0.125	0.419 0.016 0.345
TOTAL	98.0	94.9

Pharmacokinetics of Eprosartan in Rats After Single IV and Oral Administration (Rpt. # BP-1002/SKF-108566/1)

This GLP study was conducted by the Drug Metabolism and Pharmacokinetics Dept., SmithKline Beecham Pharmaceuticals, King of Prussia, PA between 4/05/91 and 3/23/92.

Eprosartan (Lot # STR 15740-287-3) was dissolved in 5% aqueous sodium bicarbonate solution and administered to male Sprague-Dawley rats intravenously (3 mg/kg bolus; n=6) or orally (10 mg/kg; n=6) by gavage. Blood samples (0.25 ml) were obtained from a previously implanted jugular vein catheter predose and at various intervals up to 720 min after IV or oral dosing for measurement of plasma eprosartan levels using HPLC techniques for determination of pharmacokinetic parameters.

Results: Following the 3 mg/kg IV dose, eprosartan disappeared from plasma in a biexponential fashion. After the 10 mg/kg oral dose, maximal plasma concentration was reached at approximately 32 min; from this point plasma concentrations declined monoexponentially. The pharmacokinetic parameters for oral and IV eprosartan are summarized in Table 3. The apparent bioavailability, assuming pharmacokinetic linearity, was estimated to be 1.7% with the 10 mg/kg oral solution of eprosartan.

Table 3. Pharmacokinetic Parameters after IV and Oral Eprosartan to Male Rats

Pharmacokinetic Parameter	3 mg/kg IV	10 mg/kg PO
Plasma Clearance (L/hr/kg)	1.05	
Volume of Distribution (L/kg)	0.21	
Cmax (μg/ml)	42.4*	0.25
Tmax (hr)		0.53
Apparent half-life (hr)	0.38	0.43
$AUC_{0-\infty}$ (μg.hr//ml)	2.98	0.17

* Value represents calculated concentration at time 0.

Pharmacokinetics of Eprosartan in Rats After Repeated Oral Administration (Rpt. # TP-1010/SKF-108566/2 and #TP-1006/SKF-108566/1)

These GLP studies were conducted by the Departments of Toxicology and Drug Metabolism, SmithKline Beecham Pharmaceuticals, King of Prussia, PA.

Pharmacokinetics of oral eprosartan were determined in Sprague-Dawley rats in conjunction with the 30-day (TP-1010/SKF-108566/2) and the 6-month (#TP-1006/SKF-108566/1) toxicity studies.

In the 30-day study, eprosartan mesylate (Lot # PL-20581-23) was suspended in aqueous 1% carboxymethylcellulose and administered to rats once daily by gavage at doses of 0, 30, 100 and 1000 mg eprosartan (non-salt) /kg (4/sex/dose group). Blood samples (0.4 ml) were obtained from the tail vein of each rat prior to dosing and at 30, 60, 120, 240, 360, 480, 720 and 1440 min after dosing on day 1 and 30 of treatment (same animals used for both test days). Plasma was analyzed for eprosartan levels for determination of pharmacokinetic parameters.

In the 6-month study, eprosartan mesylate (Lot # BCT-L-03P) was suspended in aqueous 1% carboxymethylcellulose and administered to rats once daily by gavage at doses of 0, 30, 100 and 1000 mg eprosartan /kg (3/sex/dose group). Blood samples (0.4 ml) were obtained from the tail vein of each rat at 1, 2, 4, 8, 12 and 24 hours after dosing on days 1 and 178 of treatment (same animals used for both test days). Plasma was analyzed for eprosartan levels for determination of pharmacokinetic parameters.

Results: In the 30-day repeat dose study, the mean values for Cmax and AUC increased with dose, but not dose-proportionally (Table 4). There was no evidence of drug accumulation. There were no apparent gender-related differences in any of the pharmacokinetic parameters.

Table 4. Pharmacokinetics of 30-Day Repeat Oral Doses of Eprosartan*

Pharmacokinetic Parameter	Sex	Dose Group (mg/kg/day PO)					
		Day 1			Day 30		
		30	100	1000	30	100	1000
Cmax (µg/ml)	M	0.17	0.39	0.78	0.17	0.27	1.09
Tmax (hr)		0.54	1.01	2.29	0.76	1.39	0.88
AUC_{0-24} (µg.h/ml)		0.82	2.18	4.92	0.82	1.42	4.90
Cmax (µg/ml)	F	0.14	0.48	1.67	0.24	3.81	2.03
Tmax (hr)		0.52	0.78	0.91	0.44	0.67	2.08
AUC_{0-24} (µg.h/ml)		0.58	1.98	6.28	1.24	3.51	5.40

* Values are the means from 4 animals

In the 6-month repeat dose study, the mean values for Cmax and AUC increased with dose, but were not dose-proportional, particularly at the two higher doses (Table 5). There was no evidence of drug accumulation. There were no apparent gender-related differences in any of the pharmacokinetic parameters.

Table 5. Pharmacokinetics of 6-Month Repeat Oral Doses of Eprosartan*

Pharmacokinetic Parameter	Sex	Dose Group (mg/kg/day PO)					
		Day 1			Week 26		
		30	100	1000	30	100	1000
Cmax (µg/ml)	M	0.22	0.79	1.35	0.36	0.52	1.35
Tmax (hr)		1.0	1.0	1.0	1.4	1.1	1.2
AUC_{0-24} (µg.h/ml)		0.63	2.64	6.06	1.02	1.65	5.03
Cmax (µg/ml)	F	0.24	0.59	0.86	0.29	0.88	1.09
Tmax (hr)		1.0	1.3	1.0	1.1	1.1	1.2
AUC_{0-24} (µg.h/ml)		0.63	1.93	4.96	1.08	3.16	8.12

* Values are the means from 3 animals

Pharmacokinetics of Eprosartan in Diet-Optimized Male Rats After Single Oral Administration (Study # D93070;Rpt.# TP-1005/SKF-108566/1)

This GLP study was conducted by the Departments of Toxicology and Drug Metabolism, SmithKline Beecham Pharmaceuticals, King of Prussia, PA between 6/18/93 and 7/29/93.

Eprosartan mesylate (Lot# BCT-L-05C) was suspended in 1% aqueous carboxymethylcellulose and administered orally by gavage as single doses of 100, 300, 600 or 1000 mg eprosartan/kg to male Sprague-Dawley rats (5/dose group) that were placed on a restricted diet. Following dosing, serial blood samples were obtained from a tail vein for determination of plasma levels of eprosartan measured by HPLC.

Results: In all groups, Cmax was observed at approximately 1 hour and plasma concentrations declined in a biphasic manner. Mean Cmax and AUC values increased between 100 and 300 mg/kg, but the exposure appeared to plateau at doses above 300 mg/kg (Table 6).

Table 6. Pharmacokinetics of Single Oral Doses of Eprosartan in Diet-Optimized Male Rats

Pharmacokinetic Parameter	Oral Dose (mg/kg)			
	100	300	600	1000
Cmax (µg/ml)	0.48	1.20	0.91	0.76
Tmax (hr)	0.99	0.98	1.01	1.02
AUC_{0-24} (µg.hr/ml)	1.12	2.35	2.51	2.46

Values are the means from 5 rats.

Pharmacokinetics of Repeat Oral Dose Eprosartan in Diet Optimized Rats (Rpt # SKF-108566/RSD-1003PP).

This GLP study was conducted by the Departments of Toxicology and Drug Metabolism, SmithKline Beecham Pharmaceuticals, King of Prussia, PA between 11/14/93 and 11/16/95

The repeat oral dose pharmacokinetics of eprosartan were investigated in Sprague-Dawley rats in conjunction with a 2-year carcinogenicity study in which rats were fed a restricted diet (21 and 16 gm/day of certified rodent diet for males and females, respectively). Eprosartan mesylate (Lot # BCT-K-07C and BCT-K-12C) was suspended in aqueous 1% carboxymethylcellulose and administered once daily by gavage. Serial blood samples were obtained from a tail vein up to 24 hours after dosing on days 1, 29 and 366 of treatment for determination of plasma eprosartan measured by HPLC.

Results: Plasma concentrations of eprosartan generally reached Cmax at approximately 1 hour after dosing (Table 7). Mean Cmax and AUC values increased with increasing dose, but the increase was approximately dose-proportional only at the 30 and 100 mg/kg/day doses. There were no marked

differences between male and female animals in any of the pharmacokinetic parameters.

Table 7. Pharmacokinetics of Repeat Oral Doses of Eprosartan in Diet-Optimized Male Rats

Pharmacokinetic Parameter	Sex	Dosing Day	Oral Dose (mg/kg/day)		
			30	100	600
Cmax (µg/ml)	M	1	0.15	0.53	1.32
		29	0.08[a]	0.53	1.16
		366	0.14	0.62	0.86
AUC_{0-24} (µg.hr/ml)		1	0.43	1.04	3.40
		29	0.17[c]	1.03	2.90
		366	0.48	2.28	3.76
Cmax (µg/ml)	F	1	0.09[a]	0.44	0.70
		29	0.08	0.41	0.65
		366	0.19	0.46	1.09
AUC_{0-24} (µg.hr/ml)		1	0.30[a]	0.93	1.89
		29	0.20[b]	1.40	2.04
		366	0.82[a]	1.56	5.10

Values are the means from 5 rats unless otherwise indicated ([a] n=4; [b] n=3; [c] n=1)

Absorption of Oral Eprosartan in Dogs (Rpt. # BP-1021/SKF-108566/1)

This non-GLP study was conducted by the Department of Drug Metabolism and Pharmacokinetics, Smith Kline Beecham Pharmaceuticals, King of Prussia, PA between 8/21/95 and 10/13/95.

[^{14}C]-Eprosartan mesylate (target dose=100 mg eprosartan/11 uCi/kg, Lot # SS24974-099A1) was administered orally by capsule to 2 bile-duct cannulated male Beagle dogs and to 2 non-bile duct cannulated dogs. Bile was collected at selected time intervals up to 24 hours after dosing. Urine and feces were collected at 24, 48, 72 and 96 hours after dosing. Blood samples were obtained from non-cannulated dogs at 0.5, 1, 3, 6 and 24 hours after dosing. All samples were assayed for radioactivity by liquid scintillation spectrometry.

Results: The recovery of radioactivity following administration of [^{14}C]-eprosartan mesylate to bile duct-cannulated dogs is summarized in Table 8. Based on biliary secretion and urinary excretion of radioactivity, absorption of drug-related material following single oral administration of a mean dose of 127 mg [^{14}C]-eprosartan/kg (mean dose was higher than the target dose due to an erroneous switch of doses between 2 dogs; dose levels for individual dogs shown in Table 8) was approximately 5% of the dose. Approximately 94% of the radioactivity was recovered in the feces.

Table 8. Recovery of Radioactivity after Oral [^{14}C]-Eprosartan in Dogs

Sample	Percent of Administered Dose	
	Bile Duct Cannulated [a]	Non-Cannulated [b]
Bile	4.5	-
Urine	0.74	0.57
Feces	94.3	94.3
Cage Wash	0.67	0.91
TOTAL	100.3	95.7

[a] Eprosartan Dose: Dog 1= 102.3 mg/kg Dog 2= 151.3 mg/kg
[b] Eprosartan Dose: Dog 3= 102.2 mg/kg Dog 4= 67.8 mg/kg

Pharmacokinetics of Eprosartan in Dogs After Single IV and Oral Administration (Rpt. # BP-1003/SKF-108566/1)

This non-GLP study was conducted by the Department of Drug Metabolism and Pharmacokinetics, Smith Kline Beecham Pharmaceuticals, King of Prussia, PA between 1/28/91 and 3/18/92.

Eprosartan (Lot #STR 15740-287-3) was dissolved in sterile saline with NaOH to aid dissolution and administered intravenously to 3 male Beagle dogs (via a cephalic vein) as a bolus dose of 3 mg eprosartan/kg. Blood samples were collected predose and at 1, 4 7, 10, 20, 40, 60, 120, 240, 360 480 720 and 1440 minutes after dosing for measurement of plasma eprosartan levels. After a washout interval of 2 weeks the same dogs received a single dose of 10 mg eprosartan/kg by oral gavage. Blood samples were obtained predose and 10, 20, 30, 40, 60, 90, 120, 240, 360, 480, 720 and 1440 min after dosing.

Results: Following intravenous administration, eprosartan disappeared from plasma in a triexponential fashion. The volume of distribution of 0.46 L/kg is approximately twice the extracellular fluid volume in the dog. After oral administration of 10 mg/kg, eprosartan appeared to be absorbed rapidly; the mean Tmax value was 0.62 hr. After Cmax (0.84 µg/ml) was achieved, plasma concentrations of eprosartan declined monoexponentially with a half-life of 2.8 hr, a value similar to the terminal half-life obtained after IV administration. Based on comparison of dose normalized AUC values, and assuming pharmacokinetic linearity, the apparent oral bioavailability of eprosartan was estimated to be 13.4% (Table 9).

Table 9. Pharmacokinetics of Eprosartan in Dogs After Single IV and PO Administration

Pharmacokinetic Parameter	Eprosartan Dose	
	3 mg/kg IV	10 mg/kg PO
Cmax (µg/ml)	43.0*	0.84
Tmax (hr)	-	0.62
Terminal Half-Life (hr)	2.68	2.80
Plasma Clearance (L/h/kg)	0.88	-
Volume $_{ss}$ (L)	0.46	-
AUC $_{0-24}$ (µg.hr/ml)	3.88	1.58
Bioavailability (%)	-	13.4

Values are the means from 3 dogs. * Represents calculated value at time 0.

Pharmacokinetics of Oral Repeat Dose Eprosartan in Dogs (Rpt. # TP-1009/SKF-108566/2 and # SKF108566/RSD-1003R6/1)

These two GLP studies were conducted by the Departments of Toxicology and Drug Metabolism, SmithKline Beecham Pharmaceuticals, King of Prussia, PA between 2/18/93 and 8/20/93 and between 10/31/94 and 11/01/95.

The repeat oral dose pharmacokinetics of eprosartan were investigated in Beagle dogs in conjunction with the 6-month and 1-year chronic toxicity studies. Capsules containing eprosartan mesylate (Lot# BCT-L-02P and BCT-L-04P for the 6-mo study; Lot# BCT-K-11C, BCT-K-16C and BCT-K-17C for the 1-yr study) were administered orally once daily at doses of 30, 100 and 1000 mg eprosartan/kg for both the 6-month and 1-year study (4/sex/dose group in both studies). Blood samples (via a cephalic vein) were obtained up to 24 hours after dosing on days 22 and 181 of treatment in the 6-month study and on days 30 and 359 of treatment in the 1-year study for determination of plasma eprosartan measured by HPLC.

Results: In the 6-month study (Table 10), peak plasma levels of eprosartan were observed 2 to 4 hours after dosing. Plasma levels of eprosartan were detectable 12 hours after dosing at the 30 mg/kg dose and for at least 24 hours after administration of the two higher doses. Based on Cmax and AUC values, systemic exposure to eprosartan increased with increasing dose, but in a less than dose-proportional manner (3- to 12-fold increase in Cmax or AUC values for a 33-fold increase from low to high dose). There was no evidence of drug accumulation.

The pharmacokinetic profile in the 1-year repeat dose study (Table 11) was similar to that observed in the 6-month repeat dose study. Tmax was observed between 2 and 4 hours after dosing. Systemic

exposure increased with increasing dose (approximately a 6- to 14-fold increase in Cmax or AUC values for a 33-fold increase from low to high dose) but there was no marked difference in systemic exposures (as measured by Cmax and AUC) between the 6-month and 1-year studies.

Table 10. Pharmacokinetics of 6-Month Repeat Oral Doses of Eprosartan in Dogs*

Pharmacokinetic Parameter	Sex	Dose Group (mg/kg/day PO)					
		Day 22			Week 181		
		30	100	1000	30	100	1000
Cmax (µg/ml)	M	0.57	0.63	1.90	0.54	0.83	1.75
Tmax (hr)		3.25	2.50	2.50	2.49	2.01	4.00
AUC_{0-24} (µg.h/ml)		2.31	2.35	14.6	1.89	2.36	13.4
Cmax (µg/ml)	F	0.55	0.99	3.37	0.55	0.98	2.89
Tmax (hr)		2.76	2.50	2,50	2.75	2.76	3.00
AUC_{0-24} (µg.h/ml)		2.10	3.89	24.8	2.18	4.23	20.3

* Values are the means from 4 animals

Table 11. Pharmacokinetics of 1-Year Repeat Oral Doses of Eprosartan in Dogs*

Pharmacokinetic Parameter	Sex	Dose Group (mg/kg/day PO)					
		Day 30			Week 359		
		30	100	1000	30	100	1000
Cmax (µg/ml)	M	0.53	0.86	2.52	0.33	1.03	1.89
Tmax (hr)		1.50	2.00	4.00	1.99	2.98	3.03
AUC_{0-24} (µg.h/ml)		2.58	7.12	25.2	2.04	5.63	17.4
Cmax (µg/ml)	F	0.24	1.12	3.40	0.38	1.08	2.45
Tmax (hr)		2.00	3.00	4.00	4.02	2.10	5.96
AUC_{0-24} (µg.h/ml)		1.03	8.59	25.9	2.27	5.30	20.55

* Values are the means from 4 animals

Pharmacokinetics of Eprosartan in Dogs After Single Intraduodenal Administration (Rpt.# 9340804/SKF-108566/1)

This non-GLP study was conducted by the Department of Drug Delivery, SmithKline Beecham Pharmaceuticals, King of Prussia, PA. Study dates were not given; study report dated June 1993.

Eprosartan mesylate (Lot # JRF-15948-162) was prepared as a solution (pH=8.1to 8.2) in 0.9% saline, with the addition of NaOH to aid dissolution, and administered to 5 male dogs (4 mongrel, 1 Beagle) intravenously (3 mg eprosartan/kg IV bolus) or intraduodenally (10 mg/kg via an implanted intraduodenal catheter. Eprosartan mesylate was also prepared as an aqueous suspension of small (<53 microns) and large (125-150 microns) particles and as a water-in-oil emulsion and administered intraduodenally at a dose of 10 mg eprosartan/kg. An appropriate washout interval (length not stated) was used between treatments in these animals. Blood samples were obtained via

a cephalic vein at various intervals up to 480 min for measurement of plasma eprosartan levels.

Results: After intraduodenal administration of a solution of eprosartan mesylate, the bioavailability (25.3%) was higher than that determined previously after oral administration of a solution (13.4%). The intraduodenal administration of suspensions or a water-in-oil emulsion of eprosartan did not improve the bioavailability of eprosartan (Table 12).

Table 12. Pharmacokinetics of Eprosartan in Dogs After IV and Intraduodenal Administration

Pharmacokinetic Parameter	Dose (Formulation)				
	3 mg/kg IV (Solution)	10 mg/kg ID (Solution)	10 mg/kg ID (Suspension)*	10 mg/kg ID (Suspension)‡	10 mg/kg ID (Emulsion)
Volume $_{ss}$ (L/kg)	0.53	-	-	-	-
Terminal $t_{½}$ (hr)	2.34	-	-	-	-
Cmax (µg/ml)	-	2.07	0.58	0.40	0.46
Tmax (hr)	-	0.53	0.80	0.58	0.23
$AUC_{0-\infty}$ (µg.hr/ml)	4.28	3.37	1.53	0.94	0.59
Bioavailability , %	-	25.3	11.3	6.6	16.7

* Suspension of small (<0.53 microns) particles. ‡ Suspension of large (125-150 microns) particles
Values are the means from 5 dogs

Pharmacokinetics of Oral Single Doses of Eprosartan in Humans (Rpt.# HP-1014/SKF-108566/1, # HP-1013/SKF-108566/1 and # HH-1001/SKF-108566/1)

Normal subjects received an oral solution of 100 mg [^{14}C]-eprosartan (eprosartan mesylate in aqueous 125mM sod. phosphate; pH=8.3) and an IV solution of 20 mg of [^{14}C]-eprosartan (eprosartan mesylate in normal saline) given on separate days to evaluate the oral bioavailability of eprosartan (# HH-1001/SKF-108566/1). Following each dose, radioactivity was determined in urine and feces collected at predetermined intervals up to 120 hr (urine) or 192 hr (feces). The recovery of radioactivity is summarized in Table 13. In this study, based on the comparison of urinary radioactivity concentration data following oral and IV administration, the mean absorption of drug-related material was estimated to be approximately 15%

Table 13. Recovery of Radioactivity After IV and Oral [^{14}C]-Eprosartan in Humans

Route/Dose	Percent of Administered Dose		
	Urine	Feces	TOTAL
Oral (100 mg)	7.21	90.4	97.6
IV (20 mg)	37.0	61.4	98.5

Values are the means from 4 subjects (PO) and 3 subjects (IV).

The absolute oral bioavailability of eprosartan was evaluated in a study in healthy male volunteers (HP-1013/SKF-108566/1) in which eprosartan mesylate was given as a commercial formulation at a dose of 300 mg of eprosartan. The oral bioavailability of eprosartan mesylate was found to range from 6.4% to 28.8% (average of 13.1%).

In another study (# HP-1014/SKF-108566/1), the pharmacokinetics of single oral doses of 100, 200, 400, and 800 mg of eprosartan (final commercial formulation of eprosartan mesylate) were determined in healthy male subjects. Maximum plasma eprosartan concentrations were observed at a mean time of approximately 3 hr (Table 14a). Mean Cmax and AUC values increased with increasing dose over the 100-800 mg dose range; dose-proportionality of Cmax and AUC was only evident for the 200 mg dose relative to the 100 mg values.

Table 14. Pharmacokinetics of Single Oral Dose Eprosartan Mesylate in Humans

Pharmacokinetic Parameter	Oral Dose (mg)			
	100	200	400	800
Cmax (µg/ml)	0.44	0.70	1.27	1.86
Tmax (hr)	2.85	2.92	3.15	2.88
AUC_{0-t} (µg.hr/ml)	1.40	2.55	4.66	7.44

Values are the means from 23 subjects

The pharmacokinetics of single (day 1) and repeated (day 7) oral doses of 600, 800 and 1200 mg eprosartan (administered as mesylate) was determined in patients with mild to moderate essential hypertension. Eprosartan mesylate was rapidly absorbed with eprosartan Cmax values occurring 1 to 3 hours following each dose (Table 14b). Based on trough plasma concentrations determined on days 2, 4, 6, 7 and 8, steady-state levels appeared to have been achieved by study day 4. With the exception of the AUC value obtained following the 800 mg regimen on study day 7, the increases in mean Cmax and AUC values were nearly dose-proportional.

Table 14b. Pharmacokinetics of Single or Repeated Oral Doses of Eprosartan Mesylate in Hypertensive Patients

Pharmacokinetic Parameter	Oral Dose (mg)					
	600		800		1200	
	Day 1[a]	Day 7	Day 1[b]	Day 7	Day 1	Day 7
Cmax (µg/ml)	1.62	1.61	2.08	2.10	2.79	2.96
Tmax (hr)	2.5	2.6	2.9	1.9	2.1	2.7
AUC_{0-t} (µg.hr/ml)	7.83	9.73	9.64	9.52	14.6	19.1

Values are the means from 8 patients unless otherwise indicated ([a]n=6; [b]n=7)

Distribution

Distribution of Eprosartan in Rats After Single IV Doses (Rpt.# BP-1015/SKF-108566/1 and # SKF-108566/RSD-1004G2/1)

These two GLP studies were conducted at between 9/02/93 and 7/25/94 (Rpt # BP-1015/SKF-108566/1) and between 11/28/95 and 12/15/95 (Rpt# SKF-108566/RSD-1004G2/1).

The distribution of [^{14}C]-eprosartan-derived radioactivity was determined by whole body autoradiography or by measurement of tissue radioactivity levels following intravenous administration of 3.0 or 10 mg [^{14}C]-eprosartan/kg, respectively, to male Sprague-Dawley rats (drug administered as solution in aqueous 125mM sod.phosphate; pH=8.0). After the 3 mg/kg IV dose (n=6), the animals were sacrificed at 0.25, 3, 24 hrs and 3, 7 and 21 days and immediately frozen. Whole body sections were exposed to X-ray film and autoradiograms were analyzed to quantitate the tissue radioactivity. After the 10 mg/kg IV dose, animals were sacrificed at 0.25, 1, 6,24 and 96 hrs (3 rats/time interval) after dosing and major organs and tissues were removed, oxidized using a tissue oxidizer and analyzed for radioactivity by liquid scintillation spectrometry.

At 15 min after the 3 mg/kg radiolabelled dose, radioactivity was widely distributed throughout most organs and tissues, with the exception of CNS, bone and abdominal and brown fat. High concentrations were detected in the small intestine, liver and in the urine and kidney, most likely as a result of biliary secretion and renal excretion. At 3 hours post-dose, apart from radioactivity in the GI contents and urine, lung was the only tissue with quantifiable levels of radioactivity. Elimination of all residual traces of radioactivity from the rat was completed between 7 and 21 days after dosing (Table 15).

The quantitative distribution of radioactivity after 10 mg [^{14}C]-eprosartan/kg IV (determined by excision of tissues followed by radioassay) is summarized in Table 16. The first sampling period showed the highest concentrations of radioactivity in most tissues/organs, indicating rapid distribution of drug-related material. At this time, 58% of the dose was detected in the gastrointestinal contents. Elimination of the drug occurred rapidly and by 1 hour the presence of radioactivity was greatly diminished in all tissues and organs; by 96 hrs notable radioactivity was detected only in the kidneys.

Table 15. Concentrations* of radioactivity, as determined by QWBA, in tissues, organs, and biological fluids of male rats after single intravenous administration of a 3 mg/kg dose of [^{14}C]eprosartan.

	Concentration of Radioactivity (ug equiv./g)					
Sample	15 min	3 h	24 h	3 day	7 day	21 day
Blood	1.611	ND				
Liver	5.215	ND				
Kidney	4.496	BMQL	BMQL	BMQL	BMQL	ND
Heart	0.278	ND				
Lung	0.914	0.527	ND			
Adrenal Glands	0.332	ND				
Diaphragm	0.391	ND				
Epididymus	0.255	ND				
Intra-orbital lachrymal gland	0.374	ND				
Lymph nodes	1.099	ND				
Pancreas	3.376	ND				
Pulp	2.166	ND				
Skin	0.649	ND				
Urinary bladder	0.536	ND				
Urine	90.58	0.433	BMQL			
Esophageal contents	1.528	ND	1.399	ND		
Stomach	0.253	ND				
Stomach contents	BMQL	BMQL	17.03	BMQL	BMQL	ND
Small intestinal contents	82.92	97.97	21.51	BMQL	ND	
Large intestine	0.390	ND				
Large intestinal contents	ND	ND	7.457	1.391	ND	
Cecum contents ND	128.2	7.977	0.252	ND		

* Only tissues/organs with concentrations >0.250 ug equiv./g
BMQL = Below minimum quantifiable level (<0.048 ug equiv./g) but detectable in autoradiograms.
ND = Not detected. Unless otherwise shown, concentrations at later sampling times were also ND.

Table 16. Radioactivity concentrations in tissues of male rats after single intravenous administration of [^{14}C]eprosartan at a target dose of 10 mg/kg.

	Mean (S.D.)Concentration (ugequiv.eprosartan/g)(n=3)**				
Tissue	0.25 h	1 h	6 h	24 h	96 h
Blood	3.56 ± 0.76	0.54 ± 0.09	0.05 ± 0.01	0.02 ± 0.02	0.01 ± 0.02
Plasma	5.93 ± 1.12	0.84 ± 0.14	0.06 ± 0.01	0.03 ± 0.00	0.00 ± 0.00
Liver	9.67 ± 0.64	1.54 ± 0.07	0.07 ± 0.02	0.03 ± 0.03	0.02 ± 0.03
Kidney	9.92 ± 2.97	1.90 ± 0.22	1.07 ± 0.03	0.64 ± 0.08	0.43 ± 0.06
Lung	1.90 ± 0.32	0.24 ± 0.04	0.03 ± 0.00	0.02 ± 0.01	0.01 ± 0.02
Aortic wall	4.33 ± 1.28	0.44 ± 0.11	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Skin	2.34 ± 0.16	0.34 ± 0.06	0.02 ± 0.00	0.02 ± 0.00	0.01 ± 0.00
Brown fat	2.02 ± 0.14	0.17 ± 0.05	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00
Stomach	4.77 ± 5.66	0.34 ± 0.18	0.01 ± 0.00	0.01 ± 0.00	0.00 ± 0.00
Duodenum	66.98 ± 2.78	5.46 ± 1.67	0.09 ± 0.04	0.00 ± 0.00	0.00 ± 0.00
Small intestine	18.67 ± 12.59	56.21 ± 5.92	0.30 ± 0.08	0.02 ± 0.03	0.00 ± 0.00
Large intestine	2.03 ± 0.92	0.38 ± 0.11	9.90 ± 2.00	0.52 ± 0.09	0.00 ± 0.00
Cecum	2.96 ± 1.95	1.77 ± 2.37	22.72 ± 12.37	0.49 ± 0.46	0.01 ± 0.00
Bladder	2.97 ± 0.54	0.36 ± 0.04	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Epididymus	1.83 ± 0.27	0.41 ± 0.08	0.02 ± 0.00	0.01 ± 0.00	0.00 ± 0.00
Mes.lymph.nodes	1.59 ± 0.44	0.45 ± 0.04	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00

* Only tissues with concentrations >1.50 ug equiv. eprosartan/g.

** Concentrations <0.005 are reported as 0.00.

Placental Transfer of Drug-Related Material After Single Oral Administration to Pregnant Rats
(Rpt. #SKF-108566/RSD-1003PX/1)

This GLP study was conducted by the between 2/27/96 and 3/05/96.

Placental transfer of drug-related material was studied in pregnant Sprague Dawley rats (day 18 of gestation) at various times after oral administration of single doses of 100 mg [^{14}C]eprosartan/kg (eprosartan mesylate suspended in aqueous 1% carboxymethylcellulose). The concentrations of radioactivity (determined by excision of tissues followed by radioassay) in selected maternal tissues, placentae, amniotic fluid and fetuses are summarized in Table 17. The absorbed radioactivity appeared to be rapidly distributed into the various maternal tissues analyzed. The highest concentrations of radioactivity were observed at either 0.5 or 1 h. In the amniotic fluid, radioactivity was only quantifiable at 3 h (0.02 ug equiv/g) whereas in the fetuses the concentrations of radioactivity were below the limit of quantification (<0.02 ug equiv./g) at all sampling times. These results suggested that the placental transfer of drug-related material is low in the rat.

Table 17: Concentration of radioactivity in tissues of pregnant rats after single oral administration of [^{14}C]eprosartan mesylate (100 mg eprosartan/kg).

	Concentration of Radioactivity (ug equiv of eprosartan/g)*				
Matrix	0.5 h	1 h	3 h	6 h	24 h
Blood	0.19±0.01	0.23±0.10	0.13±0.04	0.04±0.02	<0.03
Plasma	0.35±0.04	0.39±0.16	0.23±0.07	0.08±0.03	<0.13
Liver	4.60±1.35	4.66±0.21	2.19±0.65	0.79 ± 0.18	0.04± <0.011
Kidney	0.55±0.10	0.45±0.03	0.35±0.12	0.13±0.03	0.02**
Uterus	0.15±0.09	0.11±0.04	0.13±0.01	0.04±0.04	<0.02
Ovaries	0.10±0.04	0.06±0.01	0.10±0.04	0.01***	<0.03
Placenta	0.11±0.07	0.07±0.02	0.05±0.05	0.02***	<0.02
Amniotic Fluid	<0.01	<0.01	0.02 ± <0.01	<0.01	<0.01
Fetuses	<0.02	<0.02	<0.02	<0.02	<0.02

*Values represent means (S.D.) of three animals. When the levels of radioactivity were below background in all three animals, the values shown are limits of detection as calculated for each tissue.
**Concentration below the limit of detection in 1 of the 3 animals
***Concentration below the limit of detection in 2 of the 3 animals

Secretion of Drug-Related Material into Milk After Single Oral Administration to Lactating Rats
(Rpt. # SKF-108566/RSD-1004G1/1)

This GLP study was conducted by between 12/06/95 and 12/14/95.

To assess the secretion of drug-related material into milk, lactating Sprague-Dawley rats (day 12 postpartum) were given single oral doses of 100 mg [^{14}C]eprosartan/kg (eprosartan mesylate suspended in aqueous 1% carboxymethylcellulose). Milk and plasma samples were collected from three rats at selected times up to 24 hours after dosing for radioactivity determination. The secretion

of radioactivity in milk seemed to occur slowly and generally to a small extent. There was no evidence for accumulation of [^{14}C]eprosartan-derived radioactivity in the milk (Table 18).

Table 18. Secretion of radioactive material into milk of lactating rats following an oral dose of [^{14}C]eprosartan mesylate (100 mg eprosartan/kg).

Time	Mean Concentration (ug equiv. eprosartan/g)	
Post-dose (h)	Milk	Plasma
0.5	ND	0.26*
1	ND	0.79 ± 0.39
3	0.22*	1.12 ± 1.03
6	0.25**	0.22**
24	ND	ND

ND = Not Detected

Values given are the means and S.D. when concentrations were quantifiable in all three samples. When concentrations were below the detection limit (0.196 ug equiv./g) in one of three (*) or two of three (**) samples, the average was calculated assuming zero values for these samples.

In Vitro Plasma Protein Binding in Rat, Dog and Human Blood (Rpt.# 1005/SKF-108566/1)

This non-GLP study was conducted by SmithKline Beecham Pharmaceuticals, King of Prussia, PA between 3/04/92 and 4/17/92.

The *in vitro* plasma protein binding of [^{3}H]-eprosartan was determined by equilibrium dialysis over the concentration range 0.01-1000 µg/ml for Sprague-Dawley rat and Beagle dog and 0.01-100 µg/ml for human plasma. In the concentration range of 0.01-10µg/ml , the observed free fraction of eprosartan remained constant in rat, dog and human plasma (approximately 1.9%, 11.1% and 1.6%, respectively). At concentrations of 100 µg/ml and above, the free fraction increased in non-linear fashion (Table 19).

Table 19. The in vitro binding of [^{3}H]eprosartan to plasma proteins in rat, dog and human plasma.

Concentration (ug/mL)	Mean (S.D.) Percent Bound		
	Rat	Dog	Human
0.01 - 10 (n=12)*	98.12±0.18	88.88±0.48	98.42±0.22
100 (n=3)	97.64±0.04	87.33±0.09	97.59±0.10
1000 (n=3)	77.67±0.20	72.11±0.28	ND

*Percent binding at 0.01, 0.1, 1, and 10 ug/mL was approximately the same; therefore the results from these concentrations were pooled.

ND = Not Determined

The blood-to-plasma ratios were determined at concentrations used for plasma protein binding. The blood/plasma ratio of eprosartan remained constant over the entire range of concentrations studied in all three species (Table 20). The blood/plasma ratio of 0.62 for human blood suggests little association of drug with blood cells.

Table 20. The in vitro blood to plasma ratios for [^{3}H]eprosartan in rat, dog and human blood.

Concentration (ug/mL) Concentration	Mean (S.D.) Blood to Plasma Ratio (n=3)		
	Rat	Dog	Human
0.01	0.53±0.01	0.57±0.02	0.60±0.10
0.10	0.53±0.00	0.54±0.00	0.67±0.02
1.00	0.53±0.01	0.54±0.01	0.65±0.03
10.0	0.53±0.01	0.53±0.01	0.64±0.05
100	0.54±0.01	0.53±0.01	0.53±0.03
1000	0.55±0.00	0.53±0.01	ND
Average	0.54	0.54	0.62

ND = Not Determined

Metabolism

Biotransformation of [^{14}C]-Eprosartan After Single Oral or IV Administration in Rats (Rpt. # BP-1006/SKF-108566/1 and Rpt. #SKF-108566/RSD-1004HR/1)

These GLP studies were conducted by SmithKline Beecham Pharmaceuticals, King of Prussia, PA (Rpt. # BP-1006/SKF-108566/1; study conducted between 3/01/92 and 7/21/92) (Rpt. #SKF-108566/RSD-1004HR/1; study conducted between 11/08/95 and 2/28/96).

Plasma, bile and feces from Sprague-Dawley rats were analyzed by radiochromatography, HPLC and LC/MS for biotransformed products after single IV (3 mg eprosartan/kg) or oral (4 and 100 mg eprosartan/kg) doses of [^{14}C]-eprosartan mesylate.

Radiochromatographic analysis of plasma obtained from male rats at 1 hour after oral administration of a suspension (in 1% carboxymethylcellulose) of 100 mg [^{14}C]-eprosartan/kg showed only one predominant peak that corresponded to the parent compound. HPLC analysis of bile also revealed one major component (>97% of the total radioactivity was secreted in the bile) which was identified as the parent drug using LC/MS analysis. HPLC and LC/MS analysis of fecal samples, obtained from bile-duct cannulated male Sprague-Dawley rats up to 48 hours after oral administration of 100 mg [^{14}C]-eprosartan/kg (eprosartan mesylate in 1% carboxymethylcellulose suspension) showed that the parent compound constituted > 99% of the total radioactivity excreted in the feces. Similarly when 100 mg [^{14}C]-eprosartan/kg (eprosartan mesylate suspension) was administered to intact male and female Sprague-Dawley rats, radiochromatographic analysis of the feces also showed one peak which co-chromatographed with the parent compound.

In rats given 3 mg [^{14}C]-eprosartan/kg IV or 4 mg [^{14}C]-eprosartan/kg PO (as solution in 5% aqueous sodium bicarbonate), analysis of fecal samples showed one predominant peak which corresponded to the unchanged eprosartan. Fecal excretion of unchanged drug accounted for 96.0% and 87.4%

of the IV dose in males and females, respectively, and 91.6 and 90.4 of the oral dose in males and females, respectively. Two other minor peaks were occasionally detected, but each accounted for <1% of the IV or oral dose. In all plasma samples, a major peak which co-eluted with the parent compound, accounted for >91% of the plasma radioactivity after both IV and oral dosing with [^{14}C]-eprosartan.

Because urinary excretion of radioactive doses was minimal (<0.5% after oral dose and <3% after an IV dose), profiling of urinary metabolites was not performed.

Biotransformation of [^{14}C]-Eprosartan Mesylate After Single Oral or IV Administration in Dogs (Rpt. #SKF-108566/RSD-1003R1/1 and SKF-108566/RSD-1003R2/1)

These GLP studies were conducted by SmithKline Beecham Pharmaceuticals, King of Prussia, PA (Rpt. #SKF-108566/RSD-1003R1/1; study conducted between 11/30/95 and 3/01/96; (Rpt. #SKF-108566/RSD-1003R2/1; study conducted between 11/21/95 and 3/23/96).

In the SKB study, bile, feces and urine from bile-cannulated (n=2) and plasma from intact (n=2) male Beagle dogs were analyzed for radiometabolite profiles after single oral (capsule) administration of [^{14}C]-eprosartan mesylate at a dose of 100 mg eprosartan/kg. Radiochromatograms of 0-24 hr bile showed three peaks (parent drug, DB1 and DB2) which accounted for 66%, 295 and <3% of the total biliary radioactivity, respectively (or 3%, 1.4% and <0.2% of the total administered dose, respectively). Metabolite DB1 was characterized as a glucuronide conjugate of eprosartan; the structure of metabolite DB2 remains unknown.. Fecal and urine samples contained only one radioactive component which was characterized to be the unchanged eprosartan. Plasma samples obtained from intact dogs revealed only the parent drug.

In the study, Beagle dogs (3M, 3F) were dosed with [^{14}C]-eprosartan mesylate at single IV doses of 10 mg eprosartan/kg (solution in 125 mM sod. posphate; pH=8.0) and single PO doses of 100 mg eprosartan/kg (in capsules). All dogs received both IV and PO doses separated by an 11-day washout period after the IV dose. Radiometabolites were determined in feces (0-72 hr after IV administration and 0-48 hr after oral administration), urine (0-12 hr after both IV and PO administration) and plasma (up to 2 hr after IV administration). Analysis of fecal samples showed one predominant peak, which corresponded to unchanged eprosartan and accounted for 69.5% and 67.8% of the IV dose and 91.5% and 92.8% of the oral dose in males and female dogs, respectively. Two other minor peaks were detected in fecal samples from males and females after IV administration but each accounted for <1% of the IV dose. The urinary radioactivity was almost entirely comprised of unchanged drug; it accounted for 16.4% and 17.1% of the IV dose in males and females, respectively, and 0.4% and 0.42% of the oral dose in males and females, respectively.In plasma samples, the parent drug (eprosartan) accounted for >87% of the total plasma radioactivity.

Biotransformation of Single Oral and IV Doses of [^{14}C]-Eprosartan Mesylate in Humans (Rpt. # HH-1001/SKF-108566/1)

The biotransformation of [^{14}C]-eprosartan mesylate was studied when given as single oral (100 mg eprosartan as solution in phosphate buffer, pH=8.3, to 4 males) or single IV (20 mg eprosartan in saline solution given by infusion over 30 min to 3 males) doses to healthy adult subjects. Following both oral and IV administration, the parent drug was identified as the only radiolabeled component in plasma. One metabolite (characterized as an acyl glucuronide of eprosartan) was detected in urine and represented 19% of the radioactivity excreted in urine following IV or oral administration; this metabolite corresponded to 6.8% of the IV dose and 1.2% of the oral dose. The remainder of the urinary radioactivity was associated with the parent drug. The radiochromatograms of pooled fecal extracts (0-72hr) showed the presence of only one peak, after IV or oral administration, which was identified as unchanged eprosartan.

Effects of Eprosartan on Rat Hepatic Cytochrome P-450 Enzymes (Rpt. # BP-0001/SKF-108566/1)

This non-GLP study was conducted by the Drug Metabolism and Pharmacokinetics Dept., SmithKline Beecham Pharmaceuticals, King of Prussia, PA between 10/08/91 and 12/20/91.

This study examined the effects of eprosartan on hepatic cytochrome P-450 enzymes following daily oral (gavage) administration of the mesylate salt to male and female Sprague-Dawley rats at doses of 0, 30, 100 or 1000 mg eprosartan /kg/day for 30 days. At the end of treatment, rats were sacrificed, livers removed and hepatic microsomes prepared and assayed for protein and cytochrome P-450 content. Also assayed were the microsomal cytochrome P-450 activities ethoxyresorfin O-dealkylation, para-nitrophenol 4-hydroxylation and testosterone hydroxylation. These activities serve as markers for the hepatic cytochrome P-450 enzymes 1A, 2A, 2B, 2C, 2E and 3A families.

There were no significant changes from control, at any dosage of eprosartan, in hepatic microsomal protein content, total cytochrome P-450 content or in the enzyme activities involved in drug metabolism. It was concluded that eprosartan at doses up to 1000 mg/kg/day for 30 days is not an inducer of the monitored hepatic cytochrome P-450 enzymes.

Effect of Eprosartan on Drug Metabolizing Activity of Human Liver Microsomes *In Vitro* (Rpt. # BP-1019/SKF-108566/2)

This non-GLP study was conducted by the Drug Metabolism and Pharmacokinetics Dept., SmithKline Beecham Pharmaceuticals, King of Prussia, PA between 8/01/94 and 9/11/94.

This study examined the inhibitory potential of eprosartan on human cytochrome P-450 enzymes. Human livers were obtained from organ donors at time of death for preparation of human liver

microsomes. The *in vitro* metabolisms of ethoxyresorufin, coumarin, tolbutamide, S-mephentoin, bufaralol, chlorzoxazone and cyclosporin by human liver microsomes were measured in the presence and absence of eprosartan to detect a potential inhibitory effect of eprosartan on the cytochrome P-450 enzymes involved in the metabolism of these agents.

Eprosartan concentrations up to 100 μM caused no inhibition of the metabolism of the agents tested indicating that the human cytochrome p-450 enzymes CYP1A, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E and CYP3A involved in the metabolism of certain drugs are not inhibited by eprosartan.

Excretion

Excretion of Radioactivity After Single IV or Oral Doses of [^{14}C]-Eprosartan Mesylate to Rats (Rpt. # SKF-108566/RSD-1004HR/1)

This GLP study was conducted by between 11/08/95 and 2/28/96.

Radioactivity was determined in urine, feces and residual levels in the GI tract and carcass from Sprague-Dawley rats given single 10 mg [^{14}C]-eprosartan/kg IV (eprosartan mesylate solution in phosphate buffer, pH=8.0) or 100 mg [^{14}C]-eprosartan/kg PO by gavage (eprosartan mesylate suspension in 1% aqueous carboxymethylcelulose) up to 96 hours after administration. The recovery of radioactivity is shown in Table 21.

Table 21. Excretion of radioactive material following a single intravenous or oral administration of [^{14}C]eprosartan mesylate to the rat at doses of 10 mg eprosartan/kg and 100 mg eprosartan/kg, respectively.

	Percent of Administered Dose			
	Intravenous		Oral	
Sample Matrix	Males	Females	Males	Females
Urine	0.88 ± 0.26	2.14 ± 0.85	0.04 ± 0.01	0.36 ± 0.30
Feces	98.8 ± 1.72	91.6 ± 3.28	94.6 ± 2.02	94.1 ± 1.84
GI Tract	<LLQ	0.01 ± 0.00	<LLQ	<LLQ
Carcass	0.03 ± 0.01	0.04 ± 0.02	<LLQ	<LLQ
Total**	99.5 ± 1.45	94.0 ± 3.02	94.7 ± 2.01	94.5 ±1.85

* Data given are mean & S.D. values (n=3)
** Includes cage wash and cage wipe
LLQ - Lower limit of quantification

Excretion of Radioactivity After Single IV or Oral Doses of [^{14}C]-Eprosartan Mesylate to Dogs (Rpt. # SKF-108566/RSD-1003R2/1)

This GLP study was conducted by between 11/21/95 and 3/23/96.

Radioactivity was determined in urine and feces from male and female Beagle dogs (3/sex/group) given single doses of 10 mg [^{14}C]-eprosartan/kg IV (eprosartan mesylate solution in phosphate buffer, pH=8.0) or 100 mg [^{14}C]-eprosartan/kg PO (eprosartan mesylate by capsule) up to 96 hours after administration. The recovery of radioactivity is shown in Table 22. The excretion of radioactivity was quantitatively and qualitatively similar in males and females. The recovery of radioactivity in the feces following IV administration is presumed to be due to biliary secretion of drug-related material.

Table 22. Excretion of radioactive material following a single intravenous or oral administration of [^{14}C]eprosartan mesylate to the dog at doses of 10 mg eprosartan/kg and 100 mg eprosartan/kg, respectively.

	Percent of Administered Dose (0-96 h)			
	Intravenous		Oral	
Sample Matrix	Males	Females	Males	Females
Urine	19.1 ± 3.30	18.5 ± 4.77	0.70 ± 0.32	0.56 ± 0.17
Feces	71.3 ± 1.93	71.0 ± 6.74	92.9 ± 2.60	94.8 ± 5.17
Cage Wash/Wipe	1.71 ± 1.55	0.75 ± 0.87	0.23 ± 0.16	0.22 ± 0.18
Total	92.0 ± 3.88	90.3 ± 5.32	93.8 ± 2.32	95.6 ± 5.08

* Data given are mean & S.D. values (n=3)

Excretion of Radioactivity After Single IV or Oral Doses of [^{14}C]-Eprosartan Mesylate to Humans (Rpt. # HH-1001/SKF-108566/1)

This study was conducted by the Clinical Pharmacology Unit, SmithKline Beecham Pharmaceuticals, Essex, UK between 4/12/94 and 5/11/94

Radioactivity was determined in urine and feces collected at predetermined intervals up to 120 hr (urine) or 192 hr (feces) after administration of 100 mg [^{14}C]-eprosartan PO (eprosartan mesylate as solution in phosphate buffer, pH=8.3, n=4 males) or 20 mg [^{14}C]-eprosartan IV, 30 min infusion (eprosartan mesylate as solution in saline, n=3 males) to healthy human subjects. The recovery of radioactivity is shown in Table 23. The recovery of radioactivity in the feces following IV administration is presumed to be from biliary secretion of drug-related material.

Table 23. Excretion of radioactive material following single intravenous or oral doses of [^{14}C]eprosartan mesylate to healthy male subjects.

Route of Administration	Dose (mg)	Percent of Administered Dose Urine (0-120 h)	Feces (0-192 h)	Total Recovery
IV (n=3)	20	37.0 ± 3.82	61.4 ± 4.09	98.5 ± 0.41
Oral (n=4)	100	7.21 ± 3.44	90.4 ± 3.31	97.6 ± 0.30

* Data shown are means & S.D.values.

TOXICOLOGY

Single Dose Toxicity Studies

Single Oral Dose Toxicity Study of Eprosartan in Rats

Study Facility: SmithKline Beecham Pharmaceuticals, King of Prussia, PA
Study No.: D90020 (Rpt. # TP-0001/SKF-108566/1)
Study Dates: 5/08/90 to 5/22/90

GLP Compliance: No; study conducted in accordance with protocol and standard operating procedures of the Toxicology Department.

Animals: Male and female Sprague-Dawley rats (231-466 gm).

Drug Administration: Eprosartan (non-salt; Lot# JAF15805-203) was suspended in 0.5% gum tragacanth aqueous solution and administered as a single oral dose by gavage.

Dose Levels: 0 (vehicle), 3, 10, 30, 100, 300, 600, 1000 mg eprosartan/kg (2/sex/dose group).

Observations/Measurements: Rats were observed daily for 14 days after dosing for mortality and clinical signs of toxicity. Body weight measurements were performed prior to dosing, on day of dosing and on days 1-6, 8, 10 12 and 14 after dosing. Blood samples were obtained from each animal for serum biochemical and hematologic evaluation 1 and 13 days after dosing. Urine was collected from each animal 1, 2, 3, 7 and 13 days after dosing for measurement of 24-hr urine volume, urine sodium and potassium output. All animals were necropsied and examined for gross pathology 14 days after dosing.

Results: No animals died during the study. No clinical signs of toxicity were noted in any treatment group. Body weight changes in eprosartan-treated groups were comparable to control. No treatment

-related effects on hematologic, clinical chemistry or urinalysis parameters were observed. No eprosartan-related macroscopic pathology was observed. Thus, single, oral administration of eprosartan at doses up to 1000 mg/kg produced no evidence of drug-related toxicity in rats for up to 14 days after dosing.

Single Intravenous Dose Toxicity Study in Rats

Study Facility: SmithKline Beecham Pharmaceuticals, King of Prussia, PA
Study No.: D91037 (Rpt. # TP-0003/SKF-108566/1)
Study Dates: 5/20/91 to 5/23/91

GLP Compliance: No; study was conducted in accordance with protocol and standard operating procedures of the Toxicology Department.

Animals: Male and female Sprague-Dawley rats (381-487 gm).

Drug Administration: Eprosartan (Lot # JAF15805-203) was dissolved in normal saline (pH adjusted to 7.5) and administered as a single intravenous dose via a tail vein.

Dose Levels: 0 (vehicle), 10, 30, 100 mg/kg as bolus (<1 min) and 300 mg/kg as infusion over 10 min (2/sex/dose group).

Observations/Measurements: Rats were observed daily for 3 days after dosing for mortality and clinical signs of toxicity. Body weight measurements were performed prior to dosing and daily for 3 days after dosing. Blood samples were obtained from each animal for serum biochemical and hematologic evaluation approximately 48 hours after dosing. Rats were killed on day 4 after dosing, and examined for gross pathology. Sections from major organs and tissues were examined for microscopic pathology.

Results: No animals died during the study and no clinical signs of toxicity were observed. All male rats and vehicle treated rats gained from 2 to 15 gms of pre-dose body weight between day 1 and 3 of the study. The two female rats given 300 mg/kg lost 11 and 13 grams of pre-dose body weight between day 1 and day 3. Female rats given 30 and 100 mg/kg of eprosartan showed small decrements from pre-dose body weights (5 to 7 grams); body weight in female rats given 10 mg/kg remained near pre-dose levels. No eprosartan-related effects on hematological, and clinical chemistry parameters were observed. Gross and microscopic examinations showed no treatment-related macro- or microscopic pathologies.

Single and Four-Day Repeat Oral Dose Toxicity Study in Dogs

Study Facility: SmithKline Beecham Pharmaceuticals, King of Prussia, PA
Study No.: D91013 (Rpt. # TP-0005/SKF-108566/1)
Study Dates: 4/08/91 to 4/12/91

GLP Compliance: No; study conducted in accordance with protocol and Standard operating procedures of the Toxicology Department.

Animals: Male and female Beagle dogs (8.7-10.0 kg)

Drug Administration: Eprosartan (Lot # STR-15740-287-3) was placed into gelatin capsules and administered as a single or 4-day repeated oral dose.

Dose Levels: 0 (empty capsule), 30, 100, 300, 600, 1000 mg /kg (1M & 1F/dose group). Additional dogs given 100 or 1000 mg/kg (1M & 1F/dose group) doses once daily for 4 days.

Observations/Measurements: Dogs given single doses of eprosartan were observed for mortality and clinical signs of toxicity on the day of and daily for 3 days after dosing; dogs given repeat doses of eprosartan were observed daily throughout dosing and at 24 hours after the last dose. Body weights were measured daily throughout the observation period. Blood was obtained prior to dosing and at time of necropsy for hematology and clinical chemistry analyses. Blood was obtained from dogs at intervals up to 24 hours after single doses of 100 or 1000 mg/kg for measurement of plasma eprosartan levels. Dogs receiving single oral doses were killed on day 4 (approximately 72-hrs post dose) and dogs receiving repeat oral doses were killed on day 5 and examined for gross pathology. Sections from major organs and tissues were obtained for microscopic examination.

Results: No dogs died during the study. No clinical signs of toxicity were noted in dogs receiving single or 4-day repeat oral doses of eprosartan. The male dog given 1000 mg/kg/day showed whitish material in the stool after receiving the 4th daily dose; the whitish color appeared to be drug-related material. Body weights were unaffected by eprosartan treatment. Hematology and clinical chemistry parameters were comparable to pre-dose values in control and eprosartan-treated animals. Macroscopic and microscopic examination revealed no treatment-related pathologies.

Plasma levels of eprosartan detected in dogs given single oral doses of 100 or 1000 mg/kg are summarized in Table 24. Plasma levels of eprosartan increased with increasing dose.

Table 24. Toxicokinetic Values After Single Oral Dose in Dogs

Dose (mg/kg PO)	Sex	Toxicokinetic Parameter	
		Cmax, ug/ml	Tmax, min
100	M	0.456	90
	F	0.502	240
1000	M	7.13	480
	F	10.03	240

Single Intravenous Dose Toxicity Study in Dogs

Study Facility: SmithKline Beecham Pharmaceuticals, King of Prussia, PA
Study No.: D91012 (Rpt. # TP-0006/SKF-108566/1)
Study Dates: 4/16/91 to 4/19/91

GLP Compliance: No; study conducted in accordance with protocol and standard operating procedures of the Toxicology Department.

Animals: Male and female Beagle dogs (7.3-9.7 kg)

Drug Administration: Eprosartan (Lot # STR-15740-287-3) was dissolved in saline and infused intravenously over a period of 10 to 30 min; control dogs received intravenous saline.

Dose Levels: 0 (saline vehicle), 100 and 300 mg eprosartan/kg (1M & 1F/dose group).

Observations/Measurements: Dogs were observed for mortality and clinical signs of toxicity on day of dosing and daily for 3 days after dosing. Body weights were measured prior to and daily for 3 days after dosing. Electrocardiograms were obtained prior to and immediately following drug infusion. Blood samples were obtained predose on day 1 and on day 3 of the study for clinical pathology determinations. Additional blood samples were obtained prior to dosing and at intervals up to 24 hours following infusion (day 1) for measurement of plasma eprosartan levels. Dogs were killed on day 4 of the study and examined for gross pathology. Sections of major organs and tissues were examined for microscopic pathology.

Results: There were no unscheduled deaths in the study. All dogs given eprosartan had one or more incidences of emesis during the period of drug infusion. No vehicle-treated dogs vomited. Body weight was unaffected by eprosartan treatment. The female dog receiving 300 mg/kg of eprosartan showed a slight ST segment elevation immediately after dosing; no changes in the electrocardiogam were noted in other eprosartan or vehicle treated dogs. No treatment-related effects on hematology parameters were observed. The serum alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values in the male and female dog receiving 300 mg/kg were

increased on day 3. The ALP increases (1.5-fold compared to pre-drug values) were comparable for both the male and female dog. The ALT and AST values were increased 5.3- and 3.1-fold, respectively in the males dog and 2.8- and 1.6-fold, respectively, in the female dog.

Gross examination revealed no macroscopic pathology. Microscopic examination revealed liver pathology consisting of mild and multifocal cholangitis in male dogs given 100 and 300 mg/kg. These effects were characterized by mild edema and inflammatory cell infiltration around the medium-to-large branches of the common bile duct. Eprosartan-treated females or vehicle-treated males and females were unaffected.

Blood levels and AUC values obtained with intravenous infusion of eprosartan are summarized in Table 25. Both plasma concentrations and AUCs tended to be slightly higher in females compared to male dogs given the same dose.

Table 25. Toxicokinetic Values After Single IV Dose in Dogs

Infused Dose (mg/kg IV)	Sex	Toxicokinetic Parameter	
		Cmax, ug/ml	AUC_{0-24}, ug.min/ml
100 (10 min infusion)	M	691	4.42×10^4
	F	818	5.33×10^4
300 (30 min infusion)	M	708	1.15×10^5
	F	1172	1.38×10^5

Repeat-Dose Toxicity Studies

14-Day Intravenous Toxicity Study in Rats

Note: This toxicity study by the IV route was conducted to support a Phase I clinical bioavailability study in human subjects.

Study Facility: SmithKline Beecham Pharmaceuticals, King of Prussia, PA
Study No.: GP1087(Rpt. # TP-0012/SKF-108566/1)
Study Dates: Initiation of dosing: 1/21/92 Necropsy: 2/04/92

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male Sprague-Dawley rats (3 months old, 343-530 gm)

Drug Administration: Eprosartan mesylate (Lot # PL-20581-23) was dissolved in phosphate buffer (pH=8.0) and administered intravenously via a tail vein: control rats received the drug vehicle.

Dose Levels: 0 (vehicle), 1, 10 and 30 mg eprosartan/kg (5/dose group).

Observations/Measurements: Animals were observed daily during the dosing period for mortality and clinical signs of toxicity. Body weights were measured predose and daily during the dosing period. Food consumption was measured weekly during the study. Opthalmoscopic examinations were performed on all animals predose and on day 12 of the dosing period. Blood was collected on days 3 and 14 for hematology and clinical chemistry analyses. Urine was collected on days 4 and 15 for urinalysis. Rats were killed and necropsied 24 hours after the last dose (day 15). All animals were examined macroscopically and major organs were removed and weighed. Sections of organs and tissues from the control and high dose groups and any macroscopically-abnormal tissues from low and mid-dose groups were examined microscopically.

Results:

Mortality and Clinical Signs of Toxicity
No rats died during the study and no clinical signs of toxicity were observed.

Body Weights and Food Consumption
Mean body weights of eprosartan-treated animals did not significantly differ from control mean weight during the study; at study termination mean body weights of eprosartan-treated groups were slightly higher (0.7%, 3.6% and 2.7% for low, mid and high dose groups) than control. Food consumption among eprosartan-treated groups was comparable to control.

Ophthalmoscopic Examination
No eprosartan-related ophthalmoscopic effects were detected.

Hematology, Clinical Chemistry and Urinalysis
Hematology and clinical chemistry parameters were unaffected by eprosartan treatment with the exception of occult blood in the urine of 3 of 5 rats given 30 mg/kg/day.

Gross and Microscopic Examination
Microscopic examination revealed no eprosartan-related histopathology except for tissue inflammation at the tail injection site. There were no microscopic findings from tissues of the urinary tract. The sponsor suggests that bleeding from the venipuncture site, which preceded the urine collection, may have contaminated the urine.

30-Day Oral Toxicity Study in Rats

Study Facility: SmithKline Beecham Pharmaceuticals, King of Prussia, PA
Study No.: D91012 (Rpt. # TP-0010/SKF-108566/2)
Study Dates: Initiation of dosing: 10/02/91 Study termination: 11/1/91

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male and female Sprague-Dawley rats (M=377-484 gm; F=231-300 gm)

Drug Administration: Eprosartan mesylate (Lot # PL-20581-23) was suspended in 1% carboxymethylcellulose aqueous solution and administered orally by gavage; control rats received the drug vehicle.

Dose Levels: 0 (vehicle), 30, 100 and 1000 mg eprosartan/kg (6/sex/dose group for main study, 4/sex/group as satellite groups for toxicokinetics).

Note: High dose selection was based on results of a 7-day oral rangefinding study (Rpt#TP-0009/SKF-108566/1) which investigated doses of 100 to 3000 mg eprosartan/kg/day. No drug-related toxicity was observed at dosages up to 3000mg/kg/day. Systemic exposure (AUC) to eprosartan after the 3000 mg/kg/day was not appreciably higher than that seen with 1000 mg/kg/day (1.2- to 1.7-fold increase in AUC for males and females, respectively, for a 3-fold increase in dose). Also, the AUC and Cmax values increased less than 2-fold over a 10-fold dose range (300 to 3000 mg/kg/day).

Observations/Measurements: Animals were observed daily during the treatment period for mortality and clinical signs of toxicity. Body weights were measured weekly and at study termination. Food consumption was measured weekly through day 24 of treatment. Ophthalmoscopic exams were conducted prior to dosing and on dosing day 27. Blood was collected on days 8 and 27 for hematology and clinical chemistry analyses. Urine was collected on dosing day 9 and at study termination for urinalysis. Blood samples were obtained from a tail vein of rats in the satellite toxicokinetic groups prior to dosing and at 30, 60 120, 240, 360, 480, 720 and 1440 min after dosing on day 1 and day 30 for measurement of plasma eprosartan levels. At the end of the dosing period, animals were killed and examined for macroscopic pathology. Major organs were weighed and sections of major organs and tissues were fixed on slides and examined for microscopic pathology.

Results:

Mortality and Clinical Signs
No animals died during the study and no clinical signs of toxicity were noted during treatment with eprosartan.

Body Weight and Food Consumption
Body weights and food consumption among eprosartan-treated rats did not differ significantly from control.

Ophthalmology
No drug-related ophthalmologic effects were noted in any of the treatment groups.

Hematology, Clinical Chemistry and Urinalysis
Eprosartan treatment had no effect on hematology or clinical chemistry parameters. The mean urine

specific gravity for female rats given 1000 mg/kg/day (1.017) was slightly lower than the concurrent control value (1.027) on study day 31. The sponsor does not regard this finding to be toxicologically important.

Organ Weights

There were no eprosartan-related effects on brain, liver, heart, kidney adrenal and or ovarian or testis/epididymis weights.

Gross and Microscopic Pathology

No eprosartan-related gross pathology was detected. Microscopic examination showed slightly increased incidences of kidney lesions in high-dose males and females (Table 26).

Table 26. Microscopic Findings

Kidney Lesion	Sex	Incidence (# rats affected/#examined)			
		0 (Control)	30 mg/kg	100 mg/kg	1000 mg/kg
Inflammatory Cell Infiltrate	M	1/6	0/6	0/6	1/6
	F	0/6	0/6	0/6	1/6
Dilatation of Renal Pelvis	M	0/6	0/6	0/6	1/6
	F	0/6	0/6	0/6	0/6
Chronic Progressive Nephropathy	M	0/6	0/6	0/6	1/6
	F	0/6	0/6	0/6	1/6
Renal Papilla or Tubule Mineralization	M	0/6	0/6	0/6	1/6
	F	0/6	1/6	0/6	2/6

Toxicokinetics

The mean values for Cmax and AUC increased with increasing dose; however, the increases were non-dose-proportional. The Cmax values tended to be larger for mid- and high-dose females than for males but no apparent sex-related differences in AUCs were detected. There was no evidence of drug accumulation over the duration of the study (Table 27).

Table 27. Toxicokinetic Values

Dose (mg/kg PO)	Sex	Cmax (ng/ml)		AUC_{0-24} (ug.min/ml)	
		Day 1	Day 30	Day 1	Day 30
30	M	167	124	49	49
	F	142	243	35	122
100	M	388	268	131	85
	F	484	438	119	125
1000	M	780	1008	295	294
	F	1669	1238	377	324

6-Month Oral Toxicity Study in Rats

Study Facility: SmithKline Beecham Pharmaceuticals, King of Prussia, PA
Study No.: G92068 (Rpt. # TP-0006/SKF-108566/1)
Study Dates: Initiation of dosing: 8/18/92 Last day of necropsy: 2/16/93

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male and female Sprague-Dawley rats (10 weeks old, 214-418 gm)

Drug Administration: Eprosartan mesylate (Lot# BCT-L-03P) was suspended in 1% carboxymethylcellulose aqueous solution and administered orally by gavage; control rats received the drug vehicle.

Dose Levels: 0 (vehicle), 30, 100 and 1000 mg eprosartan/kg/day (12/sex/dose group).

Observations/Measurements: Animals were observed daily for mortality and clinical signs of toxicity. Body weights were determined prior to dosing, weekly during the dosing period and terminally on the day of necropsy. Food consumption was measured monthly during the dosing period. Ophthalmoscopic examinations were performed on all rats prior to the start of dosing and on dosing day 176. Blood was obtained from a tail vein on days 91 and 169 of dosing for hematology and clinical chemistry analyses. Urine was collected on days 94 and 182 for urinalysis. Blood was also obtained from the tail of 3 rats/sex/group at approximately 1, 2, 4, 8 , 12 and 24 hours after dosing on study days 1 and 178 for toxicokinetic analysis. At termination of dosing, rats were killed by carbon dioxide asphyxiation and necropsied. Major organs were removed and weighed. Macroscopic examination was performed on all animals. Sections of major organs and tissues were fixed on slides for microscopic examination. Tissues were examined for all animals in the control and high dose (1000 mg/kg/day) groups; only those tissues from the low (30 mg/kg/day) and mid (100 mg/kg/day) dose groups that showed macroscopic pathology were examined microscopically.

Results:

Mortality and Clinical Signs
One low-dose male died from leukemia on day 171 of dosing (hematology and clinical chemistry data obtained on dosing day 169 was consistent with this disease process; i.e., decrease in platelet counts, increase in atypical and immature lymphocytes and elevations in serum enzyme and urea nitrogen concentrations). Sponsor states that leukemia is a spontaneously occurring disease in this rat strain and unlikely to be drug-related.

No eprosartan-related clinical signs of toxicity were observed in the study.

Body Weight and Food Consumption

Mean body weights and food consumption among eprosartan-treated animals were comparable to control. Mean values noted at about the beginning, middle and end of study are summarized in Table 28.

Table 28. Body Weights and Food Consumption†

Measurement	Dose Group (mg/kg/day)							
	0 (Control)		30		100		1000	
	M	F	M	F	M	F	M	F
Mean Body Weight, gm								
Day 1	364	235	363	236	370	236	360	233
Day 92	612	330	630	342	621	349	601	338
Day 176	694	355	725*	369	702	377	673	370
Mean Food Consumption, gm/day								
Day 10	30	21	30	22	31	22	31	22
Day 105	30	20	30	20	31	20	30	21
Day 168	30	20	32*	20	32	20	31	22

† Values are the means from 12 rats (* n=11)

Hematology, Clinical Chemistry and Urinalysis

Hematology values among eprosartan-treated animals were comparable to those of control rats when measured on days 91 and 169 of dosing. Hematologic values obtained at dosing day 169 are summarized in Table 29.

Table 29. Hematologic Values †

Hematologic Parameter	Dose Group (mg/kg/day)							
	0 (Control)		30		100		1000	
	M	F	M	F	M	F	M	F
RBC, x10^6/uL	8.73	7.60	8.56	7.78	8.69	7.91	8.91	7.42
Hemoglobin, gm/dL	15.19	14.28	14.63	14.73	14.88	14.73	15.31	13.96
Hematocrit, %	42.9	39.7	41.5	41.2	42.0	41.1	43.4	38.9

† Values are the means from 12 rats

The mean serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities for male rats in the 30 mg/kg/day group and female rats in the 100 and 1000 mg/kg/day groups were slightly, but not significantly, higher than control on day 169 of dosing (Table 30a). There were no other remarkable effects on any of the other serum chemistry parameters measured.

Table 30a. Serum ALT and AST †

Serum Chemistry Parameter	Dose Group (mg/kg/day)							
	0 (Control)		30		100		1000	
	M	F	M	F	M	F	M	F
Serum ALT, u/L	53.0	51.5	121.0	53.5	58.6	69.2	58.1	82.1
Serum AST, u/L	105.8	96.6	397.0	108.0	109.3	129.3	112.3	145.7

† Values are the means from 12 rats

The mean urine pH values for male and female rats in the 1000 mg/kg/day groups (6.58 and 6.54, respectively) were lower than control (7.54 for males and 6.96 for females) on day 94; similar differences in pH were observed on day 171 for males and females in the 1000 mg/kg/day group. Other urinary parameters were unaffected by eprosartan treatment.

Organ Weights

The mean absolute, but not relative, brain weights for the male groups dosed with 100 or 1000 mg/kg/day were slightly higher (4.3% and 4.6%, respectively) than control; the sponsor regards this finding as toxicologically insignificant. No other treatment-related effects were noted.

Gross and Microscopic Examination

No eprosartan-related macroscopic or microscopic findings were observed.

Note: The small increase above control incidence of renal lesions noted previously in rats given 1000 mg/kg/day for 30 days was not evident in this 6-month study in rats receiving the same dose.

Toxicokinetics: The mean values for Cmax and AUC increased with dose, but were not dose-proportional, particularly at the two higher doses (Table 30b). There was no evidence of drug accumulation. There were no apparent gender-related differences in any of the pharmacokinetic parameters.

Table 30b. Toxicokinetics of 6-Month Repeat Oral Doses of Eprosartan*

Toxicokinetic Parameter	Sex	Dose Group (mg/kg/day PO)					
		Day 1			Week 26		
		30	100	1000	30	100	1000
Cmax (µg/ml)	M	0.22	0.79	1.35	0.36	0.52	1.35
Tmax (hr)		1.0	1.0	1.0	1.4	1.1	1.2
AUC_{0-24} (µg.h/ml)		0.63	2.64	6.06	1.02	1.65	5.03
Cmax (µg/ml)	F	0.24	0.59	0.86	0.29	0.88	1.09
Tmax (hr)		1.0	1.3	1.0	1.1	1.1	1.2
AUC_{0-24} (µg.h/ml)		0.63	1.93	4.96	1.08	3.16	8.12

* Values are the means from 3 animals

14-Day Intravenous Toxicity Study in Dogs

Note: This toxicity study by the IV route was conducted to support a Phase I clinical bioavailability study in human subjects.

Study Facility: SmithKline Beecham Pharmaceuticals, King of Prussia, PA
Study No.: G91088 (Rpt. # TP-0013/SKF-108566/1)
Study Dates: Initiation of dosing: 12/04/91 Necropsy: 12/18/91

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male Beagle dogs (8.7-11.1 kg)

Drug Administration: Eprosartan mesylate (Lot #PL-20581-23)) was dissolved in phosphate buffer (pH=8) and administered intravenously via a saphenous vein; control rats received the drug vehicle.

Dose Levels: 0 (vehicle), 1, 10, and 30 mg eprosartan/kg (3/dose group).

Observations/Measurements: Animals were observed daily for mortality and clinical signs of toxicity. Body weights were measured predose and on days 1, 8 and 14 of the dosing period. Food consumption was measured on days 2 and 9 of dosing. Electrocardiograms were recorded and ophthalmoscopic examinations were performed predose and on day 14 of dosing. Blood was collected predose and on days 3 and 13 for hematology and clinical chemistry analyses. Urine was collected predose and on days 3 and 13 of the dosing period for urinalysis. Dogs were killed approximately 24 hours after the last dose (day 15) and necropsied. Macroscopic examination was performed and the major organs were removed and weighed. Sections of major organs and tissues from the control and high dose groups were examined for microscopic pathology. Tissues from the low and mid dose groups that showed macroscopic abnormalities were also examined for microscopic pathology.

Results:

Mortality and Clinical Signs of Toxicity
No dogs died during the study. Emesis occurred within 1 to 5 min in 2 of 3 dogs given 30 mg/kg/day (total of 3 episodes during the study; days of occurrence not stated). No other treatment-related toxicity was observed.

Body Weights and Food Consumption
Body weight gain and food consumption among eprosartan-treated groups were comparable to control.

ECG Recordings and Ophthalmoscopic Examinations
There were no eprosartan-related electrocardiographic effects and no drug-related ophthalmoscopic changes.

Hematology, Clinical Chemistry and Urinalysis
Hematology, clinical chemistry and urinalysis parameters were unaffected by eprosartan treatment and were comparable to those of control.

Organ Weights
The absolute, but not relative, mean liver weight of dogs given 30 mg/kg/day was slightly higher (15%) than the mean liver weight of vehicle treated dogs. In the absence of microscopic findings in the livers of any dogs, the sponsor considers this observation on absolute liver weight to be non-drug-related.

Macroscopic and Microscopic Examination
Gross or microscopic examination revealed no eprosartan-related pathology. Tissue irritation at the site of injection was comparable among all groups.

30-Day Oral Toxicity Study in Dogs

Study Facility: SmithKline Beecham Pharmaceuticals, King of Prussia, PA
Study No.: G91058 (Rpt. # TP-0011/SKF-108566/2)
Study Dates: Initiation of dosing: 10/09/91; Necropsy: 10/08/91

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male Beagle dogs (9.6-14.6 kg)

Drug Administration: Eprosartan mesylate(Lot# PL-20581-23) was placed in gelatin capsules and administered to dogs orally; control dogs were given empty gelatin capsules.

Dose Levels: 0 (empty capsule), 100, 300, and 1000 mg eprosartan/kg (3/dose group).

Observations/Measurements: Animals were observed daily for mortality and clinical signs of toxicity. Body weights were measured predose, weekly during the dosing period and at the end of the dosing period (day 31). Food consumption was measured weekly during the dosing period. Electrocardiograms were recorded and ophthalmoscopic examinations were performed predose and on day 29 of dosing. Blood was collected predose and on days 8 and 29 for hematology and clinical chemistry analyses. Blood was also collected at intervals up to 24 hours following dosing on days 1 and 30 for measurement of plasma eprosartan levels. Urine was collected predose and on days 8 and 29 of the dosing period for urinalysis. Dogs were killed

approximately 24 hours after the last dose (day 31) and necropsied. Macroscopic examination was performed and the major organs were removed and weighed. Sections of major organs and tissues from all dogs were microscopically examined.

Results:

Mortality and Clinical Signs of Toxicity
No dogs died during the study. Yellow colored feces were observed throughout the study in all dogs given 300 or 1000 mg eprosartan/kg/day and in 2 of 3 dogs given 100 mg eprosartan/kg/day; the yellow color was presumably due to elimination of drug-related material. Soft/mucoid/watery feces were observed in 2/3 dogs given 1000 mg eprosartan/kg/day and in 3/3 dogs given 300 mg eprosartan/kg/day. In the low dose group, the incidence (1/3) of soft/mucoid/watery feces was comparable to control.

Body Weight and Food Consumption
Body weight and food consumption were unaffected by eprosartan treatment and were comparable to control.

ECG Recordings and Ophthalmoscopic Examinations
There were no eprosartan-related electrocardiographic effects and no drug-related ophthalmoscopic changes.

Hematology, Clinical Chemistry and Urinalysis
On day 8 of dosing, average hemoglobin (Hb) concentrations, erythrocyte (RBC) counts and hematocrit (Hct) in dogs given 100, 300 or 1000 mg eprosartan/kg/day were lower than pretreatment and concurrent control values. Lower than control values for these parameters were also observed on day 29 in dogs given 300 and 1000 mg eprosartan/kg/day (Table 31).

Table 31. Effects on Hematologic Parameters

Hematologic Parameter	Dosing Period	Eprosartan Dose (mg/kg/day)			
		0 (Vehicle)	100	300	1000
RBC Counts ($\times 10^6$ /uL)	Pre-dose	7.01	7.70	7.05	7.14
	Day 8	7.52	6.43	7.37	6.66
	Day 29	7.02	7.00	6.68	6.16
Hemoglobin (gm/dL)	Pre-dose	16.03	17.67	16.20	15.93
	Day 8	17.17	14.93	14.63	14.97
	Day 29	16.27	16.47	15.67	14.00
Hematocrit (%)	Pre-dose	47.2	51.5	47.9	47.0
	Day 8	50.1	43.4	43.0	43.4
	Day 29	46.6	46.8	44.8	39.6

On day 29, there was a slight increase (1.4 to 1.9 fold) in serum urea nitrogen values above pretreatment values in 1 of 3 dogs given 100 or 300 mg/kg/day and in 2 of 3 dogs given 1000 mg/kg/day. No other eprosartan-related effects on clinical chemistry parameters were observed. No eprosartan-related effects on urinalysis parameters were observed.

Organ Weights
Organ weights among eprosartan-treated groups did not significantly differ from control.

Gross and Microscopic Examination
Gross examination revealed no grossly observable pathologies. Follicular cell hypertrophy was observed microscopically in the thyroid of one dog in the mid-dose group. This finding was not evident in high dose animals and the sponsor considered this to be incidental and unrelated to eprosartan treatment

Toxicokinetics
The mean Cmax and AUC values increased with dose, but not dose-proportionally. There was no evidence of drug accumulation over the 30-day dosing period (Table 32).

Table 32. Eprosartan Toxicokinetics in Dogs

Dose Group (mg/kg/day)	Cmax, ng/ml		AUC_{0-24}, ug.min/ml	
	Day 1	Day 30	Day 1	Day 30
100	851	1005	202	213
300	946	865	231	267
1000	2188	2449	624	557

6-Month Oral Toxicity Study in Dogs

Study Facility: SmithKline Beecham Pharmaceuticals, King of Prussia, PA
Study No.: G93012 (Rpt. # TP-0009/SKF-108566/1)
Study Dates: Initiation of dosing: 2/18/93; Necropsy: 8/20/93

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male and female Beagle dogs (7.9-12.7 kg)

Drug Administration: Eprosartan mesylate (Lot# BCT-L-02P, BCT-L-04P and BCT-L-05C)) was placed in gelatin capsules and administered to dogs orally; control dogs were given empty gelatin capsules.

Dose Levels: 0 (empty capsule), 30, 100, and 1000 mg eprosartan/kg (4/sex/dose group).

Observations/Measurements: Animals were observed daily for mortality and clinical signs of toxicity. Body weights were measured predose, weekly during the dosing period and terminally on the day of necropsy. Food consumption was measured predose and monthly during the dosing period. Electrocardiograms were recorded predose and on day 176 of dosing. Ophthalmoscopic examinations were performed predose and on day 180 of dosing. Blood was collected predose and on days 85 and 177 for hematology and clinical chemistry analyses. Blood was also collected at intervals up to 24 hours following dosing on days 22 and 181 for measurement of plasma eprosartan levels. Urine was collected predose and on days 85 and 177 of the dosing period for urinalysis. Dogs were killed approximately 24 hours after the last dose (day 182) and necropsied. Macroscopic examination was performed on all dogs and the major organs were removed and weighed. Sections of major organs and tissues from all dogs were examined for microscopic pathology.

Results

Mortality and Clinical Signs of Toxicity

No dogs died during the study. Yellow-colored feces, presumably due to presence of drug-related material, were observed in all dogs receiving 100 and 1000 mg eprosartan/kg/day and in 3/4 males and 2/4 females that received 30 mg eprosartan/kg/day. Emesis was observed in eprosartan-treated and control dogs occasionally during the study; however, the frequency of emesis (the total # of days emesis occurred/total number of observation days per group expressed as percent) was increased in male and female dogs given 1000 mg eprosartan/kg/day and was 9 % and 7%, respectively, over the course of the study compared to 3% and 5% for control males and females, respectively.

Body Weight and Food Consumption

Mean body weights among eprosartan-treated groups were comparable to control (Table 33). Food consumption was unaffected by eprosartan treatment.

Table 33. Body Weight

Dose Group (mg/kg/day)	Sex	Mean Body Weight (kg), n=4				
		Day 0	Day 49	Day 91	Day 140	Day184
0	M	11.1	11.6	12.2	12.5	10.9
30		11.3	11.5	12.1	12.4	11.8
100		11.5	12.5	13.1	13.9	13.2
1000		11.3	12.0	12.5	13.1	11.8
0	F	10.7	10.4	10.8	11.4	9.7
30		10.2	10.2	10.6	10.9	10.8
100		10.6	11.0	11.4	11.7	10.0
1000		10.9	10.8	11.5	11.8	11.6

ECG Recordings and Ophthalmoscopic Examination

Electrocardiograms showed no eprosartan-related effects and there were no eprosartan-related ophthalmoscopic changes in this study.

Hematology, Clinical Chemistry and Urinalysis

Hematologic (RBC counts, Hb and Hct) values among males and females treated with 100 and 1000 mg eprosartan/kg/day tended to be lower than concurrent or pre-treatment controls on day 85 and/or day 177 of dosing (Table 34; no statistical test conducted).

Table 34. Hematologic Parameters (n=4)

Hematologic Parameter	Eprosartan Dose (mg/kg/day)							
	0 (control)		30		100		1000	
	M	F	M	F	M	F	M	F
RBC Counts (x 10^6 /uL)								
Predose	6.99	6.89	6.69	6.60	6.53	6.72	6.65	6.74
Day 85	6.93	6.33	6.54	6.24	6.05	6.09	6.08	5.82
Day 177	7.17	6.51	6.44	5.76	5.98	5.85	6.58	5.79
Hemoglobin (gm/dL)								
Predose	16.3	16.6	16.0	15.3	15.4	15.9	15.4	16.0
Day 85	16.5	15.4	15.8	14.8	14.6	14.8	14.4	14.4
Day 177	16.8	15.6	15.3	13.3	14.2	13.8	15.3	13.9
Hematocrit (%)								
Predose	46.7	46.7	45.1	44.2	43.8	45.3	43.6	46.0
Day 85	49.0	45.2	47.4	44.6	43.5	43.4	43.0	42.3
Day 177	52.6	47.5	47.1	42.0	43.7	42.3	47.0	42.4

Clinical chemistry parameters were not significantly affected by eprosartan treatment.

The mean urine pH values for female dogs receiving 1000 mg/kg/day (pH=5.5 and 5.6 on day 85 and day 177, respectively) were lower than concurrent control.

Organ Weights

Mean absolute adrenal weight for females given 100 mg/kg/day was approximately 50% higher than concurrent control; Mean absolute adrenal weights for low- and high-dose females did not significantly differ from control. Relative adrenal weights for eprosartan-treated males and females did not significantly differ from control.

Gross and Microscopic Examinations

No eprosartan-related macroscopic pathologies were noted at necropsy. Microscopic examination did not reveal eprosartan-related histopathology.

Toxicokinetics

Cmax and AUC values increased non-dose-proportionally after dosing with eprosartan mesylate for 22 and 181 days. Peak plasma concentrations were observed 2 to 4 hours after dosing in most animals. Cmax and AUC values on day 181 were comparable to those on day 22 ; however, Cmax and AUC values for females given 100 and 1000 mg eprosartan/kg/day were 1.2 to 1.8 times higher than those of males receiving the same doses (Table 35).

Table 35. Eprosartan Toxicokinetics in Dogs

PK Parameter	Dosing Day	Dose Group, mg/kg/day					
		30		100		1000	
		M	F	M	F	M	F
Cmax, ng/ml	22 181	571 544	546 545	629 831	988 980	1902 1750	3369 2885
Tmax, hr	22 181	3.99 2.49	3.00 3.00	2.01 1.51	2.00 3.01	2.00 4.00	2.01 3.00
AUC_{0-24}, ng.hr/ml	22 181	2314 1890	2103 2183	2352 2362	3890 4235	14575 13400	24815 20331

1-Year Oral Toxicity Study in Dogs

Study Facility: SmithKline Beecham Pharmaceuticals, Welwyn, Herts, UK
Study No.: T94676 (Rpt. # SKF-108566/RED-1003R6/1)
Study Dates: Initiation of dosing: 10/31/94; Necropsy: 11/1/95

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male and female Beagle dogs (M=10.6-18.3 kg; F=9.7-13.6 kg)

Drug Administration: Eprosartan mesylate (Lot# BCT-K-11C, BCT-K-16C and BCT-K-17C) was placed in gelatin capsules and administered to dogs orally; control dogs were given empty gelatin capsules.

Dose Levels: 0 (empty capsule), 30, 100, and 1000 mg eprosartan/kg (4/sex/dose group).

Observations/Measurements: Animals were observed daily for mortality and clinical signs of toxicity. Body weights were measured predose, weekly during the dosing period and terminally on the day of necropsy. Food consumption was measured daily throughout the study. Electrocardiograms were recorded predose and during week 52 of the study. Ophthalmoscopic examinations were performed predose and during weeks 26 and 52 of the study. Blood was collected (via cephalic or jugular vein) at intervals up to 24 hours predose and during weeks 12, 26 and 51 for hematology and clinical chemistry analyses. Blood was also collected at intervals up to 24 hours following dosing during weeks 5 and 52 of the study for measurement of plasma eprosartan levels. Urine was collected directly from the bladder at necropsy for urinalysis. Dogs were killed approximately 24 hours after the last dose and necropsied. Macroscopic examination was performed on all dogs and the major organs were removed and weighed. Sections of major organs and tissues from all dogs were examined for microscopic pathology.

Results

Mortality and Clinical Signs of Toxicity

No dogs died during the study. There was a dose related increase above control incidence and frequency of loose mucoid and abnormally colored feces which continued throughout the treatment period. Fecal discoloration was most likely due to elimination of drug-related material. In addition, an increase above control incidence of emesis, generally within 1 hour of dosing, was noted in high dose males and females.

Body Weight and Food Consumption

Body weight (Table 36) and food consumption were not affected by eprosartan treatment.

Table 36. Body Weight

Dose Group (mg/kg/day)	Sex	Mean Body Weight, Kg (n=4)				
		Wk 1	Wk 13	Wk 26	Wk 39	Wk 52
0	M F	15.7 11.7	15.6 12.3	15.2 12.8	15.2 12.8	15.7 13.1
30	M F	13.6 11.7	13.6 12.7	13.1 12.8	12.9 12.6	13.5 12.9
100	M F	13.5 11.7	13.5 12.2	13.3 12.4	13.0 12.2	13.4 12.5
1000	M F	13.9 11.6	14.2 12.6	14.2 12.3	14.3 12.2	14.6 12.2

ECG Recordings and Ophthalmoscopic Examination

No eprosartan related effects on the electrocardiogram were observed. Ophthalmoscopic examination revealed no treatment-related ocular effects.

Hematology, Clinical Chemistry and Urinalysis

Male and female dogs given 1000 mg eprosartan/kg/day showed lower (no statistical test conducted) than pre-drug or control hematologic values occasionally during the study (Table 37). At 52 weeks, the hematologic parameters in males and females given 1000 mg eprosartan/kg/day were comparable to pre-drug and control values.

Table 37. Hematology Values

Hematologic Parameter	Eprosartan Dose, mg/kg/day							
	0 (Control)		30		100		1000	
	M	F	M	F	M	F	M	F
RBC, 10^{12}/L								
Week -1	6.78	6.96	7.09	7.44	6.87	6.90	7.01	6.94
Week 13	7.04	7.28	7.17	7.07	6.79	7.12	5.92	6.25
Week 26	7.47	7.72	7.38	7.96	6.87	7.58	6,74	7.30
Week 51	7.45	7.45	6.98	7.59	7.01	7.83	7.00	7.22
Hemoglobin, g/L								
Week -1	156	161	162	167	157	159	161	160
Week 13	165	173	168	166	159	170	142	151
Week 26	171	175	167	180	155	175	154	170
Week 51	172	175	161	177	160	182	167	171
Hematocrit, %								
Week -1	48.4	50.4	50.5	52.4	48.6	49.4	50.1	49.5
Week 13	49.5	52.8	51.0	49.5	48.0	51.3	44.3	45.5
Week 26	53.5	55.5	52.5	56.5	48.8	54.3	48.8	52.8
Week 51	53.3	54.3	49.3	54.4	49.3	55.3	51.3	52.3

The mean blood urea value for male dogs given 1000 mg eprosartan/kg/day was increased 1.8 fold in week 13 of dosing compared to a pre-drug value of 4.8 mmol/L or to the concurrent control value of 4.83 mmol/L. No other treatment-related effects on clinical chemistry parameters were observed.

No treatment-related effects on urinalysis parameters were observed.

Organ Weights
Organ weights in eprosartan treated animals were comparable to control.

Gross and Microscopic Pathology
Macroscopic examination revealed no grossly observable pathology. Microscopic examination revealed a slightly higher than control incidence of basophilic renal tubules in both males and females treated with 1000 mg eprosartan/kg/day (2/4 *vs* 1/4 for either sex).

Toxicokinetics
Plasma eprosartan Cmax and AUC values increased, non-dose-proportionally, with increasing dose (Table 38). The maximum plasma concentration was observed at approximately 2 to 4 hours after dosing. There were no marked differences in Cmax and AUC values between males and females. No evidence of systemic accumulation of eprosartan was detected (AUC values for Week 52 were comparable to corresponding values obtained during Week 5).

Table 38. Toxicokinetic Results*

Dose Group mg/kg/day	Sex	Cmax, ng/ml		AUC_{0-24}, ng.hr/ml	
		Wk 5	Wk 52	Wk 5	Wk 52
30	M	525	333	2583	2042
100		857	1025	7123	5631
1000		2520	1894	25238	17398
30	F	238	377	1033	2273
100		1121	1078	8590	5303
1000		3395	2453	25864	20524

* Values are the means derived from 4 dogs

Reproductive Toxicology

Fertility Study in Male Rats (Segment I/A)

Study Facility: SmithKline Beecham Pharmaceuticals, King of Prussia, PA
Study No.: G92107 (Study Rpt. # TP-1003/SKF-108566/1)
Study Dates: Initiation of dosing: 9/07/92; Last day of necropsy: 12/23/92

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Male and female Sprague-Dawley rats (M=65-70 days old; F=100-120 days old)

Drug Administration: Eprosartan mesylate (Lot #BCT-L-03P) was suspended in 1 % aqueous carboxymethylcellulose and administered to male rats orally by gavage daily for 105-108 days. Females rats were not dosed.

Dose Levels: 0 (vehicle), 30, 100 and 1000 mg eprosartan/kg/day (25M/dose group)

Note: High dose based on findings from a 7-day dose-rangefinding toxicity study in rats which showed that the 2000 mg eprosartan/kg dose yielded only a small increase in systemic exposure (AUC) from that seen with 1000 mg eprosartan/kg suggesting a saturation of drug absorption (see note on page 42 of this review).

Observations/Measurements: After 70 days of treatment, male rats were paired with untreated, virgin females for up to 7 days. Females were checked daily for presence of sperm in a vaginal lavage as evidence of mating (day of insemination considered as Day 0 of gestation). Inseminated females were separated from males and weighed. Males who failed to inseminate a female after 7 days were paired with second virgin female and checked daily for up to 7 days for evidence of insemination. All animals were observed daily for mortality and clinical sign of toxicity. Body weights of F_0 males were measured daily and food consumption was measured weekly. Surviving F_0 males were killed on day 105 to 108 of study. The left testis, ventral prostate and one seminal vesicle were removed,

weighed and sectioned for microscopic examination. The right testis was homogenized in cold saline and spermatids were counted using a hemocytometer. Sperm counts were obtained from homogenized suspensions of epididymis (expressed as number/gm epididymis). Male rats were necropsied and tissues with macroscopic findings were retained for microscopic examination. Females (F_0) were observed daily for mortality and clinical signs of toxicity. Body weights were obtained on GD 0, 7, 14 and 21. F_0 females were killed on GD 21 and necropsied. The ovaries were removed and the corpora lutea were counted. The uterus was removed and measurements made on number of implantation sites, resorptions, and live and dead fetuses. Each fetus was weighed, sex identified and examined for external abnormalities.

Results:

Mortality and Clinical Signs of Toxicity; F_0 Males
One male in the 30 mg/kg/day dose group died prior to dosing on day 48. No deaths occurred with the two higher doses of eprosartan and the low-dose death was considered to be unrelated to drug-treatment. No clinical signs of toxicity were observed during the study.

Body Weight and Food Consumption;F_0 Males
Mean body weight, body weight gains and food consumption among eprosartan-treated males were comparable to control.

F_0 Male Reproductive Performance
Mating and pregnancy incidences among eprosartan-treated groups were not statistically different from control (Table 39). The sponsor indicates that the slightly lower pregnancy incidence (74%) with the 1000 mg eprosartan/kg/day treatment was close to the historical control range (79% to 100% from nine studies) and, although the sponsor considered this to be toxicologically insignificant, this finding may be regarded as an equivocal effect of eprosartan on pregnancy rate.

Table 39. Reproductive Performance in Male Rats

Dose Group mg/kg/day	# Male Rats	Mating Incidence # males mated/#tested (%)	Pregnancy Incidence #females pregnant/# mated (%)
0	25	24/25 (96%)	22/24 (92%)
30	24*	23/24 (96%)	20/23 (87%)
100	25	23/25 (92%)	22/23 (96%)
1000	25	23/25 (92%)	17/23 (74%)

* One rat died prior to mating

Organ Weights
Absolute and relative weights of the testis, epididymis ventral prostate and seminal vesicle among eprosartan-treated groups were not significantly different from control.

Spermatogenesis
The number of testicular spermatids and cauda epididymal sperm cells in eprosartan-treated groups were comparable to control (Table 40).

Table 40. Spermatogenesis Parameters

Dose Group mg/kg/day	Spermatids/Testis $X10^9$	Spermatids/gm Testis $X10^9$	Sperm/Epididymis $X10^9$	Sperm/gm Epididymis $X10^9$
0	197	119	289	866
30	211	122	303	908
100	218	126	289	913
1000	211	121	296	813

Macroscopic Examination

No treatment-related gross pathology was observed at necropsy.

Examination of F_0 Females and F_1 Fetuses

Pregnant females from all groups showed comparable gestational weight gain and showed no toxicities attributable to their partner's treatment (Table 41). There were no statistically significant differences among groups in the numbers of corpora lutea, implantations, resorptions, dead or live fetuses/litter. Fetal weight was unaffected by parental eprosartan treatment (Table 42).

Table 41. Maternal Body Weight (gm)

Measurement Period	Eprosartan Dose Group, mg/kg/day			
	0 (Vehicle)	30	100	1000
GD 0	321	315	311	315
GD 7	346	341	338	338
GD 14	376	371	370	373
GD 21	473	469	471	473

Table 42. F_0 Female Cesarean Section Results

Parameter	Eprosartan Dose Group (mg/kg/day)			
	0 (Vehicle, n=22)	30 (n=20)	100 (n=22)	1000 (n=17)
Corpora Lutea, mean #	16.3	17.3	16.8	16.4
Implantations, mean #	15.2	15.6	15.7	15.4
Preimplantation loss, %[a,c]	6.3	10.2	6.5	9.2
Resorptions, mean #	0.9	0.9	1.0	1.8
Implants resorbed,%[b,c]	6.6	5.3	6.7	11.8
Live Fetuses, total #	14.3	14.7	14.7	13.6
# Male	6.3	6.8	6.5	6.5
# Female	8.0	7.9	8.2	7.1
Dead Fetuses, total #	0	0	0	0
Fetus Weight, mean gm.				
Male	5.44	5.40	5.40	5.32
Female	5.23	5.03	5.12	5.20

[a] % Preimplantation loss= (# Corpora Lutea - #Implants) X100/# Corpora Lutea

[b] % Implants Resorbed = # Resorptions X 100/# Implants

[c] Derived from individual % values and not computed using group means