Placebo controlled trials

Demographics

Patient demographics, by treatment group, for the patients enrolled into 1 of the 6 placebo controlled trials are shown below.

Demographics

	placebo (N=352)	eprosartan (N=1202)
mean age	57.7 years	57.9 years
age range	24-93 years	20-93 years
≥ 65 years	35.5%	33.6%
≥75 years	8.5%	6.9%
males/females	62.2/37.8%	63.1/36.9%
white/black/other	82.1/10.2/7.7%	84.0/11.1/4.8%
mean duration on drug	53.4 days	55.3 days

table 4.3 vol 405; appendices 3.2.B and 4.2

The demographics were similar for the placebo and eprosartan groups. The mean age was less than 60 years. Just under 7% were 75 years or older; the oldest patient was 93. More than one third of patients were female and roughly 10% of all patients were black. The mean duration on drug was 2 days more for the eprosartan group, implying that the time of study drop outs was similar for the active and placebo treatment groups. In addition to the above, most patients had DBP 104 mm Hg or less (the enrollment criterion for blood pressure in the majority of the trials was an average sitting DBP between 95 and 114 mm Hg, inclusive).

Duration of treatment

The 4 fixed dose studies were 4 or 8 weeks in duration; the 2 titration studies were 9 and 13 weeks.

Duration of treatment

	eprosartan N=1202
days on drug	n (%)
less than 29	131 (10.9)
29 to 60	698 (58.1)
61 to 90	321 (26.7)
more than 90	52 (4.3)

table 3.4 vol 405

In these trials, the majority of eprosartan patients were treated for at least 29 days.

3.0 Routine adverse events

The following description of adverse events collection is taken from the sponsor's statements in the Integrated Summary of Safety.

Adverse events included any noxious, pathologic or unintended change in anatomical, physiologic or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of the clinical trial whether associated with drug or placebo and whether or not considered drug related. This includes an exacerbation of pre-existing conditions or events, intercurrent illness, drug interaction of significant worsening of the disease under investigation.

Patients with adverse experiences that onset prior to the receipt of the indicated study medication or more than 24 hours after the last dose of study medication were excluded by the sponsor [usual window for adverse events is 7 days after the last dose]. For these evaluations, patients with one or more adverse experiences within a specific classification (eg, body system, dictionary preferred term for an adverse experience, time interval, treatment regimen) were counted only once within that classification. Each adverse experience was counted from the time of first onset; multiple episodes of the same event for a single patient were counted only once. [The investigator/patient term for the adverse event was assigned a term by the autoencoder using WHOART dictionary. If there was no match, a term was assigned by the sponsor.]

At each visit, reported adverse experiences were those either observed by the study investigator/nurse or reported spontaneously by the patients. According to the protocols, patients were asked non leading questions about how they were feeling. The only exceptions were studies 014 and 053 in which specific questions that were asked of both the patient and investigator regarding cough.

3.1 All trials

Adverse events by body system reported by more than 1% of patients who received eprosartan in 1 of the 15 Phase II/III hypertension trials are shown below.

Number and (percent) of patients

body system	eprosartan^ (N=2334)
at least 1 event	1488 (63.8)
Respiratory system	460 (19.7)
Central and peripheral nervous system	428 (18.3)
Body as a whole	423 (18.1)
Resistance mechanism	361 (15.5)
Musculoskeletal system	324 (13.9)
Gastrointestinal system	312 (13.4)
Metabolic and nutritional	208 (8.9)
Psychiatric	131 (5.6)
Urinary system	114 (4.9)
Skin and appendages	94 (4.0)
Cardiovascular, general/Heart rate, rhythm	72 (3.1)/83 (3.6)
Vision	62 (2.7)
Reproductive female/male	21 (2.3)/17 (1.2)
Vascular, extracardiac	36 (1.5)
Hearing and vestibular	33 (1.4)
Liver and biliary system	29 (1.2)
Autonomic nervous system	26 (1.1)

^patients with multiple adverse experiences may appear in more than one body system.
Table 5.1 vol 405

A total of 1488 (63.8%) of patients reported at least 1 adverse event. Adverse events in the respiratory, central and peripheral nervous system, body as a whole, resistance mechanism, and musculoskeletal system, in descending order of frequency, were reported most often.

Specific adverse events reported by 2% or more of the 2334 eprosartan study patients are shown below.

Number and (percent) of patients

Adverse event	Eprosartan N=2334
Headache	289 (12.4)
Upper respiratory tract infection	254 (10.9)
Myalgia	157 (6.7)
Coughing	129 (5.5)
Pharyngitis	123 (5.3)
Rhinitis	121 (5.2)
Dizziness	112 (4.8)
Injury	101 (4.3)
Sinusitis	97 (4.2)
Viral Infection	86 (3.7)
Fatigue	71 (3.0)
Bronchitis	69 (3.0)
Back pain	67 (2.9)
Diarrhea	65 (2.8)
Arthralgia	64 (2.7)
Chest pain	61 (2.6)
Pain	58 (2.5)
Dyspepsia	50 (2.1)

Table 5.2 vol 405

The 5 most commonly reported events were headache, upper respiratory infection (URI), myalgia, coughing, and pharyngitis, which probably reflects common complaints in the population rather than drug induced events. The rather high incidence of cough is likely the result of direct questioning about cough during 2 of the studies (014 and 053). For degree of severity, headache was the only adverse event that was reported as severe in 1% or more of the cases.

The addition of the new patients to the Safety Update increased the percent of patients who reported at least 1 adverse event from 63.8% to 68.2%[1] (1614/2367). The most commonly reported events

[1]Vol 993 page 38

were headache (13.4%, up from 12.4%) and URI (13.0%, up from 10.9%). Face edema was reported by 2 patients.

3.2 Controlled trials

3.2.1 Placebo controlled trials

Adverse events reported by at least 1% of patients in the eprosartan group and reported more frequently than in the placebo group are shown below. The placebo subtracted rate is also provided.

Patients with Adverse Experience

	Eprosartan (n=1202)	Placebo (n=352)	Placebo subtracted
Adverse Experience	n (%)	n (%)	%
at least 1 event	654 (54.4)	186 (52.8)	1.6
URI	95 (7.9)	19 (5.4)	2.5
Injury	29 (2.4)	4 (1.1)	1.3
Hypertriglyceridemia	15 (1.2)	0	1.2
Rhinitis	48 (4.0)	10 (2.8)	1.2
Pharyngitis	44 (3.7)	9 (2.6)	1.1
Depression	12 (1.0)	0	1.0
Urinary tract infection	16 (1.3)	1 (0.3)	1.0
Viral infection	29 (2.4)	5 (1.4)	1.0
Coughing	42 (3.5)	9 (2.6)	0.9
Arthralgia	22 (1.8)	4 (1.1)	0.7
Abdominal pain	18 (1.5)	3 (0.9)	0.6
Dyspnea	15 (1.2)	2 (0.6)	0.6
Fatigue	18 (1.5)	4 (1.1)	0.4
Palpitation	14 (1.2)	3 (0.9)	0.3
Back pain	16 (1.3)	4 (1.1)	0.2
Chest pain	25 (2.1)	7 (2.0)	0.1
Pain	14 (1.2)	4 (1.1)	0.1

Table 5.7 vol 405

The placebo subtracted rate for eprosartan patients reporting at least 1 adverse event was 1.6%. Individual adverse events reported by > 1% of eprosartan patients and reported >1% more often in the eprosartan group compared to the placebo group were URI, injury, hypertriglyceridemia, rhinitis, and pharyngitis. Most of the adverse events reported more often in the active treatment group were respiratory complaints. Adding together these events (URI, rhinitis, pharyngitis, viral infection, and coughing) produces a rate of 21.5% (258/1202) compared to 14.8 % (52/352) for placebo. The adverse event "injury" is somewhat alarming but other events that could be indicative of hypotension such as dizziness and syncope were rarely reported. Overall, the differences in reporting rates between eprosartan and placebo for all events were small.

In summary, while many patients reported adverse events, the difference between the overall rate for placebo and active treatment groups was negligible. The events differed slightly in the all eprosartan group compared to the events reported by eprosartan patients in the placebo controlled trials. Although the events with the largest difference between drug and placebo tended to be associated with the respiratory system, an examination of only the placebo controlled trials reveal few differences in rates for individual events between drug and placebo. In general, the use of eprosartan up to 1200 mg provoked few adverse events.

3.2.1.a Dose response

Adverse events reported in the 6 placebo controlled trials were examined for a dose response relationship. Since some patients received more than 1 dose of eprosartan in a study, those patients who reported a specific adverse experience at more than one dose of eprosartan appear more than once in the table below. The events are limited to those reported by at least 3% of patients in any active treatment group. For simplicity, events reported for patients receiving the 50 (n=91), 100 (n=26), and 300 (n=22) mg doses are not included in the following table.

Number and (percent) of patients

		eprosartan total daily dose (mg)				
adverse event	placebo n=352	200 n=205	400 n=512	600 n=317	800 n=243	1200 n=72
at least 1 event	186 (52.8)	95 (46.3)	219 (42.8)	142 (44.8)	128 (52.7)	34 (47.2)
Headache	38 (10.8)	15 (7.3)	44 (8.6)	17 (5.4)	27 (11.1)	7 (9.7)
URI	19 (5.4)	13 (6.3)	31 (6.1)	18 (5.7)	18 (7.4)	4 (5.6)
Myalgia	14 (4.0)	5 (2.4)	13 (2.5)	10 (3.2)	13 (5.3)	3 (4.2)
Pharyngitis	9 (2.6)	10 (4.9)	11 (2.1)	10 (3.2)	8 (3.3)	1 (1.4)
Rhinitis	10 (2.8)	10 (4.9)	11 (2.1)	3 (0.9)	13 (5.3)	1 (1.4)
Dizziness	13 (3.7)	2 (1.0)	12 (2.3)	6 (1.9)	10 (4.1)	3 (4.2)
Sinusitis	12 (3.4)	8 (3.9)	8 (1.6)	8 (2.5)	6 (2.5)	1 (1.4)
Viral infection	5 (1.4)	2 (1.0)	10 (2.0)	6 (1.9)	6 (2.5)	3 (4.2)
Diarrhea	9 (2.6)	8 (3.9)	8 (1.6)	4 (1.3)	4 (1.6)	2 (2.8)
Chest pain	7 (2.0)	1 (0.5)	7 (1.4)	11 (3.5)	3 (1.2)	1 (1.4)
Arthralgia	4 (1.1)	3 (1.5)	6 (1.2)	1 (0.3)	8 (3.3)	1 (1.4)

Table 12.5 vol 406 and amendment 10 dated 12-16-96

The percent of patients reporting at least 1 adverse event was greater in the placebo group than in the active treatment group at these doses and no individual adverse event showed a pattern consistent with a dose response.

The following table shows the placebo subtracted rates for those events that were reported more often in the 1200 mg group than the placebo group.

Percent of patients, placebo subtracted

	total daily dose eprosartan (mg)				
	200 n=205	400 n=512	600 n=317	800 n=243	1200 n=72
at least 1 event	-6.5	-10.0	-8.0	-0.1	-5.6
Viral infection	-0.4	0.6	0.5	1.1	2.8
Injury	1.8	0.1	1.7	0.5	1.7
Dizziness	-2.7	-1.4	-1.8	0.4	0.5
Arthralgia	0.4	0.1	-0.8	2.2	0.3
URI	0.9	0.7	0.3	2.0	0.2
Myalgia	-1.6	-1.5	-0.8	1.3	0.2
Diarrhea	1.3	-1.0	-1.3	-1.0	0.2

Table 12.5 vol 406

The percent of patients reporting any adverse event was higher in the placebo group than any of the eprosartan groups. No adverse event convincingly gives any indication of being dose-related; however the number of patients in the highest treatment group is relatively small.

3.2.1.b Dosing regimen

The sponsor conducted both once daily and twice daily studies with eprosartan. The table below shows the total number of patients who reported at least one adverse event by dosing regimen. The rates for dizziness are also included because, if there is an excessive blood pressure drop with the dose given once a day, one would expect a higher rate of dizziness compared to the bid group.

Percent of patients

	total daily dose of eprosartan					
	400 mg		600 mg		800 mg	
	bid n=331	qd n=181	bid n=187	qd n=130	bid n=131	qd n=112
at least 1 event	39.6	48.6	46.5	42.3	58.0	46.4
dizziness	2.1	2.8	1.1	3.1	4.6	3.6

Tables 12.6 and 12.7

There was no consistent pattern in the percent of patients reporting adverse events who received eprosartan as either once or twice a day dose. The reporting of dizziness, an event that could be expected to

be sensitive to dosing regimen, was only slightly different when eprosartan was given once or twice daily. These data indicate that, based on safety, there is no difference between giving eprosartan once or twice daily.

3.2.2 Active controlled trials

Enalapril

There were 3 studies (014, 053, 047) that used enalapril as the control agent with one of the studies also having a concomitant placebo control (053). All studies were double blind, randomized, with parallel groups. Two of the studies (014 and 053) were designed specifically to evaluate the effect of the 2 active agents on cough (see section 3.3). The third study (047) tested these agents in patients with moderately severe hypertension (see section 9.5).

The table below shows the number and percent of patients who reported adverse events in the 3 studies combined, by treatment group. Only those events that were reported by than 4% in the eprosartan group are included.

Number and (percent) of patients

	eprosartan 200-300 mg bid n=369	enalapril 5-40 mg qd n=368	placebo n=45
at least one event	262 (71.0)	278 (75.5)	22 (48.9)
headache	50 (13.6)	53 (14.4)	5 (11.1)
pharyngitis	49 (13.3)	73 (20.4)	6 (13.3)
coughing	47 (12.7)	82 (22.3)	9 (20.0)
rhinitis	39 (10.6)	50 (13.6)	3 (6.7)
myalgia	37 (10.0)	23 (6.3)	2 (4.4)
URI	37 (10.0)	50 (13.6)	5 (11.1)
dyspnea	17 (4.6)	18 (4.9)	1 (2.2)
dizziness	16 (4.3)	23 (6.3)	1 (1.1)
fatigue	15 (4.1)	22 (6.0)	0

table 5.14 vol 405

Overall, the reporting of adverse events was similar for the 2 active treatment groups with the exceptions of coughing and pharyngitis which were reported 1.5 to 1.8 times more often than the eprosartan group.

The percent of patients who withdrew for adverse events was higher for the enalapril group (7.9%,

29/368) compared to eprosartan (4.9%, 18/369). Numbers are from the individual study reports.

Overall, the safety of enalapril and eprosartan is similar except for cough which is reported more frequently by the enalapril patients. This finding is consistent with other angiotensin II receptor antagonists. Drug induced cough is discussed in more detail in section 3.3.

Sustained-release nifedipine

Study 041 randomized patients to either eprosartan 200 mg bid or sustained-release nifedipine 60 mg qd for 6 weeks with titration to 300 mg bid and 90 mg qd, respectively, if needed for blood pressure control. This was followed by a 6 week period during which those who did not respond to monotherapy received combination therapy. The table below shows the events reported by more than 3% of either monotherapy treatment group. Also shown are the event rates for the group who received the combination.

Number and (percent) of patients

	randomized treatment groups		
adverse event	eprosartan n=103	nifedipine n=102	nifed/epro combination n=71
at least 1 event	38 (36.9)	57 (55.9)	38 (53.5)
myalgia	8 (7.8)	6 (5.9)	5 (7.0)
headache	7 (6.8)	20 (19.6)	7 (9.9)
dependent edema	2 (1.9)	13 (12.7)	3 (4.2)
arthralgia	1 (1.0)	4 (3.9)	0
coughing	0	4 (3.9)	3 (4.2)

Table 5.20 vol 405

More adverse events were reported by patients receiving nifedipine compared to patients receiving eprosartan (55.9% vs. 36.9%). Reports of headache and dependent edema were much more common in the nifedipine group, and, although to a lesser extent, in the combination therapy.

The percentage of patients who withdrew from the study because of an adverse event was 8.8% (9/102) for nifedipine and 5.8% for eprosartan (6/103) (from study report). However, the relevance of these results is influenced by the dose ranges used in the study. In this study, for instance, there was a much higher percentage of patients randomized to eprosartan who needed to have nifedipine added on to control blood pressure than the converse (48.5% vs. 20.6%). The highest dose of nifedipine used in this trial (90 mg) is the highest dose recommended by the package label. The maximum dose for eprosartan, on the other hand, will be above 300 mg bid.

3.2.3. HCTZ as background

Study 016 was a double-blind, placebo controlled, parallel group study in which hypertensive patients on HCTZ 25 mg were randomized to eprosartan 50 mg, 100 mg, or placebo bid for 4 weeks. The main objective was to compare blood pressure lowering effects of eprosartan and placebo with HCTZ 25 mg as background medication.

The routine adverse events that were reported by more than 2% of eprosartan study patients, by treatment group, are shown below.

Number and (percent) of patients

	eprosartan 50 mg bid/HCTZ n=53	eprosartan 100 mg bid/HCTZ n=51	placebo/HCTZ n=52
at least 1 adverse event	27 (50.9)	22 (43.1)	21 (40.4)
URI	2 (3.8)	6 (11.8)	3 (5.8)
headache	7 (13.2)	3 (5.9)	5 (9.6)
back pain	3 (5.7)	2 (3.9)	2 (3.8)
dizziness	2 (3.8)	2 (3.9)	2 (3.8)

table 26 from the study report

The total number of patients reporting adverse events was similar for placebo/HCTZ and eprosartan 100 mg/HCTZ and somewhat higher for eprosartan 50 mg/HCTZ, probably an aberration. Nothing in the individual adverse events is unexpected and, from this study, the use of HCTZ with eprosartan, at least with these low doses of eprosartan, does not present safety concerns.

There were 2 withdrawals because of adverse events, 1 in placebo/HCTZ and 1 in eprosartan 50 mg/HCTZ.

The use of thiazides can result in hypokalemia, hyponatremia, hypochloremia, hypercalcemia, and hyperuricemia, as well as other metabolic disturbances. Concomitant use of eprosartan could reduce or exacerbate these conditions. The table below shows the mean changes from baseline at endpoint for serum potassium, sodium, chloride, calcium, and uric acid (only includes data from patients with both baseline and endpoint data) and percent of patients in each treatment group who had normal values at baseline that became abnormal at endpoint.

Mean change from baseline at endpoint

lab parameter	eprosartan 50 mg bid/HCTZ n=53	eprosartan 100 mg bid/HCTZ n=51	placebo/HCTZ n=52	percent of patients normal at baseline and abnormal+ at endpoint pl/epro 50 mg/ epro 100 mg
potassium (mmol/l)	0.01	-0.34	0.09	(low) 6/10/4
sodium (mmol/l)	-0.23	-0.37	0.04	(low) 0/4/2
chloride (mmol/l)	-0.11	0.02	0	(low) 2/4/4
calcium (mmol/l)	-0.01	0.01	0.01	(high) 4/0/2
uric acid (micromol/L)	6.73	5.36	-8.35	(high) 4/13/6

+() denotes direction of abnormality
tables 22, 23, 37 and 38 from the study report

The use of the combination eprosartan and HCTZ had little consistent effect on the electrolyte and uric acid values compared to the use of HCTZ. The doses of eprosartan used in this study were quite small; combinations with higher doses of eprosartan and lower doses of HCTZ would be worth investigating.

3.3 Cough

All placebo controlled trials

The placebo subtracted incidence rate of reports of any cough from the eprosartan patients (n=1202) who participated in the 6 placebo controlled trials was 0.9%. When reports of cough, URI, rhinitis, pharyngitis, sinusitis are added together from these trials, the placebo subtracted rate becomes 5.4% (table 5.7 vol 405).

All enalapril controlled trials

There were 3 positive control studies in the Phase II/III hypertension program that used enalapril as the comparator; 2 studies (014 and 053 discussed below) evaluated cough and 1 study (047 discussed in section 8.6) evaluated blood pressure response in moderately severe hypertension. The incidence rates of reported adverse events that could reflect cough for the 3 studies combined, by treatment group, are shown below.

Number (and percent) of patients

	eprosartan n=369	enalapril n=368
at least 1 adverse event	262 (71.0)	278 (75.5)
at least 1 adverse event in the respiratory system	120 (32.5)	150 (40.8)
pharyngitis	49 (13.3)	75 (20.4)
coughing	47 (12.7)	82 (22.3)
URI	37 (10.0)	50 (13.6)
rhinitis	39 (10.6)	50 (13.6)
sinusitis	9 (2.4)	8 (2.2)

table 5.14, appendix 5.3.1 vol 405

The percents of patients reporting at least 1 adverse event were similar for both treatment groups. The percent of enalapril patients reporting cough, however, was nearly twice the rate of the eprosartan group. For the other events that could be associated with cough, all but sinusitis were reported more frequently by enalapril patients.

The percent dropping out for cough in the 3 studies was higher in the enalapril group (2.4%, 9 patients) compared to eprosartan (0.8%, 3 patients). [From individual study reports.] In the revised 8.3. A appendix including data from the Safety Update (amendment 45 submitted 5-6-97), 15.1% of eprosartan patients (N=2367) in Phase II/III hypertension study dropped out for cough.

Studies designed to assess cough

The sponsor conducted 2 studies that were specifically designed to compare the incidence of persistent, nonproductive (dry) cough associated with study medication in eprosartan treated patients with enalapril treated patients.

Study 014

This was a randomized, enalapril controlled, parallel group study with a 3 to 5 week single blind placebo run in phase followed by a 26 week double blind, active treatment phase. The doses of both drugs were titrated to antihypertensive effect with the range being 5-20 mg qd for enalapril and 200-300 mg bid for eprosartan. HCTZ could be added after the study drug was titrated to maximum dose. Pulmonary assessment (a detailed cough questionnaire) was obtained from patients and investigators at baseline and periodically throughout the double blind phase. The primary efficacy variable was a specific type of cough, referred to as "definite cough" that was captured by the pulmonary questionnaire investigator assessment (see appendix 3). There was also a self-administered quality of life questionnaire (QOL) that assessed cough.

Study patients were males and females at least 18 years of age with essential hypertension (sitting DBP ≥ 95 mm Hg and ≤114 mm Hg). There was no inclusion criterion relating to cough such as a history of ACE inhibitor induced cough. Patients were excluded if they had emphysema or chronic bronchitis with daily cough and sputum production, asthma with a dry cough, had a URI with symptoms within 2 weeks of screening, or were on drugs known to influence cough. Patients had to be free of an URI prior to entry into the double blind phase.

There were numerous amendments which dealt with the definition of the cough of interest and a change in the primary analysis. The following statements are from the final study report:

Amendment 3 - April 24, 1996 (protocol approval date was August 26, 1994)
The rationale for this amendment was to

- *add forms of cough that may be relevant to this study as they are reported in the literature*
- *identify the type of cough defined in the primary and secondary clinical parameters and to name additional forms of cough that may be relevant to this study as they are reported in the literature*
- *identify the type of cough defined in the primary clinical parameter in order to distinguish it from other forms of cough in the protocol and subsequent study reports*
- *identify other forms of cough that may be relevant to this study as they are reported in the literature*
- *clarify that the definition of definite cough of interest only required that the cough NOT be related to the upper respiratory tract infection*
- *to define probable cause of interest, possible cough of interest, and tickle in throat and to note that the adverse experience pages will also be examined by case report review to look for other potential coughs of interest that computer algorithms may not find*
- *identify methodology for the analysis of the additional types of cough and to delete the reference to "exploratory fashion"*

Note: This amendment was implemented before the blind was broken on May 3, 1996.

It is always of concern when the primary endpoint is altered late in the progress of the study. However, there was no obvious influence of the amendments on the outcome of the trial.

In order for a cough to be considered as the "definite cough of interest," the responses to questions #6 and #12 on the pulmonary questionnaire-investigator's assessment in the case record form (appendix 3) had to indicate a persistent and dry cough, respectively. In addition, the cough had to be present for at least 2 weeks unless the patient voluntarily discontinued because of coughing before completing 2 weeks of treatment after the cough began (question #13), and no relevant cough could be the result of an upper respiratory infection, as determined by the investigator (question #17).

The primary analysis, as stated in the protocol, was the incidence of cough at visits 2 and 4 (and before HCTZ was added) including patients who withdrew for cough provided they had been treated with study drug had been for at least 2 weeks and there was a cough assessment, or they had been withdrawn for cough associated with treatment.

Results

The study was conducted at 42 sites in U.S., Canada, Western Europe, and South Africa. There were 528 randomized patients, 264 to each treatment arm. The number of patients at various time points of the study are shown below.

Number of patients

	eprosartan n=264	enalapril n=264
randomized	264	264
visit 4+	252	241
"cough endpoint"	259	260
titration endpoint	263	263
number not included in cough analyses	5	3

+after this visit HCTZ could be added if needed
table 10 vol 251

The majority of randomized patients were male (56.3%), white (86.4%), and less than age 65 (76.3%). Treatment groups were well balanced at baseline for age, sex, race, weight, height, and severity of hypertension. Slightly more eprosartan patients had a smoking history compared to enalapril patients (13.7% and 11.8%, respectively); the rates for patients reporting smoker's cough, however, were nearly identical (1.1% and 1.5%, respectively). A history of ACE inhibitor induced cough was reported by 0.4% of patients randomized to eprosartan and 1.1% of patients randomized to enalapril.

The table below shows the number and percent of withdrawals from the double blind phase, by treatment group.

Number and (percent) of patients

	eprosartan n=264	enalapril n=264
any reason	34 (12.9)	47 (17.8)
any reason except "other"	27 (10.2)	35 (13.3)
adverse event	15^ (5.7)	23+ (8.7)
Cough	2 (0.8)	7 (2.7)
lack of effect	13 (4.9)	12 (4.5)
other	7 (2.7)	12 (4.5)

+number is 24 (9.1%) in table 48
^includes patient 014.200.01854
Tables 13 and 48 vol 251

A higher percentage of enalapril patients dropped out of the study for any reason compared to eprosartan patients. For drop outs resulting from cough, the difference between treatment groups was more than 3 fold.

There were 21 (8.0%) eprosartan and 17 (16.4%) enalapril patients who took narcotics or antitussives (a protocol violation) during the study.

Primary efficacy analysis

According to the protocol, the primary efficacy analysis was the comparison of incidence rates at visits 2 (week 6) and 4 (week 12) of the double blind phase (and before start of HCTZ) plus drop outs for cough. The statistical test used was the Cochran-Mantel-Haenszel controlling for center effect. The results are shown below.

definite cough-time points	eprosartan n=264	enalapril n=264	relative risk (95% CI)	p-value
titration week 6^	2/255 (0.8%)	4/253 (1.6%)	2.03 (0.41, 10.2)	0.432
titration week 12^^	2/248 (0.8%)	7/237 (3.0%)	4.03 (0.98, 16.7)	0.057

^visit 2
^^visit 4
Table 24 vol 251

At the protocol specified time points, there were 2 more enalapril patients than eprosartan patients who coughed but the differences were not statically significant. By week 12 the number of enalapril

patients who coughed increased and the difference approaches significance, but there was no correction for multiple comparisons.

Additional efficacy analyses

The table below compares the rate of definite cough of interest at other time points during the double bind phase.

definite cough-time points	eprosartan n=264	enalapril n=264	relative risk (95% CI)	p-value
study endpoint+	4/259^ (1.5%)	14/261# (5.4%)	3.42 (1.26, 9.35)	0.017**
any time prior to introduction of HCTZ+	4/259^ (1.5%)	14/261# (5.4%)	3.45 (1.26, 10.0)	0.018**
entire double blind treatment period	4/259^ (1.5%)	16/261# (6.1%)	3.85 (1.48, 10.3)	0.007**

+last available visit prior to the addition of HCTZ
^missing 5 patients
#missing 3 patients
**statistically significant at the 0.05 level using Cochran-Mantel-Haenszel methodology controlling for center effect.
table 24 vol 251

Patients taking enalapril were more than 3 times as likely to have "definite cough" compared to those taking eprosartan. The differences between the groups at these time points were statistically significant, but, again, without corrections for multiple comparisons. Cough data for a total of 8 patients are not included in the analyses. If one assumes that the 5 missing eprosartan patients coughed and the 3 missing enalapril patients did not cough, then, at the study endpoint, the cough rates are 3.4% for eprosartan and 5.3% for enalapril (p=0.016, per Dr. Nuri).

The incidence rates for maximum cough (including definite cough, probable and possible cough, and tickle in throat), as assessed by the investigator, were always higher for the enalapril group compared to eprosartan. At the time point prior to the introduction of HCTZ, the rate for enalapril was nearly twice the rate for eprosartan (19.9% and 10.8%, respectively; p=0.005) [from table 25 vol 251.]

Cough collected in QOL

The number and percent of patients who reported any cough in the quality of life questionnaire at baseline, the end of monotherapy, and the end of the study, by treatment group, are shown below.

Number and (percent) of patients

any cough	eprosartan n=261	enalapril n=262
at baseline	5 (1.9)	5 (1.9)
at end of monotherapy	6 (2.3)	25 (9.5)
at end of study	8 (3.1)	20 (7.6)

table 32 vol 251

The numbers of patients reporting cough at baseline were identical for the 2 treatment groups; at each time point after the start of treatment, a higher percentage of patients on enalapril reported cough compared to eprosartan patients. However, the cough reported by 5 enalapril patients at the end of monotherapy was transient and had disappeared by the end of the study.

Cough as adverse event

The number and percent of study patients who reported cough as well as any event that could be associated with cough are shown below.

Number and (percent) of patients)

	eprosartan n=264	enalapril n=264
at least 1 adverse event	201 (76.1)	213 (80.7)
at least 1 adverse event in the respiratory system	99 (37.5)	117 (44.3)
pharyngitis	44 (16.7)	64 (24.2)
coughing	34 (12.9)	59 (22.3)
URI	33 (12.5)	43 (16.3)
rhinitis	33 (12.5)	43 (16.3)
sinusitis	8 (3.0)	5 (1.9)

Tables 37 and 38 vol 251

While there were nearly twice as many enalapril patients than eprosartan patients who reported cough and nearly all of the other events were also reported more often by the enalapril group, the reporting rates for at least 1 adverse event were similar between treatment groups.

Overall, while this study did not show that there was a significant difference between the treatment induced cough as specified by the protocol, there is convincing evidence that eprosartan, like other angiotensin II receptor blockers, causes less cough than enalapril. However, the relevance of this outcome

is questioned when there is little difference in the reporting rates for any adverse event for the 2 treatment groups (76.1% eprosartan and 80.7% enalapril) and in the drop out rates for adverse events and lack of effect (10.2% eprosartan and 13.3% enalapril).

Study 053

This study was a 6 week, double blind, placebo controlled, multicenter, parallel group comparison of the cough rates in hypertensive patients taking eprosartan or enalapril who demonstrated an ACE inhibitor induced cough. Following a single blind placebo run-in period, all patients with qualifying blood pressure measurements entered a single blind enalapril challenge period during which they received enalapril 20 mg capsules (10 mg for the initial 3 days) for 3 to 4 weeks. Those patients who developed either

- a cough that satisfied the criteria for an ACE inhibitor induced cough defined as persistent (question #6), nonproductive (question #12) and not due to upper respiratory infection (question #17). The cough also must have been present for at least 2 weeks (question #13) of the Pulmonary Questionnaire-investigator assessment (see appendix 4), or

- a cough that satisfied the above criteria but which could not be tolerated for 2 weeks

during this challenge period were qualified for randomization provided the cough resolved during a washout period. In contrast to study 014, patients in this study were selected for their proven ability to cough when placed on enalapril therapy

Qualified patients were then randomized to either placebo, eprosartan 300 mg bid or enalapril 20 mg qd and treated for 6 weeks with biweekly clinic visits. During this double blind phase, patients who were withdrawn or who dropped out prematurely underwent a pulmonary assessment by the investigator as soon as possible, by telephone interview if necessary. The patients who discontinued for severe coughing were included in the definite cough incidence rate.

Study patients were males or females and at least 18 years old, had a history of cough induced by treatment with an ACE inhibitor, and developed cough during enalapril challenge. They had to have essential hypertension (DBP $\geq$95 and $\leq$114 mm Hg). Notable exclusions were patients with emphysema or chronic bronchitis with daily cough and sputum production, asthma with a dry cough, URI and symptoms within 2 weeks of screening (patients who had recent acute URI but were symptom-free for two weeks before screening could be included; patients were also required to be free of URI by the end of the placebo run in period), and those taking concomitant medication known to influence cough.

The main efficacy variable in the study was the incidence of a specific cough defined as: a) persistent, b) dry, and c) associated with study medication, as assessed by the investigator using the pulmonary questionnaire (see appendix 4). The cough had to be present for at least 2 weeks during double blind treatment unless the patient withdrew from the study because of it. The questionnaire used in this study was similar to the one used in study 014 (see appendix 3).

The primary efficacy analysis as stated in the protocol was the comparison of the incidence of

investigator assessed definite cough between treatment groups at the end of the 6 week double blind treatment period (this included patients who withdrew from the double blind phase if they received double blind medication for at least 2 weeks and had a cough assessment as well as patients who withdrew for cough associated with treatment). Patients who had cough that persisted for at least 2 weeks during the double blind treatment phase were also included in the primary analysis even if the cough was not present at the end of the double blind phase.

There was no protocol amendment that affected the primary efficacy endpoint.

Results

The study was conducted at 19 U.S. centers. There were 226 patients who received single blind placebo, 158 who entered the enalapril challenge period, 140 who entered the placebo wash out, and 136 who were randomized (45 received placebo, 46 received eprosartan, and 45 received enalapril). Of the randomized patients, 74.3% were less than 65 years of age, 52.2% were male, and 66.9% were white. The mean duration of exposure was 37.5, 39.6, and 39.4 days for placebo, eprosartan, and enalapril groups, respectively.

The protocol did not stipulate the severity of cough required for randomization although the information was collected on the case report form (question # 14 appendix 4). The table below shows the severity of cough at the end of the enalapril challenge phase (and prior to entry into the double blind phase) by randomized treatment group.

Number and (percent) of patients

cough severity at the end of the enalapril challenge	eprosartan n=46	enalapril n=45	placebo n=45
none	3 (6.5)	5 (11.1)	1 (2.2)
mild	18 (39.1)	14 (31.1)	15 (33.3)
moderate	21 (45.7)	25 (55.6)	24 (53.3)
severe	4 (8.7)	1 (2.2)	5 (11.1)

data source table 14.2.1 vol 300

A substantial number of patients (56/136, 41.2%) who were randomized either had no cough or only had a mild cough during the enalapril challenge phase. This could explain the surprisingly low number of patients who coughed when rechallenged with enalapril.

Of the 136 patients who were randomized to double blind study drug, 28 withdrew from the study prematurely. The number and reason for patient withdrawals, by treatment group, are shown below.

Number and (percent) of patients

withdrawal	eprosartan n=46	enalapril n=45	placebo n=45
any reason	7 (15.2)	10 (22.2)	11 (24.4)
adverse event	1 (2.2)	4 (8.9)	2 (4.4)
Cough	1	2	0
lack of effect	1 (2.2)	1 (2.2)	2 (4.4)
other	5 (10.9)	5 (11.1)	7 (15.6)

tables 10 and 39 vol 300

While a lower percentage of eprosartan patients dropped out of the study compared to both placebo and enalapril patients, most of the drop outs were for reasons other than adverse event or lack of effect. Only 2 enalapril patients dropped out because of cough, unusually few considering this was an enriched population.

Primary efficacy analysis

The number and percent of patients with definite cough at study endpoint (end of double blind phase plus drop outs for cough) are shown below.

Number and (percent) of patients

	eprosartan n=46	enalapril n=44#	placebo n=45
definite cough-study endpoint+	1 (2.2)	3 (6.8)	1 (2.2)

#data missing for 1 patient
+last on-therapy assessment
tables 20 and 21 vol 300

At the study endpoint (end of the 6 week double blind phase), there were more enalapril patients with investigator assessed definite cough compared to the other groups but this difference was small and not statistically significant. The removal of 24 patients enrolled at center 036 from the efficacy analysis had only a minor effect on the results (per Dr. Nuri).

Additional efficacy analyses

The table below shows the cough incidence rates at any time during the double blind phase (includes patients with a definite cough that persisted for 2 weeks but was not present at the end of the double blind period) are shown below.

Number and (percent) of patients

	eprosartan n=46	enalapril n=44#	placebo n=45
definite cough-entire double blind period	1 (2.2)	9 (20.5)**	2 (4.4)

**p=0.008 for eprosartan versus enalapril using modified Bonferroni procedure
tables 20 and 21 vol 300

Evaluating the entire double blind phase, more patients had definite cough on enalapril compared to the other 2 treatment groups and the difference between eprosartan and enalapril was significant (p=0.008). It is disturbing that less than a quarter of these highly selected patients coughed when rechallenged with enalapril and 6 of the enalapril coughers had their cough resolve while still on drug.

The table below shows the number of patients with investigator assessed definite cough at each time point during the double blind phase of the trial.

Number of patients

	eprosartan n/N	enalapril n/N	placebo n/N
definite cough-week 2	1/46	5/42	0/41^
definite cough-week 4	1/40+	7/44+	1/40
definite cough-week 6	1/38	3/36	1/34

^revised from 44 in amendment 54 dated 7-2-97
+number revised in fax dated 5-28-97 and amendment 54 dated 7-2-97
table 20 vol 300

At every time point, there were more enalapril patients with definite cough compared to the other treatment groups. Again, the number of coughers in the enalapril group is unexpectedly small.

Secondary efficacy parameters were numerous and included the incidence of probable cough, possible cough, and tickle in throat. Some of the results are shown below.

Number and (percent) of patients

coughs	eprosartan n=46	enalapril n=44	placebo n=45
probable	5 (10.9)	10 (22.7)	3 (6.7)
possible	1 (2.2)	4 (9.1)	1 (2.2)
tickle in throat	4 (8.7)	11 (25.0)	2 (4.4)

table 22 vol 300

In all cases the incidence rate for the enalapril group was more than twice the rate for the other 2 groups.

The severity of cough was collected on a 10 point scale (see question 14 appendix 4). The table below shows the number of patients in each treatment group who reported mild, moderate or severe cough at the end of the enalapril challenge phase and at study endpoint (includes only patients with cough at last evaluation and those who withdrew for cough).

Number and (percent) of patients

	eprosartan n=46	enalapril n=44+	placebo n=45
end of enalapril challenge phase			
none	3 (6.5)	5 (11.1)	1 (2.2)
mild^	18 (39.1)	14 (31.1)	15 (33.3)
moderate^^	21 (45.7)	25 (55.6)	24 (53.3)
severe^^^	4 (8.7)	1 (2.2)	5 (11.1)
study endpoint			
none	39 (84.8)	30 (68.2)	41 (91.1)
mild^	6 (13.0)	6 (13.6)	3 (6.7)
moderate^^	0	7 (15.9)	1 (2.2)
severe^^^	1 (2.2)	1 (2.3)	0

^categories 1-3 on question 14 of pulmonary questionnaire, investigator assessment
^^categories 4-7 on question 14 of pulmonary questionnaire, investigator assessment,
^^^categories 8-10 on question 14 of pulmonary questionnaire, investigator assessment
+n=45 for end of enalapril challenge phase
table 24 vol 300 and amendment 54

As discussed previously, a substantial number of randomized patients (56/136, 41.2%) either had no cough or had only a mild cough during the enalapril challenge phase. Upon rechallenge, enalapril either produced no cough (68.2% of enalapril patients were cough free throughout the study) or produced a cough that was milder in severity than that during the challenge phase (only 15.9% had moderate cough upon rechallenge compared to 55.6% at initial challenge). The sponsor should have been more careful in patient selection.

Blood pressure effect

The following table shows the sitting systolic and blood pressure response to eprosartan 300 mg given bid compared to enalapril 20 mg qd.

Mean sitting blood pressure (mmHg)

systolic/diastolic	eprosartan n=46	enalapril n=44	placebo n=44
baseline	153.1/ 101.5	154.4/ 100.7	154.0/ 99.9
endpoint	142.6/ 92.7	143.4/ 92.8	148.3/ 95.5
change from baseline	-10.5/-8.7	-11.1/-7.9	-5.7/-4.4
change from baseline- placebo subtracted	-4.8/-4.3	-5.4/-3.5	na

table 27 vol 300

The effect of enalapril 20 mg given once daily on blood pressure was similar to eprosartan 300 mg given twice a day.

Cough reported as an adverse event

The number and percent of study patients who reported cough (or an event that could be associated with cough) that was collected as a routine adverse event are shown below.

Number and (percent) of patients

	eprosartan n=46	enalapril n=45	placebo n=45
at least 1 adverse event	26 (56.5)	29 (64.4)	22 (48.9)
at least 1 adverse event in the respiratory system	13 (28.3)	26 (57.8)	13 (28.9)
pharyngitis	5	9	6
coughing	9	20	9
rhinitis	5	6	3
sinusitis	1	3	1
URI	3	5	5

tables 32 and 33 vol 300

More patients reported 1 or more adverse events if they received enalapril or eprosartan than if they received placebo. The only difference between the 3 groups was for events in the respiratory

system: there were twice the number of patients on enalapril who reported cough compared to the other 2 groups. Other adverse events including those that could reflect cough were reported at comparable rates among the 3 groups.

The percent of the enalapril coughers during the entire double blind period in the efficacy analysis was 20.5%; this is less than half the rate of reports of cough as an adverse event (44.4%). Perhaps the questionnaire completed by the investigator was inadequately designed.

In conclusion, by inspecting the adverse event reports, twice the number of enalapril patients reported coughing compared to eprosartan or placebo patients. However, the percent of patients who coughed when rechallenged with enalapril was unusually low and casts doubts upon the validity of the trial. The number of enalapril patients who dropped out because of cough during the rechallenge phase in this highly select patient population is surprisingly small and the curiosity of patients reporting cough at early visits but not at later ones is difficult to explain.

4.0 Deaths, serious safety, and withdrawals for adverse events

4.1 Deaths

4.1.1 Hypertension

Of the 2334 patients who received eprosartan in the Phase II/III hypertension trials and were reported in the NDA[1], there were 16 deaths that occurred either during treatment or within 30 days of the last dose (1 death is included that occurred 42 days after last dose of study drug). There was 1 death in a placebo patient.

The Safety Update[2] added 33 new patients (all enrolled into open label study 050) to the data base for a total of 2367 patients in the Phase II/III hypertension trials. There were no additional deaths in this data base, but 1 death (patient 055.001.00026 eprosartan) was reported in a congestive heart failure study (section 4.1.2). Also, there were 2 deaths reported in the NDA without treatment assignment because the drug code was still blinded. Since then, the blind was broken and both patients had been taking eprosartan (section 4.1.2).

Number of patients who died

deaths on eprosartan all hypertension trials (n=2367)	deaths on eprosartan placebo controlled hypertension trials (n=1202)	deaths on placebo placebo controlled hypertension trials (n=352)
16	2	1

Less than 1% of eprosartan patients died during or shortly after treatment in a hypertension trial. The number of deaths during or shortly after completion of a placebo controlled hypertension trial was exceedingly small.

Eprosartan patients

The table below displays all 16 eprosartan patients (N=2367) who died during (or shortly after) participating in a Phase II/III hypertension study. A narrative for each death follows the table.

[1]Cut off date for NDA was May 31, 1996

[2]Cut off date for safety Update was October 31, 1996

Deaths

protocol. center. pt no. Study design	age/sex/race	total daily dose of eprosartan (mg)	days on drug	cause of death	days off drug
011.019.00912 short term, vs. placebo	53/m/white	400	43	aortic dissection acute MI	-
014.023.01517 short term, vs. active	52/m/white	400	155	suicide	-
039.053.055.03067 long term, open label	73/m/other	600	192	cerebrovascular accident	-
040.017.414.00145 long term, open label	89/m/white	200	162	sudden death	-
040.017.414.00149 long term, open label	78/f/white	400	244	sudden death	-
050.049.032.03639 long term, open label	43/m/white	600	97	bleeding gastric ulcer	-
050.049.067.03682 long term, open label	74/f/white	400	83	acute MI	-
052.013.527.00253 long term, open label	52/m/white	800	54	sudden death	-
052.013.621.00261 long term, open label	70/m/white	400	173	acute MI	-
014.026.01650 short term, vs. active	47/m/white	600	61^	sudden death	-
050.011.001.00638 long term, open label	37/m/black	600	246	probable pulmonary embolism	1
039.016.002.00085 long term, open label	73/m/white	600	166	abdominal carcinomatosis	22
040.017.311.00079 long term, open label	79/f/white	600	111	cerebrovascular accident	26
041.062.04295 short term, vs. active	67/f/white	200	8	acute MI cardiogenic shock	7
050.011.011.00578 long term, open label	46/m/white	400	198	acute lymphocytic leukemia sepsis	19
017.411.00162 short term, placebo control	78/f/white	200	51	not stated; withdrawn because of pneumonia	42+

+this patient is included because she dropped out of the study for an adverse event
^dosing history was interrupted; see narrative. From 014 study report.
from appendices 6.1-6.3 vol 408 and CRFs

Narratives

Patient 011.019.00912, a 53 year old white male, collapsed suddenly at home and died on Day 43 of eprosartan therapy. Cause of death was dissecting aortic aneurysm and acute MI. Medical history included hypertension requiring triple therapy. Other reported adverse events included left upper quadrant abdominal pain about 2 weeks before death and headache.

Patient 014.023.01517, a 52 year old white male with a history of clinical depression, committed suicide about 5 months after starting eprosartan therapy. He had been discontinued from the tricyclic antidepressant doxepin at the start of the study. Other adverse events included leukopenia of unknown origin (baseline WBC 3.4 thou/MCL; lowest value on drug was 2.6 thou/MCL), and mildly decreased hemoglobin, hematocrit and RBC.

Patient 039.053.005.03067 , a 74 year old oriental male, died of a cerebrovascular event about 6 months after starting eprosartan. Medical history included hypertension, diabetes, and arthritis, hepatitis and ACE inhibitor-induced cough. During the study he had nonspecific ST segment changes and acute gastroenteritis. Blood pressure on study drug was within normal limits. Patient had participated in study 053 during which he received enalapril 20 mg for 62 days.

Patient 040.017.414.00145, an 89 year old white male, died, apparently suddenly, about 5 months after starting eprosartan. Medical history included atrial fibrillation, cerebrovascular accidents (2 events), and ischemic heart disease; an ECG recorded during the trial showed signs of myocardial ischemia. Reported adverse event included lumbodynia (lumbago). Previously, the patient had completed a double blind study, uneventfully, during which he had been on placebo for 9 weeks.

Patient 040.017.414.00149, a 78 year old white female with a history of manic depressive psychosis, hypertension, and glaucoma died suddenly on day 244 of eprosartan therapy. She had participated in a previous study during which she received placebo. Reported adverse events included hypercholesterolemia and infected ear eczema, both requiring treatment.

Patient 050.049.032.03639, a 43 year old white male with a history of gastric ulcer died on day 97 of eprosartan treatment. Cause of death was exsanguination from a gastric ulcer, confirmed by autopsy. In the previous study, he had complained of mild gastrointestinal distress with vomiting. Approximately 3 weeks before the patient died, he was reported to "act very strange" during the scheduled clinic visit. There was no follow up visit. The clinic was notified that patient was found dead in his apartment.

Patient 049.067.03682, a 74 year old white female with a history of COPD, schizophrenia, and hypercholesterolemia was found comatose on day 83 of eprosartan therapy. She died that day from an autopsy confirmed acute MI. Reported adverse events included "thoracic strain," increased cough, and cellulitis.

Patient 052.013.527.00253, a 52 year old white male with a history of diabetes and previous MI, was found dead at home on day 54 of eprosartan treatment. There were no reported adverse events. No autopsy was performed.

Patient 040.017.311.00079, a 79 year old white female with an unremarkable medical history, died of an acute cerebral hemorrhage 26 days after the last dose of eprosartan. She had received eprosartan for about 4 months and was prematurely discontinued because of diverticulitis and renal carcinoma.

Patient 052.013.621.00261, a 70 year old white male with diabetes and vascular retinopathy, died of an acute MI after 79 days on eprosartan. He had participated in a previous study during which he received placebo for 13 weeks.

Patient 039.016.002.00085, a 73 year old white male died of abdominal carcinomatosis 22 days after discontinuing eprosartan because of diverticulitis. He had been on study drug for 5.5 months during which he reported episodes of chest pain, numbness, tingling, severe sinusitis, nocturia, malaise, weakness. Past medical history included asthma and a previous MI.

Patient 014.026.01650, a 47 year old white male smoker with an unremarkable medical history, discontinued eprosartan after 61 days because of an acute MI. He recovered from the event but then had sudden death about 5 weeks later. There was an indication that he had taken at least 1 unauthorized dose of eprosartan and had abruptly discontinued his beta blocker shortly before death. No autopsy was performed.

Patient 041.062.04295, a 67 year old white female, received eprosartan for 8 days prior to being hospitalized an acute MI. She died a week later of cardiogenic shock after a difficult hospital course. Past medical history was noncontributory.

Patient 050.011.001.00638, a 37 year old black male, died of probable pulmonary embolism after 8 months on eprosartan. Shortly before death, the patient complained of back and leg pain and a presumptive diagnosis of thrombophlebitis was made. En route to the hospital, he fell, convulsed, and died. Past medical history was noncontributory.

Patient 050.011.011.00578, a 46 year old white male with an unremarkable medical history developed rash, ecchymosis, petechiae, and blood-tinged saliva after 6 months on eprosartan. A diagnosis of acute lymphocytic leukemia was made and he died 19 days after study drug was discontinued.

Patient 017.411.00162, a 78 year old white female taking eprosartan 100 mg twice daily was withdrawn from the study because of bronchopneumonia with fever, dehydration, hypotension and atrial fibrillation. The patient developed pulmonary edema about 41 days after study withdrawal and died the next day. The sponsor did not include this patient in the list of deaths because she died 42 days after last dose of study drug. She is included here because she withdrew from study medication because of an adverse event and then died. It can be debated whether or not to include this death. The cause of death was not discussed by the sponsor and the case report form was not included.

In summary, most of the deaths were cardiovascular, as is to be expected in this patient population. There were 4 sudden deaths, 4 acute MIs, 2 cerebrovascular accidents and the remaining 6 included suicide, bleeding gastric ulcer, pulmonary embolism, abdominal carcinomatosis, acute leukemia, and

possible pneumonia. There is no obvious link between eprosartan and any of these deaths.

Placebo patient

protocol. center. pt no.	age/sex/race	days on placebo	cause of death	days off drug
017.411.00166	82/f/white	63	cerebrovascular accident	11

Patient 017.411.00166, an 82 year old white female, experienced a cerebrovascular accident 4 days after the last dose of placebo. She died a week later.

4.1. 2 Other studies

In addition to the deaths in the hypertension trials, there were 3 additional deaths in patients who were either receiving eprosartan or had received eprosartan within 30 days before death: 1 patient in a diabetic study, 1 patient in a left ventricular hypertrophy study[3], and 1 patient in a heart failure study. All deaths are discussed below.

Deaths in other studies

protocol. center. pt no.	age/sex/race	dose of eprosartan (mg)	days on drug	cause of death	days off drug
Type II diabetes mellitus					
090.001.00057+	71/m/Hispanic	600	32	acute MI	-
Left ventricular hypertrophy					
051.449.00841	85/m	400	162	sudden death	1
Congestive heart failure					
055.001.00026	73/m	400	52	ischemic heart disease	23

Patient 090/090/001/00057, a 72 year old Hispanic male, received eprosartan for 32 days when he was admitted to the emergency room for chest pain. An acute MI was diagnosed and, despite thrombolytic treatment, the patient deteriorated and died. Medical history included probable old MI. This patient was enrolled by Dr. Fiddes. Attempts to obtain death certificate to verify death have been unsuccessful

Patient 051/449/00841, an 85 year old male, had sudden death after about 5 months of eprosartan

[3]Included in Safety Update, cut off date was 31 October, 1996

treatment and 1 day after completing the study. Medical history included disorientation and Parkinson's disease as well as left ventricular hypertrophy.

Patient 055/001/00026, a 73 year old patient with congestive heart failure was discontinued from eprosartan on day 52 because of ventricular tachycardia and cardiac arrest. An angiogram revealed a stenosis of the left anterior descending artery which was not corrected. He was released from the hospital and had sudden death about 3 weeks later.

In summary, these 3 deaths resulted from cardiovascular causes and occurred in patients at risk for such deaths. None can be related directly to eprosartan use.

There were no deaths in any of the 635 subjects (or patients) enrolled into a clinical pharmacology study (fax dated 5-8-97).

4.2 Serious safety (that did not lead to withdrawal from study or death)

Serious, nonfatal adverse experiences that did not lead to withdrawal were reported by 3.9% (93/2367) of the eprosartan patients enrolled into 1 of the 15 Phase II/III hypertensive trials as of August 31,1996, the cut off date for the Safety Update. For the 6 placebo controlled trials, there were 12 eprosartan patients (1.0%) and 3 placebo patients (0.9%) who reported a serious event. Of the other 81 patients, 80 reported an event while participating in a long term, open label extension trial.

The sponsor also updated serious safety for ongoing studies up through 31 October 1996. Two additional serious events were reported from an ongoing open-label extension study in hypertension (Study 105). Therefore, there was a total of 95 hypertensive eprosartan patients who reported at least 1 serious adverse event. The table below show the serious events reported by 2 or more of these patients.

Serious adverse events

serious adverse event	number of patients
at least 1 event	95
injury	11
infection	6
cerebrovascular disorder	4
cholecystitis	4
neoplasm^	6
vomiting	3
arthritis	3
MI	3
CAD	3
abdominal pain	2
aneurysm	2
atrial fibrillation	2
chest pain	2
diverticulitis	2
nausea	2
respiratory disorder	2
subarachnoid hemorrhage	2
cholelithiasis	2

^includes carcinoma

Table 7.1, appendix 7.1safety update and appendix 5.6.1.1 integrated safety summary

Serious adverse events reported by 1 eprosartan patient included myocardial ischemia, renal calculus, menorrhagia, prostatic disorder, neurosis, cerebral embolism, aphasia, testis disorder, back pain, vaginal hemorrhage, pulmonary embolism, cardiac failure, tendinitis, arthralgia, varicose vein, SGPT increase (patient also had cholecystitis and cholelithiasis), vein disorder, migraine, thrombophlebitis, hypokalemia, hypotension, uterine disorder, urinary incontinence, cellulitis, vestibular disorder, asthma, ischemic necrosis, dizziness, paresthesia, somnolence, Peyronie's disease (oculomucocutaneous syndrome), malaise, pleural effusion, fatigue, fever, diarrhea, gastroenteritis, arrhythmia, gastroesophageal reflux, bipolar affective disorder, herniated disc, ectopic pregnancy, venous insufficiency, inguinal hernia, renal colic, rotator cuff tear, gastritis, and conjunctival hemorrhage.

There were 3 additional patients who reported serious events but the study code remains intact: 1 patient with an intestinal obstruction diagnosed 1 day after start of study medication, 1 patient with femoral artery stenosis, and 1 patient with atrial fibrillation.

There was one report of ependymal tumor with hydrocephalus[1] in patient 045.003.00024 who had received eprosartan for 22 days prior to diagnosis. He remained on study drug for the remainder of the trial. Any relationship to drug in this case is highly unlikely.

Overall, none of the reported serious adverse events was unusual in this (limited) patient population and it is unlikely that there is a relationship between any of these events and eprosartan use.

[1]Described as fetal hydrocephalus in NDA section 18.1 and corrected in fax dated 5-28-97

4.3 Study withdrawals

4.3.1 Any reason

The tables below show the number of patients who withdrew for any reason by treatment group. Patients who died are excluded. All 15 Phase II/III studies are evaluated and are grouped according to study design. There is an occasional lack of consistency between what is stated in the individual study report and what is stated in the Integrated Summary of Safety and Safety Update. A notable effort was made to correct the mistakes; I am reasonably convinced that any errors remaining are probably minor and would not alter my conclusions about eprosartan. However, there are 7 eprosartan patients in appendix 8.6.1 who are listed as dropping out for adverse events but for whom no specific adverse event was reported, a reflection of poor study monitoring. Patients who are added in from appendix 8.6.1 are indicated in the footnotes of each table in this review.

Placebo controlled monotherapy trials

The numbers of patients who withdrew from 1 of the 6 placebo controlled trials, by reason, are shown below.

Number^ and (percent) of patients

	adverse event		lack of effect		other	
protocol	eprosartan	placebo	eprosartan	placebo	eprosartan	placebo
010	1+	0	1	0	2	0
011	18++	4	7	2	16	6
013	10	10	60	43	4	5
017	9@	2	1	0	2	0
045	1	3	4	2	0	1
049	12@@	4	5	3	4	5
totals	51 (4.2)	23 (6.5)	78 (6.5)	50 (14.2)	24 (2.0)	15 (4.3)

^N=352 for placebo, N=1202 for eprosartan
+patient 010.033.00108 withdrew for headache
++patient 011.008.00959 withdrew for adverse experience not specified; 011.016.00665 withdrew for carcinoma
@patient 017.611.00295 withdrew for adverse experience not specified
@@ includes all 6 patients in appendix 8.6.1
individual study reports and cited appendices from ISS

Overall, there were fewer eprosartan patients who dropped out of a study compared to placebo patients, regardless of reason, with the largest difference being for lack of effect (6.5% vs. 14.2%,

respectively). The incidence of drop outs for adverse events was similar between the 2 groups.

Withdrawals in combination with HCTZ

The table below shows the drop outs for study 016, a placebo controlled trial with all patients receiving HCTZ 25 mg as background therapy.

Number^ and (percent) of patients

	adverse event		lack of effect		other	
protocol	placebo	eprosartan	placebo	eprosartan	placebo	eprosartan
016	1 (1.9)	1 (1.0)	0	1 (1.0)	1 (1.9)	3 (2.9)

^n=52 for placebo, n=104 for eprosartan
study report and appendices 8.6, 8.6.1

Drop out rates were similar between eprosartan and placebo, regardless of reason.

Withdrawals in active controlled trials

The active controlled trials compared eprosartan to either enalapril or nifedipine extended release.

Number^ and (percent) of patients

	adverse event		lack of effect		other	
protocol	eprosartan	active/placebo	eprosartan	active/placebo	eprosartan	active/placebo
014	14	23	13	12	7	12
047	3	2	8	9	2	1
053	1	4/2	1	½	5	5/7
041	6	9	1	0	6	8
total	24 (5.1)	38 (8.1)/2 (4.4)	23 (4.9)	22 (4.7)/2 (4.4)	20 (4.2)	26 (5.5)/7 (15.6)

^n=470 for active controls, n=45 for placebo, n=472 for eprosartan
individual study reports

The drop out rates in these trials were similar for the different treatment groups, regardless of reason, except the rather large rate for the reason "other" that occurred in the placebo group.

Overall, in the controlled studies the drop out rates for any reason, including for adverse events, were similar regardless of treatment group. Withdrawal for adverse events for patients receiving eprosartan occurred at about the same rate as for patients receiving placebo rates or the 2 other antihypertensives.

Open label studies

The numbers of patients who dropped out of 1 of the 4 open label, uncontrolled extension studies are shown below. All 4 studies are ongoing. The individual study reports submitted with the NDA were prepared prior to the Integrated Summary of Safety. The sponsor submitted a document (fax dated 2-21-97) discussing the discrepancies. The table below reflects the numbers of patients who dropped out for adverse events up to the cut off date of May 31, 1996. The total numbers of study patients have not been updated.

	eprosartan patients		
protocol	adverse event+	lack of effect^	other^
039 n=140	16	32	16
040 n=253	18	4	6
050 n=336	55	30	24
052 n=68	4	4	1
total n=797	66	70	47

+from individual study reports and fax dated 2-21-97

^from individual study reports

It is difficult to draw conclusions about drop outs in long-term, open label trials. The number of drop outs for any reason do not appear to be excessive.

4.3.2 Withdrawals for adverse events

Of the 2367 eprosartan patients who received during 1 of the 15 clinical trials, 218 (9.2%) withdrew for an adverse event. The table below lists the adverse events that led to patient drop outs limited to those events causing drop outs in at least 15 patients. Patients who withdrew for abnormal laboratory values are discussed in section 5.0 and those who withdrew for abnormal ECG are discussed in section 6.0.

Number and (percent) of patients

adverse event	eprosartan patients N=2367
withdrew for any adverse event	218 (9.2)
headache	80 (3.4)
myalgia	38 (1.6)
coughing	33 (1.4)
URI	32 (1.4)
dizziness	27 (1.1)
fatigue	27 (1.1)
pharyngitis	26 (1.1)
sinusitis	21 (0.9)
diarrhea	19 (0.8)
nausea	19 (0.8)
chest pain	17 (0.7)
injury	17 (0.7)
dyspepsia	16 (0.7)
depression	15 (0.6)
viral infection	15 (0.6)

revised appendix 8.3.a. submitted 5-6-97

Reasons for withdrawal that were reported by less than 15 patients and could represent important events include myocardial infarction (12 patients), hypotension (6 patients), cerebrovascular disorder (6 patients), arrhythmia (4 patients), allergic reaction (3 patients), anemia (3 patients), cardiac failure (2 patients), syncope (2 patients), arteritis (1 patients), blindness (1 patient, described as transient loss of vision).

Placebo controlled trials

Of the patients enrolled into the 6 placebo controlled trials, 51[1] (4.2%) eprosartan patients and 23

[1]Includes patients 010.033.00108 (headache), 011.008.00959, 011.016.00665, 017.611.00295

(6.5%) placebo patients withdrew for adverse events.

The following table shows the withdrawals for adverse events by event. The total number of eprosartan patients withdrawing for adverse events, by my calculations, is 51; however, the table below relies on the number (47) given by the sponsor. This discrepancy should not alter the conclusions about eprosartan safety. Only those events reported by more than 1 eprosartan patient and reported more often in the eprosartan group compared to the placebo group are included in the table. Patients could withdraw for more than 1 event.

Number and (percent) of patients

adverse event	eprosartan n=1202	placebo n=352	placebo subtracted %
number of withdrawals	47 (3.9)	23 (6.5)	-2.6
depression	5 (0.4)	0	0.4
myalgia	5 (0.4)	0	0.4
insomnia	3 (0.3)	0	0.3
arrhythmia	2 (0.2)	0	0.2
constipation	2 (0.2)	0	0.2
dizziness	2 (0.2)	0	0.2
dyspnea	2 (0.2)	0	0.2
chest pain	6 (0.5)	1 (0.3)	0.2

Table 8.3 vol 405

A lower percentage of eprosartan patients dropped out for an adverse event compared to placebo patients, even if the number 51 is used. The most common events leading to withdrawal in the eprosartan group compared to placebo were depression and myalgia. The number of patients in each category is small.

Active controlled trials

Enalapril comparison

The table below shows the number of patients who withdrew from 1 of the 3 enalapril controlled clinical trials.

Number and (percent) of withdrawals for adverse events

	enalapril	eprosartan	placebo
protocol number	n/N	n/N	n/N
014	24+/264 (9.1)	14/264 (5.3)	-
047	2/59 (3.4)	3/59 (5.1)	-
053	4/45 (8.9)	1/46 (2.2)	2/45 (4.4)
Total	30/368 (8.2)	18/369 (4.9)	2/45 (4.4)

+includes patient 014.200.01854
from individual study reports

Overall, there were more patients who withdrew for adverse events from enalapril treatment (8.2%) compared to eprosartan treatment (4.9%) in these controlled trials, but the difference is small. In the largest study (014), the events leading to withdrawal in more than 2 patients in a treatment group were cough (enalapril 7, eprosartan 2) and pharyngitis (enalapril 3, eprosartan 0). The differences between the 2 active treatment groups are small and inconsistent from study to study. The effect of these 2 drugs on cough is discussed in section 3.3.

Nifedipine comparison

The withdrawal rates for adverse events in the study (041) that compared nifedipine and eprosartan were 8.8% (9/102) and 6.0% (6/103), respectively. No event was unexpected in this patient population. There is very little difference between these agents in regards to patient withdrawals for adverse events.

HCTZ background trial

In study 016 patients received HCTZ with either eprosartan or placebo. There were 2 patients who withdrew because of adverse events: 1 was randomized to placebo and suffered a transient ischemic attack and 1 was randomized to eprosartan and developed a pruritic rash.

In conclusion, less than 10% of the eprosartan patients who participated in a Phase II/III hypertension trial withdrew for an adverse event, and in the placebo controlled trials, there were more placebo patients than eprosartan patients dropping out for this reason. The 4 most common events in the 15 trials leading to drop outs were headache, myalgia, coughing, and URI.

5.0 Laboratory Evaluations

This section includes laboratory evaluations for all eprosartan patients studied in Phase II/III hypertension trials (N=2334) and the subgroup of patients enrolled into a placebo controlled trial. The laboratory results of the positive controlled trials were reviewed only for gross abnormalities.

Renal function (BUN and serum creatinine), liver function (alkaline phosphatase, ALAT/ASAT and total bilirubin), glucose and electrolytes (potassium and sodium), lipids, and hematology were closely examined. For each system, protocol exclusion criteria, if any, are stated. Then, means at baseline, at endpoint, and change from baseline at endpoint are shown for all patients with data. This is followed by the number and percent of patients who were classified as having a value that went from normal at baseline to above (or below) the investigator's normal range. Finally, the number and percent of patients who were considered to have an abnormal value (regardless of baseline value) according to the sponsor (referred to an sponsor-defined abnormal value) is discussed. What constitutes a sponsor-defined abnormal value is shown at the beginning of each system.

Means at baseline, at endpoint, and change from baseline at endpoint are displayed for all patients with data who received placebo (n=352) or eprosartan (n=1202) in 1 of 6 placebo controlled hypertension trial. This is followed by a comparison of the placebo patients to eprosartan patients who had values above (or below) the investigator normal range as well as for sponsor-defined abnormal values.

Grossly abnormal laboratory values, if any, are discussed, as well as any patients who dropped out of a study because of a laboratory abnormality.

The review of lipids values is limited to means at baseline, endpoint, and change from baseline at endpoint for the 6 placebo controlled trials.

5.1 Renal function

Patients were generally excluded from trials if they had significant renal disease, defined by the majority of the protocols as serum creatinine > 2.5 mg/dL (220 umol/L); a few protocols excluded patients with values above 2.0 mg/dl.

The sponsor used the following values to identify study patients who developed abnormal renal function (referred to as sponsor-defined abnormal values):

- BUN >17.85 mmol/L (> 50 mg/dl) or
- Serum creatinine > 250% upper limit of normal

All hypertension trials

The table below shows baseline, endpoint, and change from baseline at endpoint for BUN and serum creatinine for all patients with data.

Means (± SE)

	Eprosartan patients		
	baseline n=2300	endpoint n=2191	change from baseline at endpoint
BUN (mmol/L)	5.35 ± 0.03	5.71 ± 0.04	0.36 ± 0.03
Serum creatinine (umol/L)	98.13 ± 0.40	97.00 ± 0.43	-1.10 ± 0.28

table 9.1 vol 406

The changes from baseline at endpoint for the BUN and serum creatinine were small, in this population, and in the opposite direction from one another (0.36 mmol/L and -1.10 umol/L, respectively).

The percent of eprosartan patients who went from a normal value at baseline to a value above the investigator's normal range at endpoint was 1.5% for BUN (33/2162) and 1.0% for serum creatinine (21[1]/2121; table 9.2 vol 406). The patients with elevated serum creatinine were reviewed: baseline values in all instances were high normal values (between 1.3 and 1.5 mg/dl) and endpoint values were only mildly elevated (≤1.7 mg/dl) with normal BUN. There were no eprosartan patients who met the sponsor-defined abnormal values at endpoint. (table 9.3 vol 406)

Placebo controlled trials

The mean duration of treatment was approximately 54 days for both placebo and eprosartan groups. The table below show baseline, endpoint, and change from baseline at endpoint for BUN and serum creatinine for all placebo and eprosartan patients with data.

Mean (± SE)

	eprosartan			placebo		
	baseline n=1201	endpoint n=1173	change from bl	baseline n=351	endpoint n=338	change from bl
BUN (mmol/L)	5.31 ± 0.04	5.49 ± 0.05	0.19 ± 0.04	5.53 ± 0.09	5.61 ± 0.09	0.09 ± 0.07
S. Creatinine (mmol/L)	98.53 ± 0.54	98.29 ± 0.57	-0.07 ± 0.36	98.6 ± 1.1	98.26 ± 1.08	-0.36 ± 0.6

table 9.14 vol 406

There was a larger increase from baseline at endpoint in the mean BUN for patients who received eprosartan compared to patients who received placebo. The increases, however, were relatively small (0.19 and 0.09 mmol/L, respectively). There was a decrease at endpoint in mean serum creatinine for both treatment groups.

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[1]It appears that at least 2 patients were erroneously included but the decision was made to stick to the worst case scenario.

The percent of patients who had normal BUN values at baseline and but had values at endpoint that exceeded the normal investigator range at endpoint was 0.3% (1/334) for those who received placebo and 1.3% for those who received eprosartan (15/1160). On the other hand, the percent of patients who had normal serum creatinine values at baseline but had values at endpoint that exceeded the normal investigator range at endpoint was 0.9% (3/334) for those who received placebo and 0.6% for those who received eprosartan (7/1160). (table 9.15 vol 406).

One patient (049.056.03792) had increases in serum creatinine and BUN that were reported as adverse events. This patient had been receiving placebo.

Withdrawals for renal laboratory abnormalities

There were 2 patients who withdrew for abnormal serum creatinine and/or BUN values. Both were enrolled into the open label study 050.

Patient 050.032.05037 was a 63 year old white male with hypertension and elevated serum uric acid who discontinued eprosartan therapy (total daily dose 400 mg increased to 600 mg) after 45 days because of azotemia and hyperuricemia. BUN, serum creatinine and uric acid values at approximately the time of discontinuation were 50 U/l, 1.6 mg/dl, 10.8 mg/dl (upper limit of normal for uric acid was 8.0), respectively. Baseline values were within the normal range (20 U/L, 1.0 mg/dl, 6.3 mg/dl, respectively). Serum creatinine at the end of the titration phase was 1.9 mg/dl. Past medical history included hyperuricemia; reported adverse events included metallic taste. (Amendment 44 dated 4-30-97).

Patient 050.033.05084 was a 74 year old white female who discontinued eprosartan 800 mg after 80 days because of elevated serum creatinine. BUN was slightly above normal upper limit, as well. Baseline serum creatinine value was 1.6 mg/dl which increased to 2.6 mg/dl at Day 80 and 3.1 mg/dl at Day 88 (1 day after eprosartan discontinuation). Serum creatinine was 2.2 mg/dl 7 days after the last dose of eprosartan. Reported adverse events included arthralgia, fatigue, nausea, and dizziness.

In addition, patient 050.011.001.00638, a 36 year old black male with hypertension, died while receiving eprosartan of a probable pulmonary embolism (see section 4.1). On the day of his death, elevated serum creatinine (2 mg/dl) and BUN (26 mg/dl) were reported. Upon entry into the base study 011, his serum creatinine was borderline normal (1.5 mg/dl).

And finally, patient 014.502.02029 withdrew from study 040 for increased serum creatinine according to a fax sent by the sponsor dated 5-21-97. However, the interim report and case report form states that the patient withdrew for diarrhea, arthralgia, and pitting edema. The laboratory reports supplied by the sponsor showed an elevated value of 140 umol/l [2] which returned to normal with subsequent testing. Why this patient got coded as a drop out for a laboratory value remains obscure.

In summary, the data indicate that eprosartan can cause mild elevations of BUN, and less often, serum creatinine. On rare occasions these elevations can lead to drug withdrawal. For most study patients,

[2]normal range 70-130 umol/l

however, the drug had little, if any, effect on kidney function.

5.2 Liver function

Patients were generally excluded from trials if they had significant liver disease defined by the majority of the protocols as ASAT, ALAT, total bilirubin or alkaline phosphatase greater than 2.5 times (or 2.0 time in some protocols) the upper limit of the laboratory reference range.

The sponsor-defined abnormal values for liver function were:

- alkaline phosphatase >350% upper limit of normal
- ALAT > 350% upper limit of normal
- ASAT > 350% upper limit of normal

All hypertension trials

The table below shows means at baseline, endpoint, and change from baseline at endpoint for liver function tests for all patients with data.

Means (± SE)

	Eprosartan patients		
	baseline n=2300	endpoint n=2191	change from baseline at endpoint
alkaline phosphatase (U/L)	72.77 ± 0.46	69.15 ± 0.43	-3.77 ± 0.30
ALAT (U/L)	23.57 ± 0.30	24.26 ± 0.34	0.72 ± 0.26
ASAT (U/L)	21.69 ± 0.20	21.50 ± 0.22	-0.18 ± 0.18
total bilirubin (umol/L)	12.84 ± 0.10	13.06 ± 0.09	0.20 ± 0.08

table 9.4 vol 406

The mean changes from baseline at endpoint were small for all of these variables.

The percent of eprosartan patients who went from a normal value at baseline to a value above the investigator's normal range at endpoint was 1.7% for alkaline phosphatase (36/2065), 3.5% for ALAT (73/2057), 1.9% for ASAT (40/2115) (table 9.5 vol 406), and 1.1% for total bilirubin (24/2130) (appendix 9.1.2.b.2.).

The percents of eprosartan patients who met the sponsor-defined abnormal values at endpoint for elevated ALAT and ASAT were 0.2% (4/2219) and <0.1% (1/2219), respectively. There were no patients who met the definition for high alkaline phosphatase or total bilirubin (table 9.6 vol 406). The highest ALAT for the 4 patients was 207 U/L. There was 1 patient (053.051.03008 discussed below as a withdrawal) who had both an elevated ALAT (206 U/L) and ASAT (161 U/L) at endpoint (appendix

9.1.3.b cell index).

Placebo controlled trials

The tables below show mean baseline, endpoint, and change from baseline at endpoint for liver function tests for all placebo and eprosartan patients with data.

Means (± SE)

	eprosartan			placebo		
	baseline n=1201	endpoint n=1173	change from bl	baseline n=351	endpoint n=338	change from bl
alk phos (U/L)	72.98±0.63	71.19±0.62	-1.84±0.36	72.32±1.10	72.00±1.20	-0.39±0.64
ALAT (U/L)	23.31±0.41	23.85±0.43	0.58±0.27	23.64±0.08	24.00±0.84	0.28±0.46
ASAT (U/L)	21.70±0.28	21.47±0.27	-0.23±0.20	22.01±0.49	22.01±0.48	0.07±0.41
Total bili (umol/L)	12.91±0.13	12.76±0.13	-0.20±0.10	12.65±0.23	12.66±0.24	0.07±0.20

table 9.16 vol 406

The only parameter that increased from baseline at endpoint in the eprosartan group was ALAT, and this change was small (< 1 U/L) and similar to the change in the placebo group.

The table below shows the number and percent of eprosartan and placebo patients who had normal values at baseline but had values above the investigator normal range at endpoint.

Number and (percent) of patients

	eprosartan n=1173	placebo n=338
alkaline phosphatase	11 (0.9%)	10 (3.0 %)
ALAT	31 (2.6%)	10 (3.0 %)
ASAT	14 (1.2%)	10 (3.0 %)
total bilirubin	9^ (0.8%)	3+ (0.9%)

^n=1144
+n=332
table 9.17 vol 406 and appendix 9.2.2.B

In all instances, the percentages of patients with abnormalities were higher in the placebo group than in the eprosartan group.

There was only 1 eprosartan patient (and no placebo patient) who had a liver function test that met

the sponsor-defined abnormal values at endpoint. This was patient 010.009.00063 who had elevated ALAT at baseline as well as endpoint (101 and 104 U/L, respectively) (table 9.18 vol 406 and appendix 9.2.3.b.cell index).

Withdrawals for liver abnormalities

There were 4 patients who withdrew from eprosartan therapy because of abnormal liver function.

Patient 039.053.051.03008 was a 52 year old male who dropped out for increased liver enzymes and hyperglycemia after 85 days on eprosartan 600 mg and HCTZ. ASAT/ALAT were elevated throughout the study with maximum values around 140 and 190 U/L. The patient had mildly elevated values at baseline (49/58 U/L). ASAT/ALAT were still elevated at 1 month follow up but became normal the following month. Patient had participated in a previous study (053) during which he received enalapril.

Patient 040.017.411.00194 was a 65 year old white female who dropped out for (mild) jaundice and diarrhea on day 65 of eprosartan 200 mg. Two days after discontinuation, she developed painful hepatomegaly. There was no medical history suggestive of liver disease and liver enzymes were within normal range (fax dated 7-24-97). There is no further explanation of this case and the sponsor could offer no additional information (amendment 47 dated 5-15-97).

Patient 050.011.015.00800 was a 60 year old white male who dropped out for liver enzyme elevation after 99 days of eprosartan 600 mg. Baseline ASAT/ALAT were above normal (49/86 U/L). On the last day of treatment, alkaline phosphatase (116 U/L) was elevated and ASAT/ALAT had increased to 201/251 U/L. There was no discussion pertaining to these abnormalities. Medical history included hyperthyroidism, gout, and renal calculi. Adverse events included headache, sinusitis, pharyngitis, fatigue, and edema.

Patient 050.011.019.00566 was a 42 year old black female who dropped out for abnormal hepatic function after 120 days on eprosartan therapy (total daily dose 600 mg). Baseline values for ALAT/AST were 41/29 U/L which increased to 207/61 U/L at time of eprosartan withdrawal; values returned to normal about 2 weeks later. Other adverse events included constipation, rectal tear and neoplasm.

In summary, it is likely that eprosartan can cause mildly elevated liver enzymes in rare individuals, perhaps with progression to jaundice, but this is unlikely.

5.3 Glucose and electrolytes

Patients were generally excluded from trials if they had unstable diabetes mellitus.

The sponsor-defined abnormal values were:

- fasting glucose $\leq$ 60 mg/dL ($\leq$ 3.33 mmol/L) or $\geq$ 130 mg/dL ($\geq$ 7.22 mmol/L)
- potassium $\leq$ 3.0 mEq/L ($\leq$ 3.0 mmol/L) or $\geq$ 5.5 mEq/L ($\geq$ 5.5 mmol/L)
- sodium $\leq$ 130 mEq/L ($\leq$ 130 mmol/L) or $\geq$ 150 mEq/L ($\geq$ 150 mmol/L)

All hypertension trials

The table below shows mean baseline, endpoint, and change from baseline at endpoint for fasting glucose, potassium and sodium for all patients with data.

Means ± SE

	Eprosartan patients		
	baseline	endpoint	change from baseline at endpoint
fasting glucose+ (mmol/L)	5.97 ±0.04	6.14 ±0.06	0.18 ±0.05
potassium^ (mmol/L)	4.29 ±0.01	4.32 ±0.01	0.02 ±0.01
sodium^ (mmol/L)	139.86 ±0.06	139.97 ±0.06	0.09 ±0.06

+baseline n=2158, endpoint n=2020
^baseline n=2300, endpoint n=2191
table 9.8 vol 406

There were small, inconsequential changes from baseline at endpoint for these chemistry values. The largest change was for fasting glucose but it is probable that many samples collected during the study were from patients in the non fasting state.

The table below shows the number and percent of eprosartan patients who had normal values at baseline and values above (or below) the investigator normal range at endpoint.

Number and (percent) of patients

fasting glucose (mmol/L) n=1679		potassium (mmol/L) n=2150		sodium (mmol/L) n=2139	
below normal	above normal	below normal	above normal	below normal	above normal
33 (2.0)	93 (5.5)	20 (0.9)	24 (1.1)	41 (1.9)	1 (<0.1)

table 9.9 vol 406

Except for glucose above normal, the percent of patients with normal values at baseline that became abnormal was 2% or less.

The percent of patients who met the sponsor define value of concern were:

- 0.1% for low glucose,
- 12.1% for high glucose,
- < 0.1% for low potassium,
- 0.7% for high potassium,
- 0.2% for low sodium, and
- 0% for high sodium.

Vol 406 table 9.10

Less than 1% (15) of the eprosartan patients had serum potassium ≥ 5.5 mEq/L while receiving eprosartan. These 15 patients had endpoint values that ranged from 5.5 up to 7.0 mEq/L.

Placebo controlled trials

The tables below show mean baseline, endpoint, and change from baseline at endpoint for glucose, potassium, and sodium values for all placebo and eprosartan patients with data.

Means ±SE

	eprosartan			placebo		
	baseline	endpoint	change from bl	baseline	endpoint	change from bl
fasting glucose^ (mmol/L)	6.01 ±0.06	6.06 ±0.06	0.03 ±0.04	6.14 ±0.12	6.26 ±0.13	0.11 ±0.09
potassium+ (mmol/L)	4.30 ±0.01	4.34 ±0.01	0.04 ±0.01	4.25 ±0.02	4.25 ±0.02	0 ±0.02
sodium+ (mmol/L)	139.88 ±0.08	139.67 ±0.09	-0.21 ±0.10	140.02 ±0.16	139.99 ±0.18	0.01 ±0.19

^ eprosartan baseline n=1089, endpoint n=1046; placebo baseline n=325, endpoint n=308
+eprosartan baseline n=1201, endpoint n=1173; placebo baseline n=351, endpoint n=338
table 9.20 vol 406

In the placebo controlled trials, the changes from baseline at endpoint for these blood chemistries were similar for the placebo and eprosartan treatment groups.

The number and percent of patients who had normal values at baseline and values above (or below) the investigator normal range at endpoint are shown in the table below.

Number and (percent) of patients

	below normal range		above normal range	
	eprosartan	placebo	eprosartan	placebo
fasting glucose^ (mmol/L)	26 (2.5)	8 (2.6)	67 (6.4)	24 (7.8)
potassium+ (mmol/L)	10 (0.9)	4 (1.2)	17 (1.4)	6 (1.8)
sodium+ (mmol/L)	58 (4.9)	20 (5.9)	0	3 (0.9)

^n=1046 for eprosartan; n=308 for placebo
+n=1173 for eprosartan; n=338 for placebo
table 9.21 vol 406

In all cases, the percent of abnormalities was higher in the placebo group compared to the eprosartan groups.

The percents of patients who met the sponsor define value of concern at endpoint are shown below:

high fasting glucose:
- 12.0% (127/1058) of eprosartan patients vs.
- 16.7% (52/311) of placebo patients;

low fasting glucose:
- 0.1% (1/1058) of eprosartan patients vs.
- 0.3% (1/311) of placebo patients;

high potassium values:
- 0.9% (10/1174) of eprosartan patients vs.
- 0.3% (1/339) of placebo patients;

low potassium values :
- 0.1% (1/1174) patients in the eprosartan group.
- 0 placebo patients

Appendix 9.2.3.B

The percents of patients with sponsor defined values of concern were under 1% for all parameters except high glucose.

Withdrawals for glucose and/or electrolyte abnormalities

There was 1 withdrawal for hyperkalemia: patient 050.036.05120 was a 67 year old male who received 600 mg eprosartan for 162 days and dropped out for elevated serum potassium (6.4 mEq/L). Reported adverse events included fatigue, appetite increase, back pain, and myalgia. There was no discussion of the laboratory abnormality.

Overall, eprosartan appears to have little effect on these chemistry values.

5.4 Lipids

Because of large intra individual fluctuations in lipid levels that are hard to interpret, the review of lipids values is limited to means at baseline, endpoint, and change from baseline at endpoint for the 6 placebo controlled trials.

Placebo controlled trials

The following table shows the mean baseline, endpoint, and change from baseline at endpoint for total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides. The numbers of patients with data range from 710 to 836 for eprosartan and 184 to 253 for placebo.

Means ±SE

	eprosartan			placebo		
	baseline	endpoint	change from bl	baseline	endpoint	change from bl
total cholesterol (mmol/L)^	5.66±0.04	5.68± 0.04	0.03±0.02	5.61± 0.07	5.60 ± 0.06	0.03± 0.04
HDL (mmol/L)	1.36 ±0.01	1.37 ±0.01	< 0.01 ±0.01	1.36 ±0.02	1.39 ±0.02	0.02 ±0.01
LDL (mmol/L)	3.46 ±0.03	3.47 ±0.03	0.03 ± 0.02	3.43 ±0.07	3.45 ± 0.06	0.07 ±0.03
triglycerides (mmol/L)	1.95 ± 0.05	1.91 ±0.04	-0.02 ±0.04	1.97 ±0.10	1.78 ±0.08	-0.20 ±0.09

appendices 9.2.1.A and 9.2.1.B

The differences between eprosartan and placebo were negligible for the lipid values. There is no indication that eprosartan has an adverse effect on lipids.

5.5 Hematology

Patients were generally excluded from trials if they had leukocyte count < 3,000/mm^3 or platelet count < 100,000/mm^3.

The sponsor-defined abnormal hematology values were:

- hemoglobin: ≤ 80% lower limit of normal or ≥ 120% upper limit of normal
- white blood cell count: ≤ 3.0 x 10^3/mm ^{3} or ≥ 20.0 x 10^3/mm^3
- total neutrophils (absolute): ≤ 1.5 x 10^3/mm^3
- eosinophils (relative): >250% upper limit of normal
- platelet count:≤ 100 x 10^9/ L

All hypertension trials

The table below shows mean baseline, endpoint, and change from baseline at endpoint for select hematology variables for all patients with data.

Means ±SE

	eprosartan patients		
	baseline n=2298	endpoint n=2186^	change from baseline at endpoint
RBC (10^{12}/L)	4.81 ±0.01	4.74 ±0.04	-0.07 ±0.01
hemoglobin (g/L)	147.76 ±0.28	145.79 ± 0.29	-1.91 ± 0.16
platelets (10^9/L)	241.57 ±1.26	241.12 ±1.32	-0.82 ±0.77
WBC (10^9/L)	6.54 ±0.04	6.56 ±0.04	0.03 ±0.03
total neutrophils (10^9/L)	3.78 ±0.03	3.80 ±0.03	0.03 ±0.03

^n=2182 for platelets and n=1922 for total neutrophils
table 9.11 vol 406

There were small decreases from baseline at endpoint for RBC, hemoglobin (hematocrit was not discussed by the sponsor), and platelets. Eosinophils, not shown in the above table, were essentially unchanged.

The numbers and percents of eprosartan patients who had normal values at baseline and values below the investigator normal range at endpoint for select hematology variables are shown below.

- low hemoglobin: 2.6% (52/2010)
- low platelets: 0.6% (14/2126)
- low WBC: 1.9% (41/2097)
- low total neutrophils: 2.9% (52/1815)

table 9.12 vol 406

The number and percent of patients who met the sponsor define value of concern at endpoint for selected parameters are shown below:

- low hemoglobin: 0.2% (5/2216). Actual values ranged from 4.4 to 10.8 g/L,
- low platelets: 0.3% (7^3/2214). Actual values ranged from 43^4 to 98 10^9/L
- low WBC: 0.3% (6/2216). Actual values ranged from 2.1 to 2.8 10^9/L
- low total neutrophils: 1.1% (23/2041). Lowest actual value was 14.0 10^9/L

Table 9.13 vol 406 and appendix 9.1.3.A cell index

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[3]patient 011.012.00947 was erroneously included in the sponsor's table as having low platelet count (fax dated 4-23-97).

[4]patient 011.018.00405 lab comment "platelet histogram appears clumped; platelet count result may be in question."

Placebo controlled trials

The tables below show mean baseline, endpoint, and change from baseline at endpoint for select hematology variables for all placebo and eprosartan patients with data. The numbers of patients were slightly different for the different parameters.

Means ±SE

	eprosartan			placebo		
	baseline n=1200	endpoint n=1173	change from bl	baseline n=351	endpoint n=338	change from bl
RBC (10^{12}/L)	4.81±0.01	4.77±0.01	-0.05±0.01	4.78±0.02	4.81±0.02	0.03±0.01
hemoglobin (g/L)	148.11±0.39	146.58 ± 0.40	-1.59 ± 0.18	147.62±0.70	147.96±0.73	0.21 ±0.32
platelets (10^9/L)	241.90±1.71	312.01 ±71.67	-1.87 ±1.12	236.59±3.46	236.06±3.50	-1.06±1.54
WBC (10^9/L)	6.51±0.05	6.42 ± 0.05	-0.09 ±0.04	6.35±0.09	6.35±0.09	0.01±0.07
total neutrophils (10^9/L)	3.76 ± 0.04	3.68 ±0.04	-0.07 ±0.04	3.69±0.07	3.68±0.08	0.00 ±0.06

table 9.22 vol 406

Compared to placebo, there were minor decreases in RBC, hemoglobin, WBC and total neutrophil in the eprosartan group. Eprosartan, like angiotensin II receptor antagonists, probably decreases erythropoietin which results in a mild anemia. The animal studies with eprosartan also demonstrated a decrease in RBC and hemoglobin.

Reports of thrombocytopenia, anemia, leukopenia

Patient 045.004.00039 was a 44 year old black male with a baseline platelet count of 118,000/mm^3 which decreased to 101,000 mm^3 during eprosartan therapy. On day 28 platelet count was 143,000/mm^3. He completed the entire trial without further incidence. This episode of mild thrombocytopenia appears to be unrelated to eprosartan use.

Patient 014.018.01497 was a 62 year old white male who had a report of a decreased platelet count on day 3 of eprosartan therapy. Throughout the study, platelet counts were above 220,000/mm^3 except for a lab report of 18,000/mm^3 which upon repeat was 245,000/mm^3. This is most likely a case of lab error.

Anemia was rarely reported. There were reports of leukopenia in 3 eprosartan patients:

Patient 090.009.00042 had an isolated low WBC (3.4 thou/mcL) and 2 patients (049.061.03559 and

016.005.00160) had low WBC at baseline as well as throughout the study. These events appear to be unrelated with eprosartan therapy.

Withdrawals for abnormal hematology variables

Patient 049.067.03684 was a 66 year old black female who entered the study with a low platelet ($62,000/mm^3$) which remained low throughout the study. There was difficulty in obtaining an accurate platelet count because of sample clumping so there remains a question about the degree of thrombocytopenia. She was discontinued after 28 days of 400 mg eprosartan without obvious ill effects. It appears that this patient's low platelet count was unrelated to the use of eprosartan.

Patient 039.016.005.00161 was a 54 year old white female who withdrew because of ongoing thrombocythemia (baseline platelet count $527x10^3$/cumm which increased to $534x10^3$/cumm on study day 44). She had the same condition while enrolled in the base study as a placebo patient.

In summary, there is no evidence that eprosartan has an effect on hematology variables. There is an indication that mean RBC and hemoglobin are slightly decreased in patients taking this drug; this was also observed in animals.

5.6 Uric acid excretion

Preclinical studies compared the effects of losartan and eprosartan on uric acid uptake into rat proximal tubule brush border membrane vesicles. Both humans and rats possess a brush border membrane urate/anion exchanger, the first and rate limiting step in the renal reabsorption of urate and the likely site at which uricosuric drugs act. While both drugs inhibited urate transport, eprosartan was 6 fold less potent.

Study 069 compared the effect of a single dose of losartan 50 mg and eprosartan 400 mg in 12 salt replete healthy volunteers on fractional excretion of uric acid (FEUA) and the urinary uric acid to creatinine ratio (UUA/UCr). Arithmetic mean (SD) and point estimates (95% C.I.) of the difference between treatments for maximum post-dose CL_{PAH}, FEUA, and UUA/UCr are shown below. Changes from baseline were not provided.

Parameter	400 mg Eprosartan	50 mg Losartan
CL_{PAH}(mL/min)	1027 (231)	954 (113)
FEUA (%)	6.9 (1.3)	12.0 (3.5)
UUA/UCr	0.403 (0.095)	0.676 (0.202)

The mean fraction excretion of uric acid was double for losartan compared to eprosartan and the UUA/UCr was also higher. It is unknown how relevant this difference between losartan and eprosartan could be for patients who are at risk for uric acid stone formation.

5.7 Proteinuria

Protocol 090 was a 6 week, double-blind, randomized, parallel group study designed to compare the effects of eprosartan 300 mg bid and placebo on proteinuria in patients with Type II diabetes mellitus.

Following a placebo run-in period, qualified patients were randomized and entered into the 6 week double blind period. An open label period was part of the protocol but was excluded from the sponsor's interim report.

Primary efficacy analysis was the percentage change from baseline in 24-hour urinary protein excretion after 6 weeks, eprosartan versus placebo, using an analysis of variance with terms for regimen, center and regimen-by-center interaction.

Patients were male or female, at least 18 years of age, and with Type II diabetes mellitus with an average urinary protein excretion of either a) greater than or equal to 300 mg/24 hours or b) less than or equal to 3000 mg/24 hour. A total of 85 patients, 51 males and 34 females were randomized. One investigator, Dr. Fiddes, enrolled 39 patients (center 001); the next highest enrollment at one center was 10. Most of the other 11 centers enrolled 1-7 patients. The sample size calculation was 60 patients per group, this study only enrolled about 70% of the expected number of patients.

There were 10 withdrawals (eprosartan, 6 and placebo, 4) from double blind treatment, 4 for adverse events (2 per group). There was 1 death (patient 090.001.00057 experienced a myocardial infarction on Day 32 of treatment and died the same day). The drop outs for adverse events included 2 patients in placebo group (pulmonary edema and CAD and fatigue) and 2 in eprosartan (death discussed above and syncope).

Out of the 85 randomized patients, 74 (eprosartan 34 and placebo 40) had both baseline and 6 week 24-hour urine collection and were included in the for efficacy analysis. The difference between placebo and eprosartan for the primary efficacy analysis was not statistically significant.

In summary, this study stopped enrollment prematurely and failed to show that use of eprosartan, compared to placebo, causes a decrease in proteinuria in patients with type II diabetes mellitus.

6.0 Electrocardiograms and heart rate

ECG intervals, reported ECG abnormalities including withdrawals for cardiac arrhythmias, and heart rate changes for all eprosartan patients who were enrolled into 1 of the 15 Phase II/III hypertension trials are discussed in the following sections..

This section does not include ECG evidence of myocardial ischemia/infarction.

6.1 ECG abnormalities

ECG intervals

The table below shows the ECG intervals (PR, QRS, and QTc) for all patients who received eprosartan in a Phase II/III hypertension study and had data. The means at baseline, endpoint, change from baseline at endpoint and mean % change are included.

ECG parameters (msec)

parameter	n	baseline msec	endpoint msec	change from baseline msec (% change)
PR interval	2101	164.45	164.37	-0.08 (0.76%)
QRS interval	2113	86.34	86.9	0.56 (1.7%)
QTc interval	2108	415.53	416.37	0.83 (1.1%)

appendix 10.4

Overall, the changes from baseline for all parameters are negligible.

In addition, the ECG results from the 2 trials that were placebo controlled and had the widest dose range (protocols 011 and 049) were reviewed and there is no evidence that eprosartan, compared to placebo, has an adverse effect on the PR, QRS or QTc intervals (table 52 study 011 and table 46 study 049).

Reported ECG abnormalities

The table below displays the number and percent of patients who reported an ECG abnormality in 1 of the 15 Phase II/III hypertension studies. The table includes only abnormalities reported by 2 or more patients.

Number and (percent) of patient

abnormality	eprosartan N=2334
at least 1 event	83 (3.6)
palpitations	26 (1.1)
abnormal ECG (nonspecific)	13 (0.6)
tachycardia	12 (0.5)
abnormal ECG (specific)	11 (0.5)
atrial fibrillation	11 (0.5)
arrhythmia	10 (0.4)
bradycardia	7 (0.3)
extrasystoles	7 (0.3)
atrioventricular block	4 (0.2)
bundle branch block	4 (0.2)
supraventricular tachycardia	4 (0.2)
nodal arrhythmia	2 (0.1)

Table 10.5 appendix 5.1.

Events reported by only one patient include heart block, atrial arrhythmia, ventricular tachycardia, and supraventricular extrasystole.

Less than 4% of the total patient population reported any abnormality and palpitations was the only abnormality reported by more the 1% of the eprosartan population. Overall, the incidence of reported arrhythmias/ ECG abnormalities was negligible.

The tables below display the number and percent of patients, by dose, in studies 011 and 049 who had a normal ECG at baseline that became abnormal during treatment. Only the abnormalities reported by more than 2 patients for any dose group except placebo are included in the tables.

Protocol 011: number and (percent) of patients

		eprosartan dose (mg) BID				
ECG abnormality	placebo n=75	25 n=68	100 n=61	200 n=63	300 n=65	400 n=66
any new abnormality	8 (10.7)	11 (16.2)	7 (11.5)	6 (9.5)	11 (16.9)	7 (10.6)
1st degree AV block	0	3 (4.4)	1	0	0	0
sinus bradycardia	5 (6.7)	3 (4.4)	4 (6.6)	4 (6.3)	8 (12.3)	4 (6.1)

Table 51 study report

Protocol 049: number and (percent) of patients

		eprosartan dose (mg) QD			
ECG abnormality	placebo n=59	400 n=63	600 n=66	800 n=62	1200 n=60
any new abnormality	7 (11.9)	9 (14.3)	3 (4.5)	4 (6.5)	2 (3.3)
left ventricular hypertrophy	2 (3.4)	3 (4.8)	3 (4.5)	1 (1.6)	1 (1.7)
sinus bradycardia	3 (5.1)	3 (4.8)	0	2 (3.2)	1 (1.7)

Table 45 study report

The incidence rates for reports of abnormal ECGs reported by patients receiving eprosartan in both studies are similar to those reported by placebo patients, regardless of dose.

Withdrawals for arrhythmias

The patients who withdrew for arrhythmias, conduction defects, and/or other ECG abnormalities other than evidence of ischemia/infarction are discussed below. In addition, there were 3 sudden deaths (patients 052.013.527.00253, 040.017.414.00145, 040/017/414/00149[1]) that could have been the result of an arrhythmia. These patients are discussed in section 4.1.

[1]Not listed in appendix 5.6.1.1

The patients (including Safety Update, N=2367) who withdrew for an ECG abnormality and/or arrhythmia include:

- 10 (0.4%) for atrial fibrillation,
- 7 for palpitations
- 4 for arrhythmia
- 4 for abnormal ECG
- 4 for tachycardia
- 2 for extrasystoles
- 2 for ventricular extrasystoles
- 2 for supraventricular tachycardia

and 1 each for atrial flutter[2], bundle branch block, specific ECG abnormality.

appendix 8.3.A amendment 45 submitted 5-6-97

There was no obvious link between the use of eprosartan and the occurrence of an ECG abnormality including the 3 sudden deaths. In summary, there is no evidence that eprosartan has an adverse effect on the PR, QRS or QTc intervals or causes cardiac rate, rhythm, or conduction abnormalities.

6.2 Heart rate

The effect of eprosartan on heart rate was examined by reviewing the placebo controlled studies and comparing the mean change from baseline at endpoint for sitting heart rate for the eprosartan and the placebo groups. The results for the 2 placebo controlled trials that studied the widest dose range (protocols 011 and 049) are shown in the table below.

Sitting heart rate (bpm)

protocol number	eprosartan dose (mg)/regimen	n	mean baseline	mean change from baseline	difference from placebo
011	placebo	91	74.6	-1.5	-
	25/bid	90	73.5	-0.1	1.3
	100/bid	86	72.8	0.3	1.8
	200/bid	90	73.7	-0.8	0.7
	300/bid	85	74.2	0.2	1.5
	400/bid	90	74.1	0.1	1.6

[2]Coded as atrial arrhythmia

Sitting heart rate (bpm)

protocol number	eprosartan dose (mg)/regimen	n	mean baseline	mean change from baseline	difference from placebo
049	placebo	72	72.9	-0.3	-
	400/qd	72	72.9	-0.4	+
	600/qd	73	72.8	0.0	+
	800/qd	72	73.2	-0.5	+
	1200/qd	71	73.1	-1.7	+

+significant regimen-by-center interaction at the 0.10 level-no statistical inferences were made.
Table 3.16 vol 401

Baseline mean heart rates were similar for the placebo and eprosartan groups for both studies. Overall, there were small increases and decreases from baseline at endpoint for all doses of eprosartan and these changes were similar to those for placebo. It appears that eprosartan, over a wide dose range, has no effect on heart rate.

7.0 Special populations

Adverse events for the following subgroups were examined: age, gender, race, patients with impaired kidney function, patients with impaired liver function, patients with moderately severe hypertension, and patients with diabetes mellitus.

7.1 Age

The possibility of age influencing the safety of eprosartan was explored by a.) examining adverse events reported by all eprosartan patients who were enrolled in 1 of the 15 Phase II/III hypertension trials by age group (< 65 years and ≥ 65 years) and b.) examining the safety results of study 017 which evaluated the efficacy of eprosartan in elderly hypertensive patients. The reported adverse events from a subset of patients, the old old (≥ 75 years), were also examined.

All trials

Of the 2334 patients who received eprosartan in the hypertension trials, 29.2% (681) were at least 65 years of age. The incidence rate of patients who reported at least 1 adverse event was higher in the younger patients (< 65 years) compared to older patients (65.5%, 1082/1653, vs. 59.6%, 406/681, respectively). The only individual adverse events that were reported by at least 2% of the patients and were reported more often in the older patients compare to the younger patients include urinary tract infection (2.3% vs. 1.5%) and hypercholesterolemia (2.9% vs. 1.4%). (table 14.2 vol 406)

There were 124 (5.3%) study patients who were at least 75 years of age (the old old). While it is difficult to try to draw conclusions based on such a small sample size, there was no obvious difference in the total number of patients who reported adverse events in the old old group compared to their younger counterparts (61.3% and 63.9%, respectively). The events that were reported by more than 3% of the old old patients and were reported more often by them than the younger group included: chest pain (3.2% vs. 2.8%), injury (5.6% vs. 4.3%), hypercholesterolemia (4.8% vs. 1.7%), back pain (3.2% vs. 2.9%), depression (3.2% vs. 1.2%), and bronchitis (3.2% vs. 2.9%). (appendix 14.2.2).

Study 017

Study 017 was a double blind, placebo controlled trial in elderly patients 63 years of age or older with mild to moderate hypertension. The 2 eprosartan dose groups were 100 mg bid and 200 mg bid. The mean age of the 230 patients randomized was approximately of 72 years. The incidence rates for patients who reported at least one adverse events were similar for placebo and the eprosartan treatment groups.

A subset analysis of patients less than 75 years and ≥ 75 years was conducted for reported adverse events. The table below shows the number and percent of patients who reported at least 1 adverse event by age and treatment group.

Number and (percent) of patients

< 75 years of age		≥ 75 years of age	
placebo n=32	eprosartan n=129	placebo n=15	eprosartan n=54
11 (34.4)	43 (33.3)	9 (60.0)	25 (46.3)

Data source table 15.3.2 study report

The only specific adverse events reported by more than 2 eprosartan old old patients included atrial fibrillation (3) and urinary tract infection (3). There were no placebo patients in this age group who reported these events. In this study, although the samples sizes are very small, there was no indication that old old patients experienced more adverse events while receiving eprosartan compared to their placebo counterparts.

Eprosartan does not appear to be less safe in the elderly population.

7.2 Gender

Of the 2334 eprosartan hypertensive patients, 922 (39.5%) were female. The rate of females reporting at least 1 adverse event was similar to the rate reported by males: 66.6% and 61.9%, respectively. The adverse events reported by 2% or more patients of either sex and reported 2% more often in one group compared to the other are shown in the table below. Of course, without a placebo comparison it is difficult to draw any meaningful conclusions.

Number and (percent) of patients

adverse event	females n=922	males n=1412
at least 1 event	614 (66.6)	874 (61.9)
headache	125 (13.6)	164 (11.6)
pharyngitis	62 (6.7)	61 (4.3)
coughing	66 (7.2)	63 (4.5)
bronchitis	42 (4.6)	27 (1.9)
urinary tract infection	38 (4.1)	3 (0.2)

Table 14.3 vol 406

There is no indication that the safety profile of eprosartan is influenced by gender.

7.3 Race

The racial breakdown of the 2334 eprosartan patients was 81.6% white, 10.9% black and 7.5% "other." The table below displays the number and percent of patients reporting at least 1 adverse event, by racial group.

	whites n=1904	black n=255	other n=175
at least 1 event	1220 (64.1)	156 (61.2)	112 (64.0)

table 14.4 vol 406

Only headache shown a sizable disparity in reporting pattern: 11.7% in whites, 11.8% in blacks, and 21.1% in other. Of course, without a placebo control for comparison and with such small sample sizes in the non-white groups, it is difficult to draw any conclusions except that, overall, there is no evidence of ethnicity influencing reported adverse events by patients taking eprosartan.

7.4 Kidney function

Phase I study 021 evaluated the effect of impaired renal function of the plasma concentration of eprosartan; study 026 evaluated the effect of eprosartan on glomerular filtration rate and effective renal plasma flow in patients with mild to moderate hypertensive patients; study 044 was designed to compare the effect of eprosartan and captopril on renal hemodynamic parameters, effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) in subjects with normal renal function and in patients with impaired renal function (since this study was terminated early, only safety results were reviewed); and study 099 evaluated the effect of a single dose of eprosartan in patients receiving hemodialysis.

Study 021

This was an open-label, multiple dose pharmacokinetic study with all patients receiving 200 mg of eprosartan bid for 7 days. The primary objective was to determine if the plasma concentration of eprosartan is altered in patients with impaired renal function. Patients were stratified based on creatinine clearance (Clcr): 8 had normal renal function and 26 had varying degrees of renal impairment. The results, shown in the table below; excluded 5 patients: 1 with normal renal function and 4 with moderately impaired renal function. (The sponsor did not determine AUC(0-inf), half-life and accumulation ratios.)

Means (SD)

PK parameter	normal Clcr > 80 mL/min n=7	mild Clcr 60 - 80 mL/min n=8	moderate Clcr 30 - 59 mL/min n=11	severe# Clcr 5 - 29 mL/min n=3
AUC (0-12 h) ng.h/mL	2961 (1558)	2239 (867)	3711 (1772)	4597 (1423)
Cmax (ng/ml)	590 (318)	536 (217)	795 (388)	888 (202)
CLr (ml/min)	39.2 (27.1)	45.6 (7.3)	23.1 (17.4)^	2.16 (0.57)+
%dose excreted	2.78 (1.56)	3.00 (1.14)	2.18 (1.41)^	0.28 (0.05)+

^n=8
+n=2
#patients were not receiving hemodialysis
tables 10 and 13 study report

Cmax and AUC(0-12) values for eprosartan increased and clearance and the percent of the dose excreted decreased with decreasing renal function. The clearance of eprosartan in patients with severe renal failure dropped to about 6% of the clearance for normals.

In this study, there were no deaths or serious adverse experiences. There were 3 patients who withdrew because of adverse events:
-Subject 022, a patient with moderate renal impairment, developed a urinary tract infection considered to be unrelated to study medication; he was subsequently re-enrolled;
-Subject 023, a patient with moderate renal impairment, developed severe diarrhea and nausea;
-Subject 024, a subject with normal renal function, developed moderate hypesthesia, shortness of breath, upset stomach and tachycardia.

In conclusion, clearance of eprosartan is decreased in patients with renal impairment, especially those with creatinine clearance less than 30 ml/min. There is no evidence that dose adjustment is necessary; but it might be prudent to do so for those with severely impaired renal function.

Study 026

This placebo controlled cross over study was conducted to assess the effects of eprosartan compared to placebo on renal hemodynamics in 14 subjects with mild to moderate essential hypertension. Overall, there were no relevant differences in glomerular filtration rate and effective renal plasma flow between eprosartan 300 mg and placebo administered for 28 days. One subject (001) with a history of acute pancreatitis and ethanol abuse was withdrawn from eprosartan because of severe pancreatitis and dehydration on day 17.

Study 044

This was a partial double-blind, placebo controlled, crossover pharmacodynamic study comparing the effect of eprosartan 300 mg, open label captopril 25 mg, and placebo on renal hemodynamic parameters, effective renal plasma flow and glomerular filtration rate, in subjects with normal renal

and those with renal impairment. The study was terminated early and there were significant carry over effects. A total of 35 subjects received at least 1 dose of study drug and 30 patients completed the study.

There were no deaths; 4 patients dropped out because of adverse events: subject 028 was diagnosed with adenocarcinoma of the colon while taking eprosartan, subject 046 developed leg edema requiring hospitalization while taking captopril, subject 012 had nausea and vomiting while receiving placebo, and subject 042 dropped out for rash, urticaria and pruritis while on captopril.

Study 099

This open label study evaluated the pharmacokinetics of eprosartan in 9 patients receiving hemodialysis. After a single 400 mg dose, the AUC (o-t) and Cmax of eprosartan were increased by 60% and 22%, respectively, in the hemodialysis patients (with considerable variablity) compared to 10 normal volunteers. In addition, hemodialysis did not affect the clearance of eprosartan.

Combined studies

The sponsor reviewed the safety of 53 eprosartan patients with renal impairment enrolled into studies 021 and 044. The adverse events reported by at least 3 eprosartan patients are shown below with placebo as the comparator.

Number and (percent) of patients

adverse event	eprosartan n=53+	placebo n=27
at least 1 event	32 (60.4)	8 (29.6)
headache	16 (30.2)	4 (14.8)
fatigue	6 (11.3)	1 (3.7)
diarrhea	5 (9.4)	0
abdominal pain	5 (9.4)	0
dizziness	3 (5.7)	0
vomiting	3 (5.7)	0
nausea	3 (5.7)	0

+ a total of 56 patients were studied but 3 did not receive eprosartan, from fax dated 5-5-97. appendix 5.8

Patients with renal impairment who received eprosartan reported adverse events twice as frequently as did patients who received placebo.

7.5 Liver impairment

Study 022 was an open label, single 100 mg dose study comparing the pharmacokinetics of eprosartan in 16 subjects: 8 normals and 8 with hepatic impairment (1 advanced cirrhosis, 5 moderate impairment, and 2 minimal impairment based on Child's classification).

The table and figures below show the pharmacokinetic results.

Means (SD)

pharmacokinetic parameter	normals n=8	hepatic impairment n=8
$AUC_{(0-t)}$ (ng.h/ml	1616 (379)	2610 (1624)
Cmax (ng/ml)	428 (128)	486 (243)
median Tmax (h)	4	6

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Figure 11.1
Plasma SK&F 108566 Concentrations Following Single Oral 100 mg Dose Administration to Subjects with Hepatic Impairment

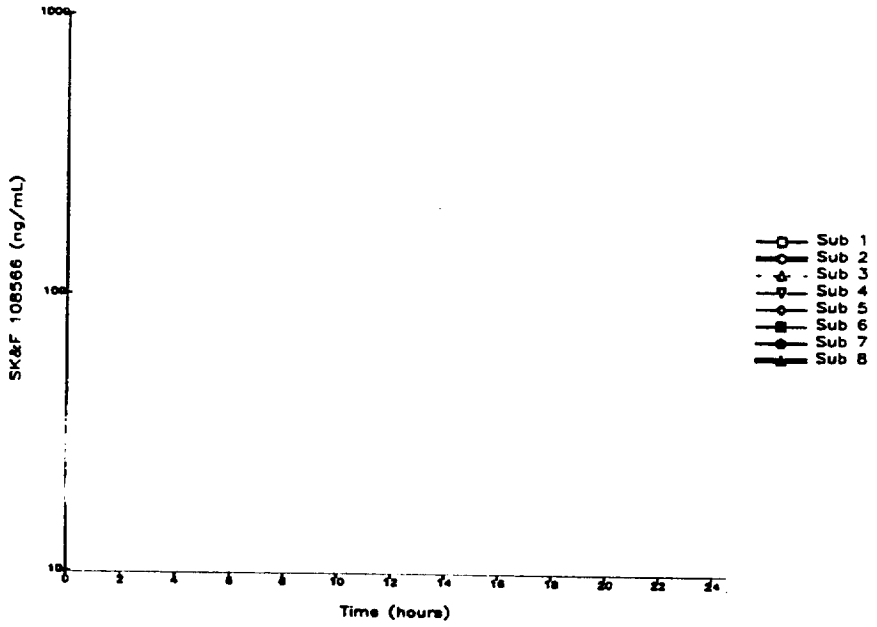
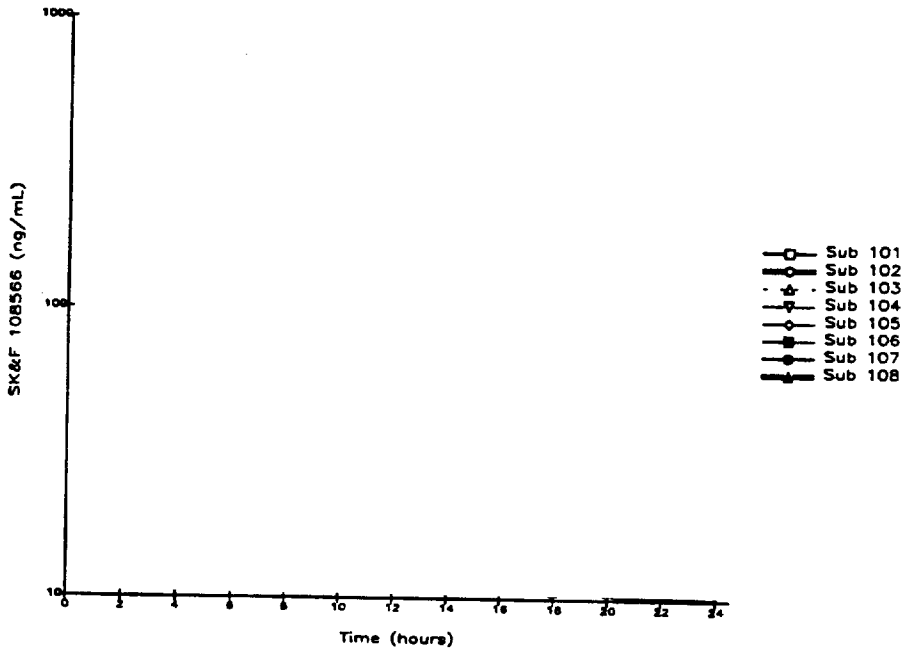


Figure 11.2
Plasma SK&F 108566 Concentrations Following Single Oral 100 mg Dose Administration to Healthy Subjects



The AUC and median Tmax, but not Cmax, for eprosartan were increased in patients with hepatic impairment compared to normals. The AUC was increased by 61.5% in patients with liver impairment compared to the normals. Subject 4 with moderate hepatic impairment (caused by alcoholism and hepatitis C) had an AUC that was 3 times higher than the mean for the 7 other patients (6073 ng.h/ml compared to the mean 2610 ng.h/ml). This value was viewed by the sponsor as an aberration. However, dose adjustment in patients with decreased liver function should be considered.

7.6 Moderately severe hypertension

Study 047 was a double-blind, parallel group, active control design study that compared the effect of eprosartan and enalapril in patients with moderately severe hypertension (defined as a sitting diastolic blood pressure 115 mmHg to 125 mmHg, inclusive). Doses of eprosartan were 200 to 400 mg twice daily and doses of enalapril were 10 to 40 mg once daily with drugs titrated to effect. Duration of treatment was for a maximum of 12 weeks.

There were 2 serious adverse events in the enalapril arm (1 suspected fracture following a fall and 1 planned surgery) and none in the eprosartan arm. No deaths during the study were reported. Routine adverse events were reported by slightly more patients who received enalapril (61.0%) compared to eprosartan patients (59.3%). Headache was reported more often by the enalapril patients (23.7%) compared to eprosartan (15.3%) while myalgia was reported by more eprosartan patients (16.9%) than enalapril patients (8.5%).

7.7 Diabetes mellitus

There were 173 patients (7.4%) in the Phase II/III hypertension study with a secondary diagnosis of diabetes mellitus. Of these, 59.5% (103) reported at least 1 adverse event compared to 63.7% (2005) of the patients who did not have a secondary diagnosis of prior MI, renal impairment, or gout. The events reported by at least 5 diabetic patients that occurred at least 1% over the rate of reporting by the patients without one of the secondary diagnosis included hyperglycemia (7.5% v. 0.9%), back pain (4.0% vs. 2.9%), and bronchitis (4.6% vs. 2.8%). Table 15.1 vol 406.

Study 090 was a 6 week, double-blind, placebo-controlled study followed by a 6 week open-label extension that evaluated the effects of eprosartan 300 mg bid on proteinuria in patients with type II diabetes mellitus. Patients were those with controlled Type II diabetes mellitus of at least 12 months duration with glycosylated hemoglobin (HbA1C) < 9% at screening. There were 45 placebo and 40 eprosartan patients and the percent of patients reporting at least 1 adverse event were 44.4% and 50.0%, respectively. Adverse events reported by at least 3 eprosartan patients and reported more often by the eprosartan group than the placebo group were dizziness (15.0% and 6.7%), fatigue (5.9% and 4.4%), and UTI (7.5% and 0%). Table 14. Dr. Fiddes enrolled nearly half of the patients so the validity of data from this study is questionable.

There was 1 death. Patient 090.001.00057 was a 71 year old Hispanic male who was randomized to eprosartan and died of an acute myocardial infarction on Day 32. He is discussed in section 4.1.2. There were 4 drop outs for adverse events: 2 placebo patients (pulmonary edema/coronary artery disease and fatigue) and 2 eprosartan patients (myocardial infarction followed by death-- patient 090.001.00057--and syncope).

Mean percent change from baseline at endpoint for plasma glucose was -2.92% for the placebo patients and -1.95% for the eprosartan patients. The mean percent change from baseline at endpoint for both BUN and serum creatinine values were elevated for the eprosartan patients (5.3% and 2.37%, respectively) compared to the placebo patients (1.93% and -1.58%, respectively). It appears that patients with diabetes could have their renal function worsen while taking eprosartan (Table 22 study 090).

8.0 Drug-drug interactions

There is no evidence for major pathways of transformation of eprosartan. Drug-drug interaction studies were conducted with digoxin, warfarin (eprosartan is highly bound to plasma proteins with *in vitro* plasma protein binding ranging from 98.0% to 98.4%), ranitidine, fluconazole, and ketoconazole in healthy volunteers. A brief summary of the findings of observational studies (safety and efficacy studies that allowed concomitant medication) is also included.

Digoxin (protocol 023)

This was an open-label two crossover single dose digoxin study during which volunteers received digoxin either alone or with multiple dose 200 mg eprosartan bid. The use of these drugs together did not affect the pharmacokinetics of digoxin or overall safety. There were no deaths, serious adverse events, or drop outs for adverse events. There were no routine adverse events that were reported by more than one individual. Therefore, dose adjustment of digoxin when administered with eprosartan is not necessary.

Warfarin (protocol 027)

This was a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effect of 300 mg eprosartan bid taken for 7 days on warfarin dosed to achieve a baseline INR of 1.3 to 1.6. The concomitant use of eprosartan did not meaningfully affect the INR for warfarin (1.42 for warfarin administered with and 1.35 for warfarin administered without eprosartan). There were 2 adverse events (dizziness and dyspepsia) reported by volunteers receiving the combination that were not reported by volunteers receiving only warfarin. There were no deaths, serious adverse events, or drop outs for adverse events in this study.

Glyburide (protocol 028)

This was a randomized, double-blind, placebo-controlled, crossover study in patients with non-insulin-dependent diabetes mellitus taking the oral hypoglycemic glyburide. The dose of glyburide was individualized but had to be between 3.75-10 mg once daily and dosing had to have been started at least 30 days prior to the study. Patients then received either eprosartan 200 mg or placebo bid concomitantly with glyburide for 7 days. Eprosartan had no effect on glucose profiles or mean 24-hour plasma glucose concentrations when taken with glyburide. The mean plasma glucose concentration on the last day of dosing with the combination was similar to that on the last day of dosing with glyburide alone (203 mg/dL and 212 mg/dL, respectively). There were no deaths, serious adverse events, or drop outs for adverse events in this study.

Ranitidine (protocol 029)

This was an open-label crossover study in which subjects received a single dose of eprosartan 400 mg alone as well as with ranitidine 150 mg (following a three-day ranitidine 150 mg bid run-in period). There was a minimum 7 day washout period between treatment phases. There were small

differences in the mean Cmax, AUC, and clearance between eprosartan alone and eprosartan plus ranitidine.

Parameter	Eprosartan	Eprosartan plus Ranitidine	Ratio* (95% CI)
Cmax ng/mL	2260	2019	0.93
	(1465)	(1173)	(0.81, 1.07)
AUC(0-t) ng.h/mL	8042	7504	0.89
	(4128)	(4635)	(0.77, 1.03)
Clr mL/min	31.2	27.3	0.96
	(17.4)	(10.5)	(0.64, 1.43)

* Ratio of geometric means for eprosartan plus ranitidine relative to eprosartan alone
(Standard deviations)

There were no deaths or serious adverse events. One subject withdrew after involvement in a motor vehicle accident. One subject had a vasovagal response 2 hours after receiving eprosartan plus ranitidine which required treatment with saline infusion and the incident was resolved a short time later.

Fluconazole (protocol 094)

This was an open-label parallel-group study in which subjects were randomly assigned to receive multiple doses of either eprosartan 300 mg bid, losartan 100 mg qd, or placebo for 20 days. After 11 days of dosing, subjects received concomitant fluconazole 200 mg once daily. Losartan, unlike eprosartan, is metabolized by CYP2C9, a hepatic enzyme that is inhibited by fluconazole.

As expected, this study showed that the metabolism of losartan (but not eprosartan) to its active metabolite was slowed when losartan was given concomitantly with fluconazole. AUC and Cmax for losartan were increased by 69% and 31%, respectively, and the level of its active metabolite was decreased by about 43%. However, since the dose of losartan is titrated to effect, and there are no known dose related side effects for losartan, this finding is basically irrelevant. There were no deaths or serious adverse events; the one drop out for adverse event (for insomnia) occurred in the eprosartan group.

Ketoconazole (protocol 095)

This was an open-label parallel group study in which subjects were randomly assigned to receive either eprosartan, losartan or placebo for 10 days along with ketoconazole, a potent inhibitor of CYP3A4, for 5 days. Eprosartan is not metabolized so pharmacokinetic parameters were expected to be similar for eprosartan alone and eprosartan plus ketoconazole and this was what was observed. However, pharmacokinetic parameters, also, were no different for losartan and losartan plus ketaconazole, leading one to believe that losartan is not metabolized by this enzyme. There were no deaths or serious adverse events; the 1 drop out for adverse event (vomiting) occurred in the eprosartan plus ketoconazole group.

Observational studies

The table below shows 6 common adverse events reported by patients who received eprosartan alone, or eprosartan plus aspirin, cholesterol reducing agents, or diuretics in safety and efficacy studies.

Number and (percent) of patients^

adverse event	eprosartan alone n=1417	plus aspirin n=330	plus HMG-CoA reductase inhibitors n=96	plus diuretics n=655
any event	800 (56.5)	232 (70.3)	67 (69.8)	358 (54.7)
headache	134 (9.5)	52 (15.8)	8 (8.3)	43 (6.6)
dizziness	45 (3.2)	18 (5.5)	4 (4.2)	30 (4.6)
arthralgia	23 (1.6)	15 (4.5)	4 (4.2)	17 (2.6)
myalgia	70 (4.9)	21 (6.4)	2 (2.1)	31 (4.7)
URI	105 (7.4)	36 (10.9)	8 (8.3)	67 (10.2)

^Patients who received more than one type of selected concomitant medication are counted separately for each category.

Table 13.2 vol 406

Not surprisingly, patients who received additional drugs reported more adverse events. While it is difficult to draw conclusions from observational data, the differences for the reporting incidence of the events were minor and probably not clinically meaningful. Overall, there is no evidence that a particular drug cannot be given concomitantly with eprosartan and there is no evidence that there is any need for a dose adjustment.

In addition, one *in vitro* study was conducted to evaluate the interaction of drugs that, like eprosartan, are highly protein bound. The results showed that eprosartan, at concentrations up to 5 ug/ml (Cmax for 600 mg steady state oral dose was 16 ug/ml), had no effect on the extent of binding of [14C]phenytoin or [14C]warfarin at concentrations of 10-20 ug/mL or 0.2-10 ug/mL, respectively.

In conclusion, there should be no restrictions placed on the use of eprosartan with other medications.

9.0 Clinical Pharmacology Studies (safety review)

There was a total of 29 clinical pharmacology studies for eprosartan which included 26 studies that used only the oral formulation, 2 studies that used both oral and intravenous formulations and 1 study that used only intravenous (study 004 with 12 subjects). Of the 26 studies with only the oral formulation, 23 included healthy or patient volunteers, and 3 included hypertensive patients (appendix 2). A total of 32 subjects received the intravenous formulation. The sections below are divided into single and multiple dose studies and include both healthy volunteers and patients together.

Any dose of eprosartan

A total of 635 subjects received at least 1 dose of eprosartan in the clinical pharmacology program. The numbers of subjects by type are shown below.

Eprosartan clinical pharmacology population	
Healthy Volunteers	479
Patients:	
Hypertension	68
Diabetes Mellitus	15
Renal Insufficiency	53
Hepatic Disease	8
intravenous only	12
total	635

table 3.6 vol 405

Single dose

A total of 407 unique subjects (399 healthy volunteers and 8 patients with hepatic impairment) received a single oral dose of eprosartan on one or more occasions in 16 studies. Since subjects were allowed to enter more than 1 study, the total number of dosing exposures to single dose eprosartan monotherapy was 838. Most of the dosing exposures were in the dose range 300-400 mg (appendix 5.6.1.2). Of the total 838 dosing exposures, there were 127 exposures (15.2%) that produced at least 1 report of an adverse event. The adverse events reported by at least 1% of the population included headache (7.4%), dizziness (2.1%), and nausea (1.0%). Appendix 5.6.1.1.

Multiple dose

A total of 216 subjects (80 healthy volunteers, 68 hypertensive patients, 53 patients with renal impairment, and 15 patients with diabetes) received multiple oral doses of eprosartan up to 28 days of consecutive dosing in 10 studies.

The total number of exposures to eprosartan monotherapy was 255 with the majority of subjects receiving 400 mg (appendix 5.6.2.2). Of these, there were 85 exposures (33.3%) that produced at least 1 report of an adverse event. The 3 most frequently reported events were headache (17.6%), fatigue (4.7%), and dizziness (3.5%). Appendix 5.6.2.1.

Deaths, serious safety, and drop outs for adverse events

Deaths

There were no deaths in any of the 635 subjects (or patients) enrolled into a clinical pharmacology study (Amendment 47 dated 5-15-97).

Serious adverse events

The only report of a serious adverse event not leading to drop out was in study 038 where subject 038 developed renal pain after a single dose of eprosartan 400 mg. (Amendment 47 dated 5-15-97).

Drop outs for adverse events

In the 3 clinical pharmacology studies (009, 048, and 026) with a total of 68 patients, there were 2 study withdrawals for adverse events. Both are shown in the table below.

protocol	subject number	medication at time of event	total daily dose/ time on drug	adverse event
026	001	eprosartan	600/17 days	pancreatitis, dehydration
026	005	placebo	NA	chest pain

appendix 8.10

Patient 001 was a 48 year old black male with a past medical history of hypertension, acute pancreatitis, and ethanol abuse. The patient withdrew from study 026 on day 17 of eprosartan 300 mg bid treatment because of severe pancreatitis and moderate dehydration. He was admitted to hospital and his amylase level was 404 U/L. Screening laboratory showed elevated blood glucose of 117 mg/dl, AST 50 U/L, ALT 64 U/L and GGT 119 U/L. Other events included headache and flu symptoms. He was discharged from the hospital about 1 week later in improved condition.

There were 3 of 53 eprosartan patients enrolled into a renal impairment study (021 and 044) who dropped out because of an adverse event. There was 1 captopril patient who withdrew because of leg edema.

protocol	subject number	total daily dose of eprosartan (mg)	time on drug	adverse event
021	022	400	3 doses	UTI, fever, dysuria
021	023	200	NA	nausea, diarrhea
044	028	600	7 days	adenocarcinoma

appendix 8.11

Of the healthy volunteers who dropped out because of an adverse event,

- 4 received a single dose of eprosartan and dropped out because of sinus pause and syncope; extrasystoles; diarrhea; fever, dizziness, viral infection, pharyngitis; increased ALT; hematuria and renal pain.
- 3 received a single dose of placebo and dropped out because of extrasystoles; arrhythmia (2); ventricular tachycardia.
- 2 received multiple doses of eprosartan and dropped out because of anxiety and chest pain; hypesthesia, dyspnea, dyspepsia, and tachycardia),
- 1 received multiple doses of captopril and dropped out because of rash, urticaria, and pruritus.

appendix 8.11

In clinical pharmacology studies, laboratory transitions of potential clinical concern were rare. Abnormalities included:

- 1.5% (2/130) incidence of BUN > 1.5 times upper limit of normal,
- 1.1% (6/523) incidence of serum potassium >0.5 mEq/l above limit of reference range,
- 0.9% (5/509) incidence rate of ALAT > 2 times upper limit of normal, and
- 0.1% (1/511) incidence rate of ASAT > 2 times upper limit of normal.

APPEARS THIS WAY
ON ORIGINAL

10.0 Long term safety

Eprosartan was administered to hypertensive patients for up to 2 years in 4 open labeled, uncontrolled, extension trials (039, 040, 050, 052). The majority of these patients had previously participated in a double blind, controlled (base) study before entering the extension study. Patients who participated in a base study but received different study medication or had a period of at least 15 days between exposure to the same drug were counted as new patients in the extension study and their exposures to study medications were not combined. Any off-drug periods were not included in determining the overall exposure to a study medication.

protocol no./base studies	doses (mg)/ dosing regimen
039/014, 016, 041, 053	100-300 bid
040/014, 017, 051, 047	100-300 bid
050/011,049	400-800 qd
052/013	400-800 qd

As of May 31, 1996, eprosartan with and without HCTZ has been administered to 1417[1] patients in the 4 studies combined. The mean duration of exposure for these patients was 198 days. The break down by the length of exposure is shown below.

Number and (percent) of patients

length of exposure (months)	eprosartan n=1417
< 6	736 (51.9)
6-12	515 (36.3)
> 12	166 (11.7)

Appendix 17.1.A

Of the 1417 patients, 802 were male (57%) and 615 were female (43%). The age range was 24 to 93 years, with a mean age of 57 years; 31% were ≥ 65. The population was mostly white (82%).

Deaths

Of the 16 eprosartan patients who died during or shortly after treatment, 11 were participants in 1 of the long term studies (see section 4.1). There was no obvious link between eprosartan and any of the

[1]table 8.E.2 summary table of investigations adds up to 1422 patients; the individual reports were not as current as the integrated summary of safety.

deaths.

Withdrawals

The number of patients who withdrew from 1 of the open label extension studies by reason is shown below.

Number of eprosartan patients

protocol	adverse event	lack of effect	other
039 n=140	13	32	16
040 n=253	13	4	6
050 n=336	38	30	24
052 n=68	2	4	1
total n=797	66	70	47

individual study reports

Withdrawals for adverse events

All 4 studies are still ongoing. Approximately 8% of patients studied thus far stopped therapy with eprosartan because of an adverse event. This is not an unusually high drop out rate for studies lasting a year or longer. An updated report from the sponsor added 27 additional drop outs but the number of patients studied was not supplied (fax dated 2-21-97). One patient (011.015.00800) withdrew for moderately increased liver enzymes (see section 5.2). Withdrawal for adverse events is discussed in section 4.3.

Routine adverse events

The incidence rate for the long term patients[2] reporting at least 1 adverse event was 67.8% (961), again not a surprisingly high rate for patients treated over 1 year. The overall cumulative incidence rates for any adverse event as well as for selected adverse events (only those events reported by more than 6% of patients) at various time intervals are shown below.

[2]N=1416, 1 patient had no data

	Cumulative incidence rates+ (%)				The maximal interval risk rate
	1 month	3 months	6 months	12 months	(per 1000)
any event	33.1	60.0	70.9	80.6	34.3
headache	5.3	10.4	14.4	16.9	3.5
URI	3.9	8.9	13.0	19.7	1.4
myalgia	2.4	5.5	8.4	10.1	1.1
coughing	2.1	5.1	6.6	8.8	1.8

+1 mo = upper interval day 29; 3 mo = upper interval day 91; 6 mo = upper interval day 181; 12 mo = upper interval day 361.
table 17.3 vol 406

The reported events were similar to those reported for the controlled, short term trials.

Laboratory values

The means at endpoint were similar to the means at baseline for most of the laboratory parameters. Those variables showing some change included hemoglobin (147.0 g/l at baseline and 145.1 g/L at endpoint) and BUN (5.3 mmol/L at baseline and 5.8 mmol/L); these changes were small and inconsequential. Consistent with other angiotensin II receptor antagonists, eprosartan appears to cause a small decrease in hemoglobin and a small increase in BUN. Mean serum creatinine was decreased (Table 17.5 vol 406).

The table below shows the number and (percent) of long term eprosartan patients who had laboratory values outside the sponsor defined levels of concern (either low or high) at baseline and at endpoint.

	Baseline		Endpoint	
	n/N	%	n/N	%
Worst Case (Low)				
Platelets (10^9/L)	3/1395	0.2	5/1352	0.4
Total Neutrophils (10^9/L)	11/1289	0.9	17/1337	1.3
WBC Count (10^9/L)	5/1396	0.4	3/1352	0.2
Hemoglobin (g/L)	1/1396	0.1	3/1352	0.2
Worst Case (High)				
ALAT (IU/L)	0/1397	0.0	3/1351	0.2
Alk Phos (IU/L)	0/1397	0.0	0/1351	0.0
ASAT (IU/L)	0/1397	0.0	1/1351	0.1
BUN (mmol/L)	0/1397	0.0	0/1351	0.0
Creatinine (umol/L)	0/1397	0.0	0/1351	0.0

table 17.6 vol 406

At endpoint, there were slightly more patients with low platelet values, low total neutrophil count, and/or decreased hemoglobin compared to baseline. On the other high, there were fewer patients with low WBC count at endpoint compared to baseline.

There was no consistent pattern for changes in liver enzymes:

- ALAT 23.2 IU/L at baseline and 24.10 IU/L at endpoint,
- Alk Phos 73.0 IU/L at baseline and 68.50 IU/L at endpoint,
- ASAT 21.4 IU/L at baseline and 21.3 IU/L at endpoint,
- T. Bili 12.7 umol/1 at baseline and 13.2 umol/l at endpoint.

And very few patients had sponsor defined abnormal liver function tests (see previous page).

In summary, these data suggest that long term treatment with eprosartan has little effect on hematology and blood chemistry with the exception of minor decrease in hemoglobin and minor increase in BUN. Adverse events reported by patients participating in long term studies were similar to those reported by patients in the short term controlled trials. The safety of eprosartan does not appear to change with long term use.

11.0 Abrupt withdrawal effects

Although no formal studies were conducted to evaluate the effects of abrupt withdrawal of eprosartan, all 6 placebo controlled studies had a 2 week post treatment period. Following the completion of the double-blind treatment period, patients, with the exception of those who continued into an extension study, returned for a clinic visit 7 to 14 days after the last dose of study medication. There was no tapering of the dose of eprosartan prior to discontinuation.

Approximately half of the patients enrolled into 1 of the placebo controlled trials were evaluated at the end of the 2 week post treatment period (52%, 625/1202 eprosartan and 56%, 197/352 placebo patients).

Overall, there was no difference in the reporting incidence of adverse events during this time period by the 2 treatment groups: 9.0% (56/ 625) of the eprosartan and 9.1% (18/197) of the placebo patients reported at least 1 event. The most commonly reported adverse event for both groups was headache: 1.3% for the eprosartan patients and 2.0% for the placebo patients. All other events were reported by less than 1% of the eprosartan patients. (Table 18.1 vol 406)

There is no evidence that abrupt withdrawal of eprosartan is harmful to patients.

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PHASE II/III CLINICAL STUDIES

HYPERTENSION: COMPLETED

PLACEBO CONTROLLED, MONOTHERAPY

Study	Country	Study Dur.	Design[1]	Treatment	Dose (mg)	Received Med.	Completed Study	Sex M/F
010	US Multicenter (18 Investigators)	4W	DB, PLC, R, PRL	Eprosartan	50 bid 100 bid 150 bid 200 bid	26 26 22 22	24 24 22 22	96/0
				Placebo		22	22	22/0
011	North America Multicenter (34 Investigators)	8W	DB, PLC, R, PRL	Eprosartan	25 bid 100 bid 200 bid 300 bid 400 bid	445	406	287/158
				Placebo		93	81	60/33
013	UK Multicenter (27 Investigators)	13W	DB, PLC, R, PRL	Eprosartan Eprosartan	400 to 800 qd 200 to 400 bid	157	83	90/67
				Placebo		86	28	46/40
017	UK Multicenter (19	9W	DB, PLC, R, PRL	Eprosartan	100 bid 200 bid 300 bid	183	171	78/10

[1]DB=double blind, PLC=placebo controlled, R=randomized, POS=active controlled

	Investigators)			Placebo		47	45	17/30
045	US	4W	DB, PLC, R, PRL	Eprosartan	400 od	31	26	31/0
	Multicenter (8 Investigators)			Placebo		30	24	30/0
049	US	8W	DB, PLC, R, PRL	Eprosartan	400 qd 600 qd 800 qd 1200 qd	290	269	176/114
	Multicenter (32 Investigators)							
				Placebo		74	62	44/30

HYPERTENSION: COMPLETED
PLACEBO CONTROLLED, HCTZ AS BACKGROUND THERAPY

016	North America	4W R, PRL	DB, PLC,	Eprosartan +HCTZ 25 mg	50, 100 bid	104	99	73/31
	Multicenter (12 Investigators)			Placebo +HCTZ 25 mg		52	50	39/13

HYPERTENSION: COMPLETED
ACTIVE CONTROLLED

014	Europe, North America, S.Africa	26W	DB, POS, R, PRL	Eprosartan	200 bid 300 bid	264	230	150/114
	Multicenter (42 Investigators)			Enalapril	5 qd 10 od 20 od	264	217	147/117

Study	Country/ Investigator	Study Dur.	Design	Treatment	Dose (mg)	No. Received Med.	Completed Study	Sex M/F
ACTIVE CONTROLLED (CONT)								
041	US Multicenter (20 Investigators)	12W[2]	DB, POS, R, PRL	Eprosartan	200 to 300 bid	103	90	64/39
				Nifedipine	60 to 90 qd	102	85	62/40
047	Europe and South Africa Multicenter (19 Investigators)	10W	DB, POS, R, PRL	Eprosartan	200 to 400 bid 400 + HCTZ	59	46	29/30
				Enalapril 10 to	40 qd 40+ HCTZ	59	47	28/31
053	US Multicenter (23 Investigators)	6W	DB, PLC, POS, R, PRL	Eprosartan	300 bid	46	39	27/19
				Enalapril	20 od	45	35	23/22
				Placebo		45	34	21/24

[2]First 6 weeks were monotherapy and last 6 weeks were combination therapy if needed.

HYPERTENSION: ONGOING
OPEN LABEL, UNCONTROLLED

Study	Country/ Investigator	Study Dur.	Design [3]	Treatment	Dose (mg)	No. Rec'd Med.	Sex M/F
039	North America Multicenter (25 Investigators)	2Y	O, UC, NR	Eprosartan With and Without HCTZ	100 bid 200 bid 300 bid	353	232/121
040	UK Multicenter (27 Investigators)	2Y	O, UC, NR	Eprosartan With and Without HCTZ	100 bid 200 bid 300 bid	338	146/192
050	North America Multicenter (33 Investigators)	2Y	O, UC, NR	Eprosartan With and Without HCTZ	400 to 800 qd	609	374/235
052	UK 2Y Multicenter (13 Investigators)		O, UC, NR	Eprosartan With and Without HCTZ	400 to 800 qd	122	54/68

[3] O=open, UC=uncontrolled, NR=nonrandomized

26 CLINICAL PHARMACOLOGY STUDIES (oral formulation)

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION
POPULATION: NORMAL HEALTHY VOLUNTEERS

Study	Country	Study Design[1]	Treatment	Dosage	Duration	Received Study Medication
003	US	SB, PLC, R,	Eprosartan	1, 3, 10, 30, 50, 100, 200, 350 mg (single dose)	4 days	21
005	Germany	O, UC, R, XO	Eprosartan	20 mg iv, 300 mg oral (single dose)	3 days	18
007	US	O, UC, R, XO	Eprosartan	350 mg (single dose)	2 days	12
008	US	O, UC, R, XO	Eprosartan	100, 200, 400, 800 mg (single dose)	4 days	23
018	US	O, UC, R, XO	Eprosartan	100 mg (single dose)	3 days	24
020	Europe	O, UC, R, XO	Eprosartan (single dose)	100 mg oral, 20 mg iv	2 days	4 (3 received iv)
025	US	O, UC, PRL	Eprosartan	200 mg (single dose)	1 day	24: 16 young 8 elderly (men)
034	US	O, R, XO	Eprosartan	200 mg bid of old and new formulations	3.5 days in each of 4 periods	32
035	US	O, UC, R, XO	Eprosartan	400 mg; single doses of 3 formulations	3 days	64
086	US	O, UC, R, XO	Eprosartan	800 mg (single dose)	2 days	20
089	US	O, UC, R, XO	Eprosartan	300 mg (single dose)	2 days	48
092	US	O, UC, R, XO	Eprosartan	300 mg (single dose)	2 days	48

[1] O=open, UC=uncontrolled, R=randomized, XO=crossover

POPULATION: PATIENT VOLUNTEERS

Study	Country	Study Design[2]	Treatment	Dosage	Duration	Received Study Medication
Patients with Hypertension						
009	US	DB, PLC, R, XO	Eprosartan	50 mg qd 100 mg qd 350 mg qd 150 mg bid	7 days	33
048	US	DB, PLC, R, XO	Eprosartan	600 mg qd 800 mg qd 1200 mg qd	7 days	24
Patients with Renal Dysfunction						
021	US	O, UC, NR, PRL	Eprosartan	200 mg bid	7 days	34: 26 Renal impaired, 8 Healthy
Patients with Hepatic Dysfunction						
022	US	O, UC, PRL	Eprosartan	100 mg (single dose)	1 day	16: 8 Hepatic Disease 8 Healthy

[2]DB=double blind, NR=nonrandomized, PRL=parallel groups

PHARMACODYNAMIC DOSE RESPONSE STUDIES

POPULATION: NORMAL HEALTHY VOLUNTEERS

Study	Country	Study Design	Treatment	Dosage	Duration	Received Study Medication
006	US	DB, PLC, R, XO	Part 1:			
			Eprosartan	350 mg (single dose)	3 days	12
			Placebo			
			Part 2:			
			Eprosartan	10, 30, 50, 70, 100, 200 mg (single dose)	4 days	14
			Placebo			
			Part 3:			
			Eprosartan	50, 100, 350 mg (single dose)	3 days	5
			Placebo			(27 Received Eprosartan)

PHARMACODYNAMIC EFFECTS UNRELATED TO THERAPEUTIC EFFECT

POPULATION: NORMAL HEALTHY VOLUNTEERS

Study	Country	Study Design	Treatment	Dosage	Duration	Received Study Medication
024	US	O, POS, PLC, R, XO	Eprosartan plus captopril Captopril plus eprosartan SB 203220 plus captopril	300 mg bid plus 25 mg 25 mg tid plus 300 mg 600 mg qd plus 25 mg	7.5 days on Day 8 7.5 days on Day 8 8 days on Day 8	14 (Total of 13 Received Eprosartan)
043	US	Part 1A: O, UC, NR Part 1B: O, PLC, R, XO Part 2: DB, PLC, POS, R, XO	Part 1A: Eprosartan Part 1B: Eprosartan Placebo Part 2: Eprosartan Captopril Placebo	 50 to 400 mg up to 400 mg up to 400 mg 25 mg (single dose)	 3 days 2 days 1 day	9 6 14 (each subject participated in only one part of study)
069	US	O, POS, R, XO	Eprosartan Losartan (single dose)	400 mg 50 mg	2 days	12

PHARMACODYNAMIC EFFECTS UNRELATED TO THERAPEUTIC EFFECT

POPULATION: PATIENT VOLUNTEERS

Study	Country	Study Design	Treatment	Dosage	Duration	Received Study Medication
Patients with Hypertension						
026	US	DB, PLC, R, XO	Eprosartan	300 mg bid	4 weeks	14
			Placebo			(11 Received Eprosartan)
Patients with Renal Dysfunction						
044	US	DB, PLC, POS, R, XO	Eprosartan	300 mg bid	7 days	Healthy: 5 (4 Received Eprosartan)
			Captopril	25 mg bid		Renal Insufficiency:30 (27 Received Eprosartan)
			Placebo			

DRUG INTERACTION STUDIES

POPULATION: HEALTHY VOLUNTEERS

Study	Country	Study Design	Treatment	Dosage	Duration	Received Study Medication
023	Germany	O, R, XO	Eprosartan plus digoxin	200 mg bid plus 0.6 mg 0.6 mg 1 day	7 days on Day 4	12
027	US	DB, PLC, R, PRL	Eprosartan plus warfarin	300 mg bid	7 days	11
			Placebo plus warfarin			7
029	US	O, R, XO	Eprosartan	400 mg	1 day	17
			Eprosartan plus ranitidine	400 mg plus after 3.5 days 150 mg bid	On Day 4	

POPULATION: PATIENT VOLUNTEERS

Patients with Diabetes Mellitus

028	US	DB, PLC, R, XO	Eprosartan plus glyburide	200 mg bid plus up to 10 mg/day	7 days	15
			Placebo plus glyburide	plus up to 10 mg/day		