CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-268

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation I

SUBMISSION DATES:

NDA 21-268 (Original) August 30, 2000
IND [redacted] Serial No. 425) April 25, 2001
IND [redacted] Serial No. 429) May 15, 2001
IND [redacted] Serial No. 435) May 24, 2001

Teveten[R] HCT 600/12.5 mg Tablets
Teveten[R] HCT 600/25 mg Tablets
(Eprosartan Mesylate/Hydrochlorothiazide)
UNIMED Pharmaceuticals, Inc.
Deerfield, IL

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Original New Drug Application

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EXECUTIVE SUMMARY

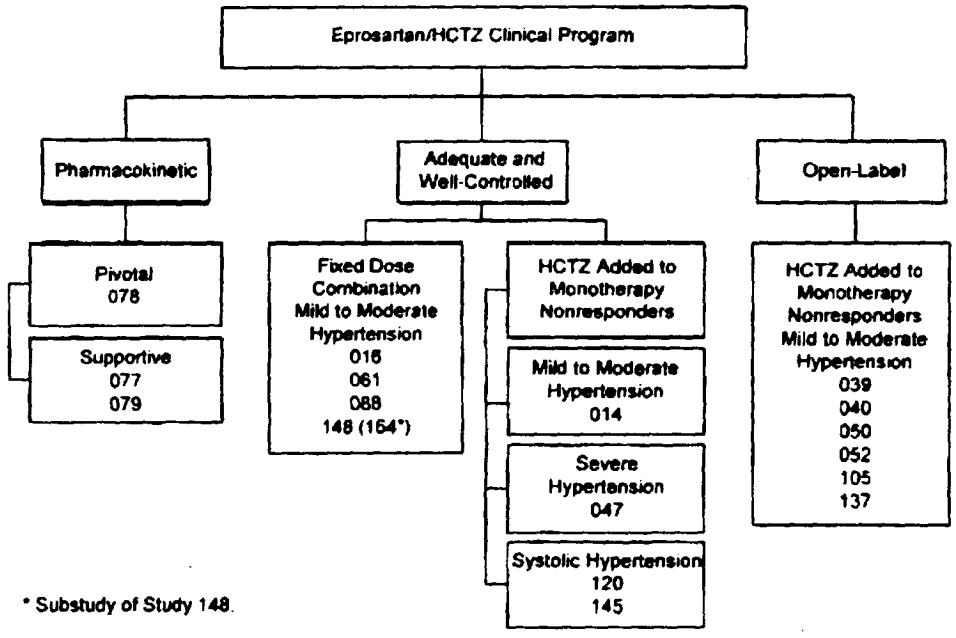
In this original NDA, the sponsor is seeking approval of two strengths of eprosartan/HCTZ combination tablet containing eprosartan 600 mg/HCTZ 12.5 mg and eprosartan 600 mg/HCTZ 25 mg. The proposed indication for the combination tablets is the treatment of hypertension.

Original NDA 20-738 for eprosartan was filed on Oct 11, 1996 and was approved for the treatment of hypertension on Dec 22,1997. Eprosartan is a potent, selective, competitive, non-peptide angiotensin II receptor (AT_1 subtype) antagonist approved by the FDA for the treatment of patients with hypertension at doses of 400 to 800 mg/day as single or divided doses.

HCTZ is a thiazide diuretic used in the management of edema and hypertension. Thiazide diuretics act by increasing the excretion of sodium, chloride, and water through the inhibition of sodium ion transport across the renal tubular epithelium.

The combination of HCTZ and eprosartan has been shown to be effective when eprosartan alone does not control blood pressure. The increased efficacy of the combination is due to a different mechanism of action for each of the two drugs. Indirectly, the diuretic action of HCTZ reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the increase in the renin-angiotensin system seen with the administration of HCTZ.

To support the approval of the eprosartan/HCTZ combination product, seventeen clinical studies were included in the clinical program. The organization of the clinical program is provided in the next Figure.



The clinical studies were as follow: Eight adequate and well-controlled studies [014,016,047, 061,088, 120, 145 and 148 (and its substudy 164)], were conducted in Phase III to evaluate eprosartan and HCTZ. Four of the studies [Studies 016,061,088, and 148 (and its substudy 164)] evaluated a fixed dose combination, while the other four studies (Studies 014,047, 120, and 145) evaluated the addition of HCTZ to monotherapy nonresponders. In addition, open-label, multicenter, long-term (6 months to 2 years) studies (039, 040,050, 052, 105, and 137) were conducted in patients previously treated in other eprosartan studies and in de novo patients. Study 161 was an open-label, long-term (12 months) study in patients currently on eprosartan monotherapy or de novo patients. The patients received either 600 or 1200 mg eprosartan with the optional addition of 25 mg of HCTZ per day, in order to achieve adequate blood pressure control.

Four clinical pharmacology and biopharmaceutic studies (077, 078, 079, and S1711006) were conduced to evaluate the effect of food on bioavailability of the eprosartan + HCTZ combination product, the bioequivalence of the tablets proposed for marketing and the tablets used in clinical studies, and the pharmacokinetic interaction between eprosartan and HCTZ. Studies 077, 078, and 079 were included in the original NDA dated August 30, 2000 and study S1711006 was included in IND [redacted] Serial No. 425) dated April 25, 2001.

- Study No. 077 entitled, "*A Study to Evaluate the Relative Bioavailability and the Effect of Food on the Pharmacokinetics of Eprosartan/Hydrochlorothiazide (HCTZ) Combination in Healthy Adult Volunteers*". The effect of food on bioavailability was assessed in this supportive bioavailability study that compared the bioavailability results for the eprosartan 400 mg/HCTZ 6.25 mg combination tablet in the fed and fasted state to the bioavailability of the eprosartan 400-mg commercial tablet and the HCTZ 6.25-mg capsule each given separately in the fed state. The results showed that food delayed, but did not decrease, the absorption of eprosartan. Food had minor effects on the absorption of HCTZ.

- Study No. 078 entitled, "*A Study to Determine the Bioequivalence of the Proposed Commercial Combination Formulation of Eprosartan Plus Hydrochlorothiazide (600/12.5 mg) Relative to the Clinical trials Combination Formulation of Eprosartan Plus Hydrochlorothiazide (2 X 300/6.25 mg) in Healthy Volunteers*". This pivotal bioequivalence study was performed comparing equal doses of the eprosartan 600 mg/HCTZ 12.5 mg strength combination tablet proposed for marketing and the eprosartan 300 mg/HCTZ 6.25 mg strength combination tablet used in clinical trials. The overall results indicate that eprosartan 600 mg/HCTZ 12.5 mg combination tablet proposed for marketing achieved bioequivalence with an equal dose of the eprosartan 300 mg/HCTZ 6.25 mg combination tablet used in clinical trials with respect to eprosartan AUC(0-t) and HCTZ AUC(0-t) and Cmax, but not with respect to eprosartan Cmax.

- Study No. 079 entitled, "*A Study to Evaluate the Pharmacokinetics of Eprosartan and Hydrochlorothiazide (HCTZ) When Administered Alone or in Combination in Healthy Adult Volunteers*".
  The pharmacokinetic interaction between eprosartan and HCTZ was assessed in this study that compared the bioavailability results for a combination of the eprosartan 400-mg commercial tablet administered with the HCTZ 6.25-mg capsule relative to the same dose of eprosartan and HCTZ each administered separately. The results of the study showed that the pharmacokinetics of eprosartan were similar, whether administered alone or concomitantly with HCTZ. For HCTZ, there was a slight decrease (approximately 20%) in AUC(0-t) and Cmax when coadministered with eprosartan. The renal clearance of HCTZ was not affected by the coadministration of eprosartan.

- Study No. S1711006 entitled, "*A Randomized, Single-Dose, Two-Period, Cross-Over Study to Compare the Bioavailability of One Combination Tablet of Eprosartan 600 mg/Hydrochlorothiazide 25 mg Relative to the*

Coadministration of One 600-mg Eprosartan Tablet and One 25-mg Hydrochlorothiazide Tablet in Healthy Male and Female Volunteers". The purpose of this study was to assess the bioavailability of the eprosartan 600 mg/HCTZ 25 mg combination tablet relative to the coadministration of one 600-mg eprosartan tablet and one 25-mg HCTZ tablet. Bioequivalence criteria were achieved for AUC(0-t) and Cmax for HCTZ, but they were not achieved for AUC(0-t') and Cmax for eprosartan. The AUC(0-t') of eprosartan was 18% lower, on average, for the 600/25 mg combination tablet, with 90% confidence intervals ranging from 73% to 93%. The Cmax of eprosartan was 14% lower, on average, for the 600/25 mg combination tablet, with 90% confidence intervals ranging from 77% to 95%. Additionally, eprosartan's data were stratified by gender. The results indicate that the bioequivalence of the treatments is influenced by gender. Eprosartan bioequivalence for the two treatments appears to be demonstrated for females but not for males. However, this observation is based on data from 18 males and females.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPEI) has reviewed the information included in original NDA 21-268 dated August 30, 2000 and IND [redacted] (Serial No. 425) dated April 25, 2001 for Teveten[R] HCT 600/12.5 mg & 600/25 mg Tablets and has the following Comments:

- ***Dissolution:*** Based on the review of the submitted dissolution data, OCPB considers that the proposed dissolution method is acceptable only on an interim basis. Additional dissolution data at 50 rpm and 75 rpm and if necessary different dissolution media should be submitted within one year from the date of approval. With respect to the proposed dissolution specifications of Q=( )% in 45 minutes for eprosartan and Q=( )% in 60 minutes for HCTZ are less than appropriate and are not acceptable. It is recommended that the specifications be changed to not less than ( )% at 30 minutes for both eprosartan and HCTZ components. These specifications would be also on an interim basis. Final dissolution specifications would be set at a later time and they would be based on the review of the additional dissolution information that is being requested.

- ***Bioequivalence:*** Although the results of bioequivalence studies No. 078 and S1711006 showed that the eprosartan/HCTZ 600/12.5 mg and 600/25 mg strengths of the to be marketed and the clinical tablet formulations are not bioequivalent with respect to eprosartan's Cmax, the medical reviewer of the DCTDP considers that the failure to pass the bioequivalence for Cmax will not have any clinical consequences because eprosartan has a very wide therapeutical range.

- ***Labeling:*** The clinical pharmacology and biopharmaceutic information for eprosartan and HCTZ included in the proposed labeling is appropriate and acceptable.

Please convey the Recommendation and dissolution comment as appropriate to the sponsor.

/S/ 6/4/01

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT Initialed by Patrick Marroum, Ph.D. /S/ 6/5/01

Briefing Day 5/31/01 (Mehta, Sahajwalla, Marroum, Dorantes, Taur, Lee)

cc: NDA 21-268, IND [redacted] HFD-110, HFD-860 (Dorantes, Mehta), and CDR (Biopharm).

QUESTION BASED REVIEW

1. How was the new tablet formulation developed?

The product was developed as a line extension to the marketed product eprosartan 600 mg tablets using the same eprosartan granulate to which hydrochlorothiazide is added prior to the incorporation of the disintegrant and lubricant. The compositions of the to-be-marketed eprosartan/HCTZ 600/12.5 mg and 600/25.0 mg combination tablets are shown below.

Composition of to-be-marketed 600/12.5 & 600/25 mg Eprosartan/HCTZ Tablets

COMPONENT	FUNCTION	600/12.5 Mg/TABLET	600/25 Mg/TABLET
Eprosartan internal granules:	Intermediate Product	-	-
Eprosartan mesylate	Active	735.8 (=600 mg eprosartan)	735.8 (=600 mg eprosartan)
Microcrystalline cellulose			
Lactose			
Prregelatinized starch			
Water			
Hydrochlorothiazide	Active		25.0
Crospovidone			
Magnesium stearate			
Opadry White OY-3736	Coating		-
Opadry II Pink 33G24616	Coating	-	
Total Weight		**1004**	**1017**

Reviewer Comments:

- *None of the clinical Phase II/III studies provided in the original NDA to support the registration of 600 mg eprosartan/12.5 HCTZ and 600 mg eprosartan/25 HCTZ combination tablets were conducted with the proposed commercial combination products. Instead the studies were conducted with lower strengths of the eprosartan/HCTZ combination tablets or with the individual eprosartan and HCTZ tablets.*
- *To link the clinical-tablets to the to-be-marketed combination tablets, bioequivalence study No. 078 and study No. S1711006 were conducted.*

2. Are the proposed dissolution methodology and specifications acceptable?

The proposed dissolution methodology and specifications for the eprosartan/HCTZ combination tablets are as follow:

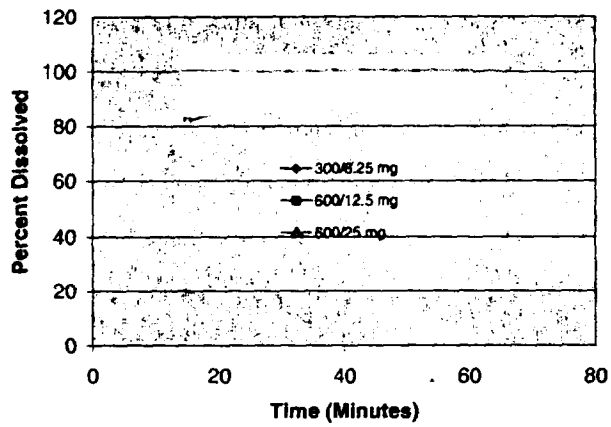
PROPOSED DISSOLUTION METHOD AND SPECIFICATIONS FOR TEVETEN-HCT TABLETS

Variable	Parameter
Apparatus Type	USP Apparatus 2
Dissolution Medium	De-aerated 0.2 M phosphate buffer, pH 7.5
Volume of Medium	1000 ml
Temperature of Medium	37°C
Speed of Rotation	100 rpm
Sample Pull Volume	20 ml
Sample Pull Times	Eprosartan, 45 minutes; HCTZ, 60 minutes
Units Tested	6
Acceptance Limits (per USP <711>)	Eprosartan, Q= % HCTZ Q= %

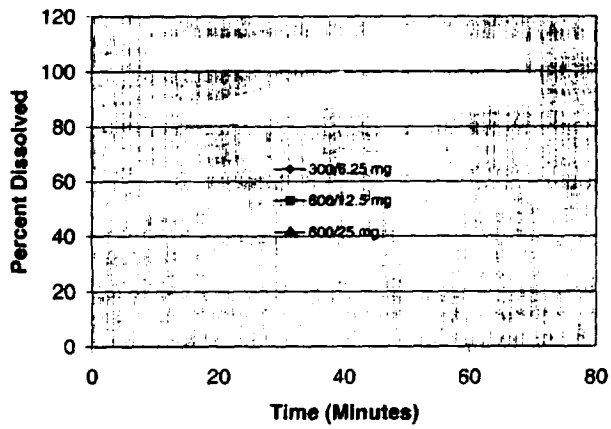
The dissolution data and profiles for the lots used in Studies 078 and S1711006 are presented below.

BATCH No.	FORMULATION/ STRENGTH	% DISSOLVED EPROSARTAN (N=12)				% DISSOLVED HCTZ (N=12)			
		15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
U98250	Combination Tablet 300 mg/6.25 mg								
U98200	Combination Tablet 600 mg/12.5 mg								
00H304	Combination Tablet 600 mg/25 mg								

Eprosartan Dissolution Profiles



HCTZ Dissolution Profiles



Reviewer Comments:

- *Based on the review of the submitted dissolution data, OCPB considers that the proposed dissolution method is acceptable only on an interim basis. This recommendation is due to the fact that the proposed dissolution method uses 100 rpm speed of rotation. This speed is very fast for a paddle method and is usually not recommended. Thus, the sponsor should provide additional dissolution data at lower speeds of paddle rotation (50 rpm and 75 rpm) and if necessary different dissolution media within one year from date of approval.*

- *With respect to the proposed dissolution specifications of Q[ ]% in 45 minutes for eprosartan and Q[ ]% in 60 minutes for HCTZ are less than appropriate and are not acceptable. It is recommended that the specifications be changed to not less than [ ]% at 30 minutes for both eprosartan and HCTZ components. These recommended specifications are also acceptable on an interim basis. Final dissolution specifications would be set at a later time and they would be based on the review of the additional dissolution information that is being requested.*

3. What analytical methodology was used to determine eprosartan and HCTZ ?

The next table presents a summary of the analytical methodology used to assay eprosartan and HCTZ in the provided studies.

SUMMARY OF IN VIVO ANALYTICAL METHODS- EPROSARTAN

Study No.	Type of Biological Fluid	Method	Sensitivity of Method/ Range (ng/ml)	Specificity
078				
077				
079				
S1711006				

SUMMARY OF IN VIVO ANALYTICAL METHODS- HCTZ

Study No.	Type of Biological Fluid	Method	Sensitivity of Method/ Range (ng/ml)	Specificity
078				
077				
079				
S1711006				

Reviewer Comment:

- *It should be noted that complete validation information for the analytical methodology used to quantify eprosartan was provided in the original NDA for Teveten Tablets. . Regarding the [ ] analytical methodology that was used to assay eprosartan and HCTZ in the BE studies, appropriate validation data were provided (see validation summaries in Attachment I). Also, this submission included Quality Control data for the determination of eprosartan in plasma and HCTZ in plasma and urine. These Quality Control data showed that the accuracy and precision for both eprosartan and HCTZ are in the expected range for the used analytical methodologies.*

4. What are the highlights of the pharmacokinetics of eprosartan and HCTZ in the provided studies?

The following table presents an overall summary of the eprosartan and HCTZ pharmacokinetic and bioavailability parameters for the 4 studies provided in the NDA.

MEAN ±SD PHARMACOKINETIC PARAMETERS FOR EPROSARTAN AND HCTZ

		EPROSARTAN				
Protocol No.	Route of Administration/ Dosage Form	Dose $(mg)_t$	Cmax (ng/ml)	Tmax* (hr)	AUC(0-t) (ng*h/ml	Half-life (hr)
078	Oral/ Combination Tablet, (eprosartan/HCTZ), Fasted	600	2798 ±1398	1.0 (0.5- 4.0)	9582 ±4684	6.95 ±3.42
	Oral/ Combination Tablet, (eprosartan/HCTZ), Fasted	2 x 300	2361 ±1150	1.0 (0.6 -4.0)	8618 ±4296	6.37 ±3.69
077	Oral/ Combination Tablet, (eprosartan/HCTZ), Fasted	2 x 400	2657 ±1073	1.27 (0.5 - 3.02)	10484 ± 3831	NM
	Oral/ Combination Tablet, (eprosartan/HCTZ), Fed	2 x 400	1770 ±590	3.96 (1.45- 5.98)	9741 ±2598	NM
	Oral/ Commercial eprosartan Tablet, Fasted	2 x 400	2773 ±1241	1.25 (0.95- 2.97)	9982 ± 3089	NM
079	Commercial eprosartan Tablet, Fasted	2 x 400	3310 +1873	1.0 (1.0 - 3.0)	10567 ±4613	NM
	Oral/Commercial eprosartan Tablet + HCTZ Capsule, Fasted	2 x400	3025 ±1362	(2.0 1.0 (1.0 - 3.0)	10571 ±4881	NM
S171-1006	Oral/ Combination Tablet, (eprosartan/HCTZ), Fasted	600	2257 +1070	1.5 (0.5-8.0)	8456 ±3920	NM
	Commercial eprosartan Tablet, Fasted	1 x 600	39	1.5 (0.5-8.0)	9854 ±4313	NM
		HYDROCHLOROTHIAZIDE				
Protocol No.	Route of Administration/ Dosage Form	Dose $(mg)_t$	Cmax (ng/ml)	Tmax* (hr)	AUC(0-t) (ng*h/ml	Clearance (ml/min)	Half-life (hr)
078	Oral/Combination Tablet, (eprosartan/HCTZ), Fasted	12.5	51.1 ±12.6	2.0 (1.0-4.0)	280 ± 92	NM	4.78 ± 1.66
	Oral/ Combination Tablet, (eprosartan/HCTZ), Fasted	2 x 6.25	54.2 +13.2	2.25 (1.0-4.0)	289 ±76	NM	5.07 ±2.11
077	Oral/ Combination Tablet, (eprosartan/HCTZ), Fasted	2 x 12.5	125 ±32	1.96 (0.98-3.98)	839 ±208	NM	9.79 ±1.89
	Oral/ Combination Tablet, (eprosartan/HCTZ), Fed	2 x 12.5	117 ±21	2.99 (1.47-5.98)	878 ± 245	NM	11.06 ± 2.13
	Oral/Capsule (HCTZ), Fasted	2 x 12.5	167 ± 47	1.68 (0.95-4.02)	1062 + 235	NM	9.52 ± 2.27
079	Oral/Capsule (HCTZ), Fasted	2 x 12.5	155 ±50	1.53 (0.98-3.0)	1046 ± 254	215 + 66	9.42 ±1.34
	Oral/Commercial eprosartan Tablet + HCTZ Capsule, Fasted	2 x 12.5	127 ±52	1.97 (0.98-2.98)	850 ±228	195 + 72	10.95 ±2.97
S171-1006	Oral/ Combination Tablet, (eprosartan/HCTZ), Fasted	25	155 ±52	2.0 (1.0-6.0)	950 ± 371	NM	NM
	Commercial HCTZ Tablet, Fasted	1 x 25	151 ±60	2.5 (1.0-6.0)	976 ±386	NM	NM

*Median value with range

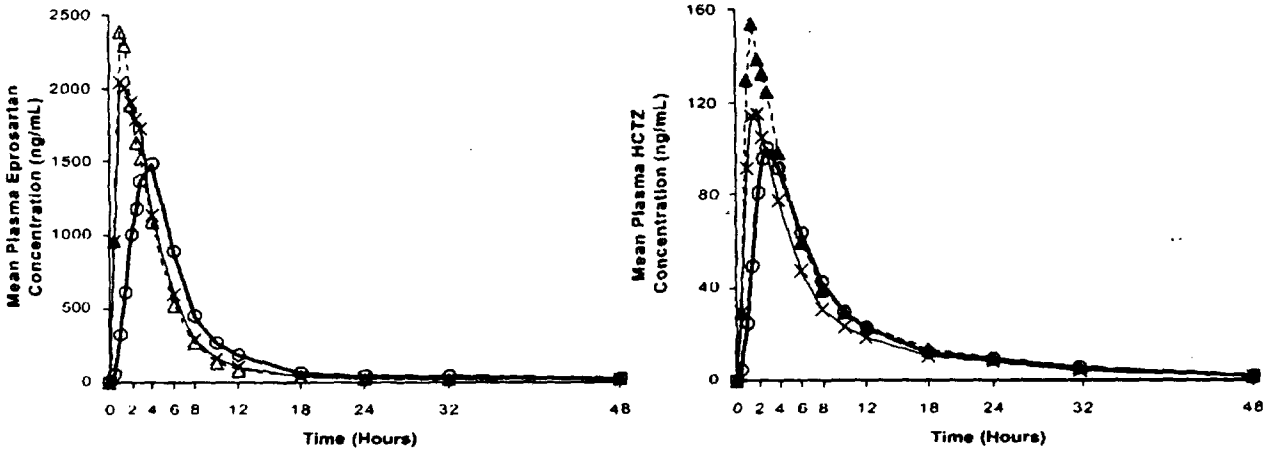
NM = Not measured

5. Is food affecting the bioavailability of eprosartan and HCTZ ?

The effect of food on bioavailability was assessed in bioavailability study No. 077 that compared the bioavailability results for the eprosartan 400 mg/HCTZ 6.25 mg combination tablet in the fed and fasted state to the bioavailability of the eprosartan 400-mg commercial tablet and the HCTZ 6.25-mg capsule each given separately in the fed state. Study 077 was a randomized, open-label, four-way, period-balanced, crossover study conducted in 16 subjects (13 men/3 women). Each subject received a single oral dose of the dosing regimens with 240 ml of tepid water. Subjects receiving the fed regimens were given a standard high fat breakfast approximately 30 minutes before dosing. Heparinized blood samples were obtained for pharmacokinetic analysis at specific times. There was a 7-day washout between doses.

Figure 1 illustrates the mean plasma eprosartan and HCTZ concentrations versus time for 2 x eprosartan 400 mg tablets in the fasted state compared to 2 x eprosartan 400 mg/HCTZ 12.5 mg combination tablets in the fasted and fed state.

FIGURE 1



Mean Plasma Eprosartan and HCTZ Concentrations Following a Single Dose of 2 x Eprosartan 400 mg Commercial Tablet in the Fasted State (- -Δ- - or - -▲- -) or 2 x Eprosartan 400 mg/HCTZ 12.5 mg Combination Tablets in the Fasted (-X-) and Fed (-O-) State

For HCTZ, AUC and Cmax were similar in the fed and fasted states. In the fed state, Tmax was prolonged. For eprosartan, AUC was similar in the fed and fasted states. However, in the fed state, Cmax was on average 39% lower and Tmax was delayed when compared to the fasted state. Thus, food appeared to delay, but not decrease, the bioavailability of eprosartan.

Reviewer Comment:

- *Overall, the results of this study showed that administration of eprosartan with food delays absorption, and causes variable changes in Cmax and AUC. These results agreed with the results obtained in the food-effect studies conducted under NDA 20-738 for Teveten tablets.*

6. Are the to-be-marketed combination tablet formulations bioequivalent to the formulations used in the clinical trials ?

Bioequivalence study No. 078 compared equal doses of the eprosartan 600 mg/HCTZ 12.5 mg strength combination tablet proposed for marketing and the eprosartan 300 mg/6.25 mg strength combination tablet used in clinical trials. Study 078 was conducted as an open-label, randomized, two-period, period-balanced, crossover study including 72 healthy male volunteers. Following an overnight fast, each of the 72 men received a single oral dose of the combination tablet of eprosartan and HCTZ, administered as one of two different regimens as follows: Eprosartan 600 mg/HCTZ 12.5 mg combination tablet, or 2 x eprosartan 300 mg/HCTZ 6.25 mg combination tablet. Blood samples (approximately 5 ml) for eprosartan and HCTZ pharmacokinetic analysis were collected at specified times. There was a 7-day washout between doses.

The focus of the statistical analysis was to determine the equivalence of the proposed commercial combination formulation of eprosartan/HCTZ 600/12.5 mg (regimen A) relative to two times the clinical trials combination formulation of eprosartan/HCTZ 300/6.25 mg (regimen B), based on the primary pharmacokinetic parameters. Thus, point estimates and associated 95% confidence intervals (CI) were computed for the ratio of A:B for AUC(0-t') and Cmax of both eprosartan and HCTZ. The summary statistics for study No. 078 are presented below.

	EPROSARTAN			HYDROCHLOROTHIAZIDE		
Parameter	**Comparison**	**Estimate**	**95% CI**	**Comparison**	**Estimate**	**95% CI**
AUC_{0-t} (ng.h/ml)	A/B	1.11*	100-123**	A:B	0.96*	91-100**
C_{max} (ng/ml)	A/B	1.16*	103-132**	A:B	0.94*	89-100**
T_{max} (hour)	A-B	A-B 0.00 h	-0.5, 0.25 h	A-B	A-B 0.0 h	-0.5, 0.25 h

A = eprosartan/HCTZ 600/12.5 mg (test formulation)
B = 2 x eprosartan/HCTZ 300/6.25 mg (reference formulation)
* data presented as ratio of adjusted geometric means (A:B)
** alpha level adjusted for interim analysis (= 2.5% at each look)

The 95% confidence intervals data indicate that bioequivalence was achieved for AUC for eprosartan and HCTZ and Cmax for HCTZ but not for eprosartan Cmax (CI= 103-132%). Thus, the eprosartan 600 mg/HCTZ 12.5 mg combination tablet proposed for commercial use was not proven to be bioequivalent to an equal dose of the eprosartan 300 mg/HCTZ 6.25 mg combination tablet used in clinical trials.

Bioequivalence study No. S1711006 compared equal doses of the eprosartan 600 mg/HCTZ 25 mg strength combination tablet proposed for marketing and the eprosartan 600 mg and HCTZ 25 mg strength individual tablets used in the clinical trials. It was a randomized, open-label, balanced, two-period, crossover, single oral dose study in 36 healthy volunteers. Each subject received two treatments in randomized order. Treatment A consisted of a single eprosartan 600 mg/HCTZ 25 mg combination tablet. Treatment B consisted of one 600-mg eprosartan tablet and one 25-mg HCTZ tablet. These two single-dose treatments were separated by a 7-day washout period. Blood samples for each time point for the determination of eprosartan and HCTZ plasma concentrations were collected at specified times. Blood samples obtained from subjects who completed both single dose treatments were eligible for pharmacokinetic analysis.

Following the natural log-transformation, AUC(0-t') and Cmax of eprosartan and HCTZ were analyzed separately with the analysis of variance (ANOVA) model, fitting terms for sequence, subject within sequence, period, and treatment (A and B). Point estimates and associated 90% CIs were calculated for the difference A-B. Analysis of Tmax focused on estimation of the difference between the test formulation A and the reference formulation B. Based on the non-parametric approach, point estimates and associated 90% CIs were constructed for the median difference A-B. The next Table presents summary statistics for eprosartan and HCTZ.

	EPROSARTAN			HYDROCHLOROTHIAZIDE		
Parameter	**Comparison**	**Point Estimate**	**90% CI**	**Comparison**	**Point Estimate**	**90% CI**
AUC_{0-t} (ng.h/ml)	A/B	0.82	73-93	A/B	0.97	91-104
C_{max} (ng/ml)	A/B	0.86	77-95	A/B	1.05	99-113
T_{max} (hour)	A-B	0.00^	-0.5, 0.25	A-B	-0.5^	-0.5, 0

Regimen A: Eprosartan 600 mg/ HCTZ 25 mg (test formulation)
Regimen B: 1 x eprosartan 600 mg + 1 x HCTZ 25 mg (reference formulation)
Point estimate represents the ratio of geometric means (A/B)
^ Point estimate represents the median difference (A-B)

As shown in the above table bioequivalence was demonstrated for the HCTZ components but not for the eprosartan components of the combination tablets. For eprosartan the 90% confidence interval AUC(0-t') was completely contained within the acceptance range of 80-125%; however, the upper bound of the 90% confidence interval for Cmax was slightly greater than 125% (i.e., 132%). Point estimates for AUC and Cmax increased 11 to 16% on average for the proposed commercial formulation and Tmax values were similar between the formulations. Based on these data, it appears that there was a minor increase in the extent of absorption but no change in the rate of absorption for the proposed commercial formulation.

Reviewer Comments:

- *It should be noted that for study No. 078 an interim analysis to assess bioequivalence was conducted after the first cohort of 72 subjects completed the study, therefore, the sponsor paid a penalty for the interim look. Therefore, in this study, 95% CI were used for the assessment of bioequivalence, instead of the typical 90% CI.*
- *Data from study S1711006 were also stratified by gender. The results indicate that the bioequivalence of the treatments is influenced by gender. Eprosartan bioequivalence for the two treatments appears to be demonstrated for females but not for males. However, this observation is based on data from 18 males and females.*
- *Due to the wide safety margin in doses up to 1200 mg, the high variability of kinetics, and flat dose-response curve at and above the 600 mg daily dose, the medical officer of the DCRDP consider that the failure to pass the Agency's 80-125% bioequivalence criteria for Cmax would not have any clinical consequences in the efficacy and safety of the product. Therefore, this reviewer considers that bioequivalence studies 078 and S1711006 can be used to support the approval of Teveten HCT 600/12.5 & 600/25 mg Tablets.*

7. Is there a drug-interaction effect between eprosartan and HCTZ ?

The pharmacokinetic interaction between eprosartan and HCTZ was assessed in study No. 079 that compared the bioavailability results for a combination of the eprosartan 400-mg commercial tablet administered with the HCTZ 6.25 mg capsule relative to the same dose of eprosartan and HCTZ each administered separately. Study 079 was conducted as a randomized, open-label, single-dose, three-period, period-balanced, crossover study in 18 healthy adults. Following an overnight fast, each of 18 subjects (15 men/3 women) received a single oral dose of one of the following regimens in random order: eprosartan commercial tablet (2 x 400 mg), HCTZ capsule (2

x 12.5 mg), or eprosartan commercial tablet (2 x 400 mg) + HCTZ capsule (2 x 12.5 mg).

For each regimen, heparinized blood samples were collected prior to dosing (time 0) and at nominal times of 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 36, and 48 hours after dosing. Following dosing of HCTZ regimens, all urine was collected immediately prior to dosing and at the following post-dose time intervals: 0-4, 4-8, 8-12, 12-18, 18-24, 24-32, and 32-48 hours. Figure 3 shows the mean plasma eprosartan and HCTZ concentrations versus time for the three regimens.

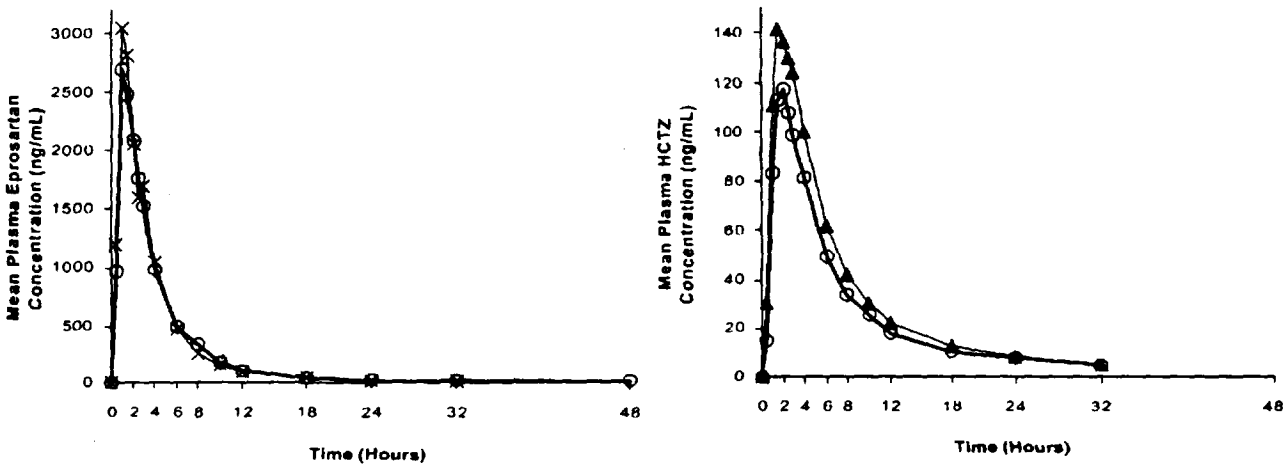


FIGURE 3. Mean Plasma Eprosartan and HCTZ Concentrations Following A Single Dose of 2 x Eprosartan 400 mg or 2 x Commercial Tablets (–X–) or HCTZ 12.5 mg Commercial Capsule (–▲–) or 2 x Eprosartan 400 mg Commercial Tablets Plus 2 x HCTZ 12.5 mg Capsules (–O–)

The results of this drug interaction study showed that the pharmacokinetic parameters AUC, Cmax, and Tmax for eprosartan were similar, whether administered alone or concomitantly with HCTZ. For HCTZ, there was a slight decrease (approximately 20%) in the AUC and Cmax when coadministered with eprosartan as compared to administration of HCTZ alone. Renal clearance and Tmax of HCTZ did not appear to be affected by the coadministration of eprosartan.

Reviewer Comment:

- *When eprosartan and HCTZ are given concomitantly, HCTZ does not affect the pharmacokinetics of eprosartan but eprosartan has a small effect in the bioavailability of HCTZ (statistically significant decrease in AUC and Cmax).*

8. Is the clinical pharmacology information included in the proposed labeling acceptable?

A copy of the proposed labeling is included in Attachment II.

Reviewer Comments:

- *It should be noted that the clinical pharmacology and biopharmaceutic information included in the different sections of the proposed labeling for the eprosartan/HCTZ combination product, is exactly the same information that was included in the individual labelings of previously approved eprosartan and HCTZ products.*
- *Due to the fact that the overall format of the proposed labeling is similar to the format of previously approved combination products and to the fact that the proposed labeling does not include any new clinical pharmacology information, this reviewer is of the opinion that the proposed labeling is appropriate and acceptable.*

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Attachment I

Includes

NDA 21-268

"Summaries of Individual Studies & Dissolution Data:

Study No. 077 entitled, "A Study to Evaluate the Relative Bioavailability and the Effect of Food on the Pharmacokinetics of Eprosartan/Hydrochlorothiazide (HCTZ) Combination in Healthy Adult Volunteers".

Study No. 079 entitled, "A Study to Evaluate the Pharmacokinetics of Eprosartan and Hydrochlorothiazide (HCTZ) when Administered Alone or in Combination in Healthy Adult Volunteers".

Study No. 078 entitled, "A Study to Determine the Bioequivalence of the Proposed Commercial Combination Formulation of Eprosartan Plus Hydrochlorothiazide (600/12.5 mg) Relative to the Clinical trials Combination Formulation of Eprosartan Plus Hydrochlorothiazide (2 X 300/6.25 mg) in Healthy Volunteers"

Dissolution Data: Dissolution results for the batches used in bioequivalence studies No. 078 and S1711006.

Study Report Summary

Study No. 077

Study Title: A Study to Evaluate the Relative Bioavailability and the Effect of Food on the Pharmacokinetics of Eprosartan/Hydrochlorothiazide (HCTZ) Combination in Healthy Adult Volunteers.

Principal Investigator/Investigation Site:
Bernard E. Lison, M.D., SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center of Philadelphia, University of Pennsylvania Health System, Philadelphia, Pennsylvania.

Objectives:
The objectives of this study were:

- To estimate the effect of food on the pharmacokinetics of eprosartan and HCTZ when administered as eprosartan/HCTZ commercial combination formulation.
- To estimate the relative bioavailability of the eprosartan (or HCTZ) component of the commercial combination formulation as compared to commercial eprosartan (or HCTZ) alone.
- To evaluate safety of eprosartan/HCTZ commercial combination formulation when administered in fed and fasted states.

Patient Population:
Sixteen subjects were randomized to treatment and all sixteen of these subjects completed the study. Of the sixteen subjects who completed this study, thirteen were male (81%) and three were female (19%), There were no withdrawals from the study. All subjects were healthy adult volunteers. None of the subjects had presenting conditions or medical history, which the investigator considered sufficient to affect the conduct of the study or which, might have represented a potential risk to the subject during participation in the study.

The demographic data for these subjects are displayed below.

GROUP	PARAMETER	AGE	WEIGHT	HEIGHT
		(years)	(kg)	(m)
All Subjects	n	16	16	16
	Mean	33	73.49	1.74
	SD	9.0	13.22	0.10
	Range	18-54	51.50-99.70	1.59-1.94

Study Design:
This was a randomized, open-label, four-way, period-balanced crossover study. Each subject received a single oral dose of the following regimens with 240 ml of tepid water.

A= eprosartan 400 mg plus HCTZ 12.5 mg x 2 (Lot No. U96214) combination tablet fasted

B= eprosartan 400 mg plus HCTZ 12.5 mg x 2 combination tablet, fed,

C= eprosartan 400 mg x 2 (Lot No. U96205) commercial tablet, fasted or

D= HCTZ 12.5 mg x 2 (Lot No. U96254) tablet, fasted

Formulations:

The formulation, dose unit, and lot number of the medications used in the study are presented in the table below.

STUDY DRUGS	APPEARANCE	FORMULATION	DOSE UNIT	LOT NO.
SK&F 108566 (Eprosartan)	Oval, light to moderate pink colored, aqueous film coated Tiltab™ with a score on one side, and with SB and 5044 debossed on both sides at opposite ends of the tablet	Tablet Formula AZ	400 mg	U96205
SK&F 008476 (Hydrochlorothiazide)	A uniform white to off white powder contained in a size 2 hard gelatin capsule comprised of an opaque white body and cap	Capsules Formula AH	12.5 mg	U96254
SK&F 108566-J/ SKF 08476 (Eprosartan/ Hydrochlorothiazide)	Oval, pale yellowish pink colored, aqueous film coated Tiltab™ with SB debossed on both sides	Tablet Formula AW-AA	400 mg/12.5 mg	U96214

Collection of Samples:

Blood samples (approximately 10 ml for regimens A and B or 5 ml for regimens C and D) for pharmacokinetic analysis were collected into tubes containing heparin at the following nominal times: predose (0 hours), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 32, and 48 hours following dose administration.

Analytical Methods:

Plasma concentrations of eprosartan and HCTZ were quantified by [ ]. The lower limits of quantification (LLQ) for eprosartan and HCTZ were [ ]

]

DATA ANALYSIS:

- ***Safety:*** Blood pressure, pulse rate, and clinical laboratory data were reviewed on an ongoing basis during the study to evaluate the safety of subjects. Any clinically relevant abnormalities or values of potential clinical concern were described.

- ***Pharmacokinetics:*** PK analysis of the plasma concentration-time data was performed within the Department of Pharmacokinetics, SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania. Pharmacokinetic parameters AUC, Cmax, and Tmax were obtained by noncompartmental methods.

  For calculation of mean plasma eprosartan and HCTZ concentration-time plots, a value of 1/2 LLQ (and ng/ml, respectively) was assigned to NQ values. If the calculated mean value at a time point was less than the LLQ of the assay, the value was omitted from the

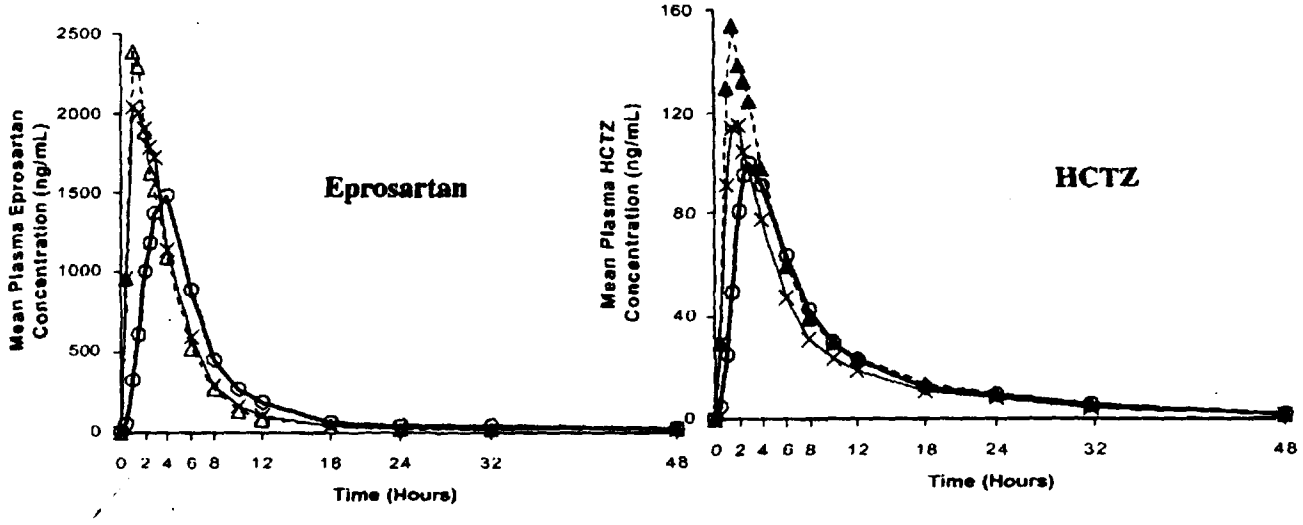
mean plot.

- ***Statistics:*** Following $\log_e$-transformation, AUC_{0-t} and Cmax of HCTZ were analyzed separately by analysis of variance (ANOVA) with terms for sequence, subject within sequence, period, and regimen. The point estimates and associated 90% confidence intervals for the ratios of B:A and A:D for HCTZ were constructed using the residual variances. AUC_{0-t} and Cmax of eprosartan were similarly analyzed with terms for first-order carryover included in the ANOVA model. The point estimates and associated 95% confidence intervals for the ratios of B:A and A:C for eprosartan were constructed. Tmax of eprosartan and HCTZ were analyzed separately using the Wilcoxon's Matched Pairs Method to compute point estimate and 95% confidence intervals for the median differences B-A and A-C for eprosartan and B-A and A-D for HCTZ.

RESULTS:

- ***Safety:*** A total of fifteen adverse experiences (AEs) were reported for 5 subjects following treatment with the study medication. Of these, nine AEs in 5 subjects occurred following administration of eprosartan 800 mg plus HCTZ 25 mg fed, one AE occurred following administration of eprosartan 800 mg fasted and two AEs occurred following HCTZ 25 mg fasted. All of these AEs were mild in severity. The most common AE was headache. There were no withdrawals due to AEs, there were no serious, non-fatal AEs and there were no deaths during the study. There were no clinically significant changes in vital signs or safety laboratory values attributable to study medication.

- ***Pharmacokinetics:*** Mean concentration-time profiles for eprosartan and HCTZ following administration of regimens A, B, and C or D are illustrated below.



Mean Plasma Eprosartan and HCTZ Concentrations Following a Single Dose of 2 x Eprosartan 400 mg Commercial Tablet in the Fasted State (- -Δ- - or - -▲- -) or 2 x Eprosartan 400 mg/HCTZ 12.5 mg Combination Tablets in the Fasted (-X-) and Fed (-O-) State

The next Table presents the mean (SD) pharmacokinetic values and summary statistics for eprosartan and HCTZ following regimens A, B, and C or D.

Summary of Pharmacokinetic Parameters and Statistics for Eprosartan and HCTZ

EPROSARTAN							
PHARMACOKINETICS				STATISTICS			
				Comparison B:A		Comparison A:C	
Parameter	Regimen A	Regimen B	Regimen C	Estimate	95% CI	Estimate	95% CI
AUC_{0-t} (ng.h/ml)	10484 (3831)	9741 (2598)	9982 (3089)	0.88	70-111	1.20	94-152
C_{max} (ng/ml)	2657 (1073)	1770 (590)	2773 (1241)	0.61	45-83	1.17	85-160
T_{max} (hour)	1.27 (0.5-3.02)	3.96 (1.45-5.98)	1.25 (0.95-2.97)	B-A 1.96 h	1.0, 2.5h	A-C 0.03 h	-0.23, 0.55h
HYDROCHLOROTHIAZIDE							
PHARMACOKINETICS				STATISTICS			
				Comparison B:A		Comparison A:D	
Parameter	Regimen A	Regimen B	Regimen D	Estimate	95% CI	Estimate	95% CI
AUC_{0-t} (ng.h/ml)	839 (208)	878 (245)	1062 (235)	1.04	97-112	0.78	73-84
C_{max} (ng/ml)	125 (32)	117 (21)	167 (47)	0.95	85-107	0.75	67-84
T_{max} (hour)	1.96 (0.98-3.98)	2.99 (1.47-5.98)	1.68 (0.95-4.02)	B-A 1.25 h	0.53, 1.75h	A-D -0.10 h	-0.53, 0.27h

CONCLUSIONS:

- Single doses of eprosartan 800 mg and HCTZ 25 mg, given alone or in combination, were safe and well tolerated in healthy adult male and female volunteers.
- For eprosartan, following administration of the eprosartan/HCTZ combination tablet, AUC was similar in the fed and fasted states. In the fed state, Cmax was, on average, 39% less than that observed in a fasted state, and Tmax increased, on average 1.96 hours. Thus, food appeared to delay the absorption of eprosartan.
- The pharmacokinetic parameters AUC, Cmax and Tmax of eprosartan were on average similar, whether administered alone or concomitantly with HCTZ.
- For HCTZ, following administration of the eprosartan/HCTZ combination tablet, AUC and Cmax were similar in the fed and fasted states. In the fed state, Tmax increased on average, 1.25 hours. After administration of the combination tablet in a fasted state, HCTZ AUC and Cmax were reduced approximately 25%, than when HCTZ was administered alone. Tmax of HCTZ was similar following administration of the combination tablet relative to administration of HCTZ alone.

REVIEWER COMMENT:

It should be noted that complete analytical validation information for eprosartan was submitted under the original NDA. This report only included Quality Control data for the determination of eprosartan and HCTZ. The provided Quality Control data showed adequate assay precision and accuracy for both drugs.

Study Report Summary

Study No. 078

Study Title: A Study to Determine the Bioequivalence of the Proposed Commercial Combination Formulation of Eprosartan Plus Hydrochlorothiazide (600/12.5 mg) Relative to the Clinical Trials Combination Formulation of Eprosartan Plus Hydrochlorothiazide (2 X 300/6.25 mg) In Healthy Volunteers.

Principal Investigator/Investigation Site:
Jerry Herron, MD, Arkansas Research, Little Rock, Arkansas.

Objectives:
The objectives of this study were:

- To determine the bioequivalence in healthy volunteers of the combination formulation of eprosartan plus hydrochlorothiazide (600/12.5 mg) proposed for commercial use relative to the combination formulation of eprosartan plus hydrochlorothiazide (2 x 300/6.25 mg) used in clinical trials
- To assess the safety and tolerability of eprosartan and hydrochlorothiazide in healthy volunteers.

Study Population:
Healthy men and non-pregnant, non-lactating women who were between 18 to 55 years of age were eligible for enrollment in the study. Seventy-two healthy adult male volunteers enrolled in and completed the study.

Demographic data for all subjects are presented below:

GROUP	PARAMETER	AGE	WEIGHT	HEIGHT
Males (n=72)		(years)	(kg)	(m)
	Mean	40	80.5	1.79
	SD	6.7	10.92	0.065
	Range	20-55	58.2-105.5	1.65-1.93

Race: 24 white (33.3%), 47 black (65.3%), 1 other (1.4%)

Study Design:
This study was conducted as an open-label, randomized, two period, period balanced crossover study in healthy volunteers. Subjects were to be studied in two cohorts. Seventy two subjects were enrolled in the first cohort to ensure at least 66 evaluable subjects for an interim bioequivalence analysis and, if necessary, up to 60 subjects were to be enrolled into the second cohort to ensure at least 54 evaluable subjects in the second cohort.

Each subject received a single oral dose of the combination tablet of eprosartan and hydrochlorothiazide (HCTZ), administered as one of two different regimens: A) eprosartan and HCTZ combination (600/12.5 mg) and B) eprosartan and HCTZ (2 x 300/6.25 mg). Subjects were randomized to one of two treatment sequences (AB or BA). After an overnight fast, subjects were

admitted to the Clinical Research Center (CRC) on the morning of dosing. An unblinded sub-investigator administered study medication during each study session with 240 ml water as follows:

Regimen A: 1 x eprosartan/HCTZ 600/12.5 mg
Regimen B: 2 x eprosartan/HCTZ 300/6.25 mg

Pharmacokinetic samples were collected immediately prior to drug administration and up to 32 hours post-dose. There was a 7 day washout between doses.

Formulations:

The formulations, dose units, and Lot numbers of the medications used in the study are presented in the table below.

STUDY DRUGS	APPEARANCE	FORMULATION	DOSE UNIT	LOT NO.	LOT SIZE
Eprosartan plus hydrochlorothiazide	Pale butterscotch colored, aqueous film coated caplet with SB debossed on one side of the tablet	Tablet	600/12.5 mg	U98200	183,465 Tablets
Eprosartan plus hydrochlorothiazide	Oval, white, aqueous film coated Tiltab with a score on one side and with SB debossed on both sides at opposite ends of the tablet.	Tablet	300/6.25 mg	U98250	100,000 Tablets

SmithKline Beecham supplied study medication:

Collection of Samples:

Blood samples (approximately 5 ml) for eprosartan and HCTZ pharmacokinetic analysis were collected into heparinized tubes prior to dosing and at the following nominal times after drug administration: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24, and 32 hours.

Analytical Methods:

Plasma concentrations of eprosartan and HCTZ were analyzed using [redacted]. The lower limit of quantification for eprosartan was [redacted] ng/ml and for HCTZ was [redacted] ng/ml, based on a [redacted] aliquot of plasma.

DATA ANALYSIS:

- ***Safety:*** Blood pressure, pulse rate, and clinical laboratory data were reviewed on an ongoing basis during the study to evaluate the safety of subjects. Any clinically relevant abnormalities or values of potential clinical concern were described.

- ***Pharmacokinetics:*** Blood samples for pharmacokinetic analysis were obtained prior to dosing and up to 32 hours after dosing. Noncompartmental pharmacokinetic analysis of the eprosartan and HCTZ plasma concentration-time data provided estimates of Tmax, Cmax, T1/2, AUC(0-inf), AUC(0-t), and AUC(0-t'), where t' was the time of the last quantifiable concentration in common for all regimens for each subject.

- ***Statistics:*** An interim analysis to assess bioequivalence was conducted after the first cohort of approximately 72 subjects had completed. Dosing of the remaining subjects (up to 60), if

necessary, was to continue upon completion of the interim analysis. However, following review of the interim results by the sponsor, the study was terminated and no other subjects were enrolled in the study.

- ***Sample Size Considerations:*** Sample size calculations were based on within-subject coefficients of variation for eprosartan observed in previous studies No. 127 and 153 in which eprosartan was administered as the 600 mg reduced-weight tablet and on within-subject coefficients of variation for HCTZ observed in previous studies No. 077 and 079 in which HCTZ was administered with eprosartan. The maximum observed CV for eprosartan was 33.7% for Cmax in study 127 and for HCTZ was 20.2% for Cmax in study 079. Thus, sample size calculations were based on the highest CV of 33.7%. Based on the precision of the observed variance estimates in study 127, it was possible that increased variation of up to 45% could be observed simply due to sampling variation.

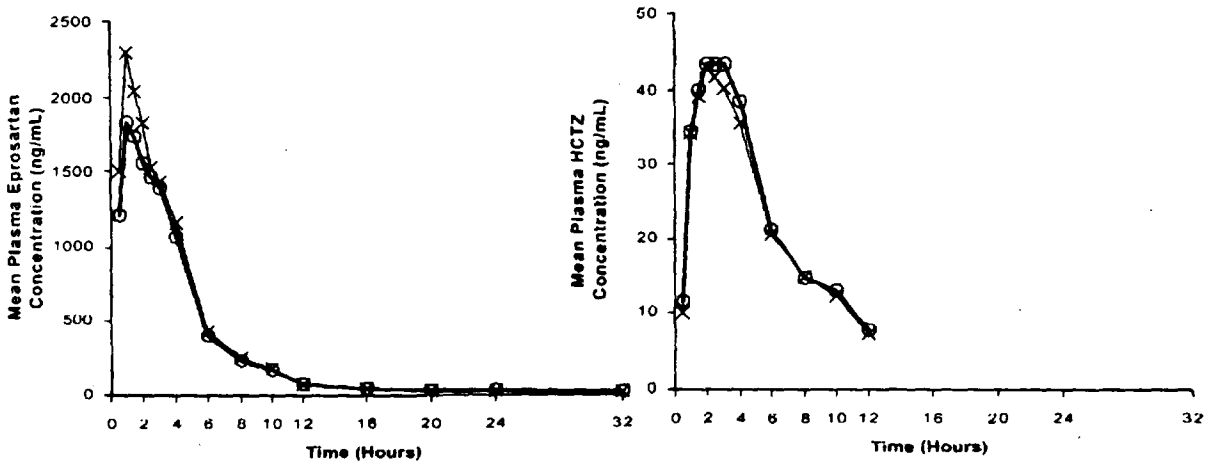
  - At interim analysis, it was estimated that a sample size of 66 subjects would provide at least 90% power to demonstrate equivalence for AUC and Cmax if the CV was 33.7% and at least 80% power if the CV was 40%. Equivalence is demonstrated when the 95% confidence interval for the ratio test:reference (A:B) was contained within the range (80-125%) for both AUC and Cmax of eprosartan and HCTZ. This range represents a symmetric 20% range on the $\log_e$-scale. This calculation was based on a two one-sided testing procedure with a type I error rate of 2.5% and a true ratio of unity. Seventy-two subjects were to be studied in the first cohort to allow for a 10% dropout rate.

  - At final analysis, if required, based on the highest estimate of within-subject variation of 45%, it was estimated that a total of 120 subjects would provide at least 90% power to demonstrate equivalence for AUC and Cmax if the CV was 45% and at least 80% power if the CV was 50%. Equivalence was demonstrated when the 95% confidence interval for the ratio test:reference (A:B) was contained within the range (80-125%) for both AUC and Cmax of eprosartan and HCTZ. This range represents a symmetric 20% range on the log scale. This calculation was based on a two one-sided testing procedure with a type I error rate of 2.5%, a true ratio of unity and assumed that the within-subject variability and average difference in test:reference would be similar between cohorts. One hundred and thirty two subjects were to be studied in total to allow for a 10% dropout rate.

- ***Comparisons of Interest:*** The primary pharmacokinetic parameters were AUC(0-t') and Cmax of eprosartan and HCTZ. Secondary pharmacokinetic parameters were AUC(0-t), AUC(0-inf), and Tmax of eprosartan and HCTZ. The focus of the statistical analysis was to determine the equivalence of the proposed commercial combination formulation of eprosartan/HCTZ 600/12.5 mg (regimen A) relative to two times the clinical trials combination formulation of eprosartan/HCTZ 300/6.25 mg (regimen B), based on the primary pharmacokinetic parameters. Thus, point estimates and associated 95% confidence intervals (CI) were computed for the ratio of A:B for AUC(0-t') and Cmax of both eprosartan and HCTZ. At interim or final analysis, equivalence would be demonstrated when the 95% CI were completely contained within the range 0.80 to 1.25 for both AUC and Cmax of both eprosartan and HCTZ.

RESULTS:

- ***Pharmacokinetics:*** Mean concentration-time profiles for eprosartan and HCTZ following administration of regimens A and B and mean (SD) pharmacokinetic values and summary statistics for eprosartan and HCTZ are presented next.



Mean Plasma Eprosartan and HCTZ Concentrations Following a Single Dose of Eprosartan 600 mg/HCTZ 12.5 mg Combination Tablet (-X-) or Two Eprosartan 300 mg/HCTZ 6.25 mg Combination Tablets (-O-)

Summary of Pharmacokinetic Parameters and Statistics for Eprosartan and HCTZ

EPROSARTAN					
	PHARMACOKINETICS		STATISTICS		
Parameter	**Regimen A**	**Regimen B**	**Estimate**	**95% CI**	**CV resid (%)**
AUC_{0-t} (ng.h/ml)	9582 (4684)	8618 (4296)	1.11*	100-123**	32.3
C_{max} (ng/ml)	2798 (1398)	2361 (1150)	1.16*	103-132**	39.2
T_{max} (hour)	1.00 (0.5-4.00)	1.00 (0.50-4.00)	A-B 0.00	-0.5, 0.25	-
HYDROCHLOROTHIAZIDE					
	PHARMACOKINETICS		STATISTICS		
Parameter	**Regimen A**	**Regimen B**	**Estimate**	**95% CI**	**CV resid (%)**
AUC_{0-t} (ng.h/ml)	280 (92)	289 (76)	0.96*	91-100**	13.4
C_{max} (ng/ml)	51.1 (12.6)	54.2 (13.2)	0.94*	89-100**	17.1
T_{max} (hour)	2.00 (1.00-4.00)	2.25 (1.00-4.00)	A-B 0.0 h	-0.5, 0.25	-

* data presented as ratio of adjusted geometric means (A:B)
** alpha level adjusted for interim analysis (= 2.5% at each look)
A = eprosartan/HCTZ 600/12.5 mg (test formulation)
B = 2 x eprosartan/HCTZ 300/6.25 mg (reference formulation)

The 95% confidence intervals for the ratio of adjusted geometric means for AUC(0-t') of eprosartan and AUC(0-t') and Cmax of HCTZ were completely contained within the equivalence range of 80-125%. However, the 95% confidence interval for Cmax of eprosartan was not completely contained within the equivalence range as the upper bound of the confidence interval

was greater than 125%, indicating that the two formulations were not equivalent. Cmax of eprosartan was 16% greater, on average, for the 600/12.5 mg combination tablet, with 95% confidence intervals ranging from 103% to 132%. The 95% confidence intervals for AUC(0-t) and AUC(0-inf) for both eprosartan and HCTZ were also completely contained within the equivalence range. On average, Tmax for both eprosartan and HCTZ were similar.

Safety:

There were no deaths, serious adverse experiences or withdrawals due to adverse experiences reported during this study. All non-serious, treatment emergent adverse experiences reported during the study are summarized in the table below. Each of these adverse events was suspected to be related to study medication and all were mild or moderate in nature.

	REGIMEN A	REGIMEN B	TOTAL
Total Number of AEs	13	12	25
Most frequently reported AE = Headache	8	4	12
Number of, subjects with AEs	13	12	24
Number of subject sessions	72	72	144

A= Eprosartan/HCTZ (1 X 600/12.5); B= Eprosartan/HCTZ (2 X 300/6.25)

Discussion

An interim analysis to assess bioequivalence was conducted after the first cohort of 72 subjects completed. Per protocol, dosing of the second cohort of subjects (up to 60 to ensure that an additional 54 subjects complete) was to begin upon completion of the interim analysis if the assessment of bioequivalence was inconclusive (i.e., the 95% CI for AUC or Cmax for eprosartan or HCTZ extended beyond the range 0.80 to 1.25, but the point estimate was within the range). However, based on point and variability estimates from first cohort, even with these additional subjects from the second cohort, the power to demonstrate equivalence would be < 50%. As inference would be unlikely to change if an additional 54 subjects were studied, the sponsor elected to terminate the study.

CONCLUSIONS:

- The purpose of this study was to determine the bioequivalence of the eprosartan/HCTZ 600/12.5 mg combination tablet formulation proposed for commercial use with the eprosartan/HCTZ 300/6.25 mg combination tablet formulation used in clinical trials. Bioequivalence was demonstrated for the HCTZ components but not for the eprosartan components of the combination tablets.
- For eprosartan, the 95% confidence interval for AUC(0-t') was completely contained within the acceptance range of 80-125%; however, the upper bound of the 95% confidence interval for Cmax was slightly greater than 125% (i.e., 132%). Point estimates for AUC and Cmax increased 11 to 16% on average for the proposed commercial formulation and Tmax values were similar between the formulations. Based on these data, it appears that there was a minor increase in the extent of absorption but no change in the rate of absorption for the proposed commercial formulation.
- The combination formulation of eprosartan plus hydrochlorothiazide (600/12.5 mg) proposed for commercial use was as safe and as well tolerated as the combination formulation of

eprosartan plus hydrochlorothiazide (2 x 300/6.25 mg) used in clinical trials.

REVIEWER COMMENTS:

1. *It should be noted that complete analytical validation information for eprosartan was submitted under the original NDA. This report only included Quality Control data for the determination of eprosartan and HCTZ. The provided Quality Control data showed adequate assay precision and accuracy for both drugs.*
2. *Bioequivalence could not be shown for eprosartan. The combination and individual tablets were not bioequivalent with respect to eprosartan's Cmax. The 95% CI exceeded the upper bound of the bioequivalence range of 80-125%. With respect to HCTZ, the combination and individual tablets were bioequivalent with respect to all pharmacokinetic variables.*
3. *Although the results of this study showed that the combination and individual tablets are not bioequivalent with respect to eprosartan's Cmax, based upon the adequate safety profile of eprosartan at doses up to 1200 mg and high intra-subject variability for Cmax (approximately 40% in this study), it is not expected that the failure to pass the Agency's 80-125% bioequivalence criteria will have any clinical consequences.*

APPEARS THIS WAY
ON ORIGINAL

Study Report Summary

Study No. 079

Study Title: A Study to Evaluate the Pharmacokinetics of Eprosartan and Hydrochlorothiazide (HCTZ) When Administered Alone or in Combination in Healthy Adult Volunteers.

Principal Investigator/Investigation Site:
Bernard E. Ilson, M.D., SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center of Philadelphia, University of Pennsylvania Health System, 51 North 39th Street, Philadelphia. Pennsylvania, 19104, USA

Objectives:
The objectives of this study were:

- To compare the pharmacokinetics of eprosartan when administered alone and when co-administered with hydrochlorothiazide (HCTZ).
- To compare the pharmacokinetics of HCTZ when administered alone and when co-administered with eprosartan.
- To evaluate the safety of eprosartan and HCTZ when administered alone or when co-administered.

Study Population:
Eighteen (18) subjects were randomized to treatment and all eighteen (18) of these subjects completed the study. Of the eighteen subjects who completed this study, fifteen were male (83%) and three were female (17%). There were no withdrawals from the study. The demographic data for all subjects are presented below:

GROUP	PARAMETER	AGE	WEIGHT	HEIGHT
All subjects		(years)	(kg)	(m)
	n	18	18	18
	Mean	30	73.61	1.76
	SD	8.2	17.26	0.10
	Range	19-53	50.6-111.3	1.60-2.00

Study Design:
This was a randomized, open-label, single dose, three-period, period balanced crossover study in healthy adult volunteers. There were three treatment sessions in this protocol. After fasting overnight, subjects received a single, oral dose of either eprosartan 800 mg, HCTZ 25 mg, or eprosartan 800 mg plus HCTZ 25 mg, with 240 ml of tepid water at each of the study sessions. There was a minimum of 7 days between doses of study medication.

Each subject received a single oral dose of the following regimens in random order:
A) Eprosartan commercial tablet (2 x 400 mg)
B) HCTZ capsule (2 x 12.5 mg)
C) Eprosartan commercial tablet (2 x 400 mg) + HCTZ capsule (2 x 12.5 mg)

Formulations:

The formulations, dose units, and Lot numbers of the medications used in the study are presented in the table below.

STUDY DRUGS	APPEARANCE	FORMULATION	DOSE UNIT	LOT NO.
SK&F 108566 (Eprosartan	Oval, light to moderate pink colored, aqueous film coated Tiltab™ with a score on one side, and with SB and 5044 debossed on both sides at opposite ends of the tablet	Tablet Formula AZ-AA	400 mg	U96205
SK&F 008476 (Hydrochlorothiazide)	Oval, white, aqueous film coated Tiltab with a score on one side and with SB debossed on both sides at opposite ends of the tablet.	Capsules Formula AH-AA	12.5 mg	U96254

SmithKline Beecham supplied study medication:

Collection of Samples:

Blood: For each regimen blood samples were collected prior to dosing (time 0) and at nominal times of 0.5, I, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 36, and 48 hours after dosing. The volume of each blood sample was 5 ml for regimens A and B and 10 ml for regimen C.

Urine: Following dosing of HCTZ (regimens B and C), all urine was collected into labeled bottles for the following post-dose time intervals: 0-4, 4-8, 8-12, 12-18, 18-24, 24-32, and 32-48 hours and the volumes recorded. In addition, a urine sample was collected immediately prior to dosing. A 20 ml aliquot of each well mixed urine sample was frozen at -20°C.

Analytical Methods:

Eprosartan and hydrochlorothiazide (HCTZ) were isolated from human plasma by[ ]. The lower limits of quantification (LLQ) for eprosartan and HCTZ were[ ] plasma. HCTZ was isolated from human urine[ ]. The lower limit of quantification (LLQ) for HCTZ was[ ] µg/ml, utilizing[ ] µL of urine. Quality control (QC) samples for each assay were analyzed with[ ]. The results of the analysis of the QC samples were used to assess the day-to-day performance of each assay.

DATA ANALYSIS:

- ***Safety:*** Blood pressure, pulse rate, and clinical laboratory data were reviewed on an ongoing basis during the study to evaluate the safety of subjects. Any clinically relevant abnormalities or values of potential clinical concern were described.

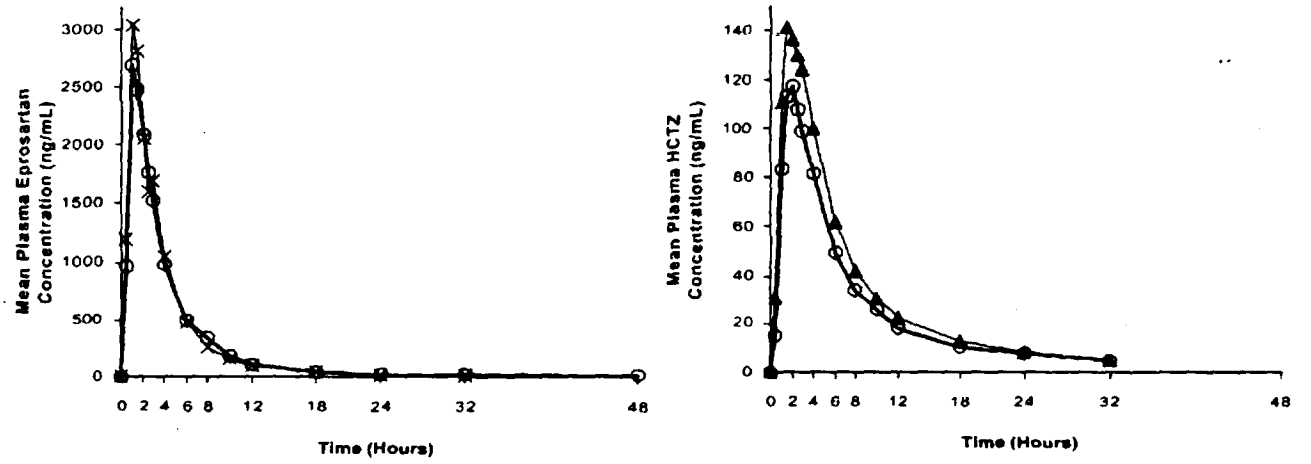
- ***Pharmacokinetics:*** Blood samples for pharmacokinetic analysis were collected prior to dosing and at time-points up to 48 hours following single dose administration. Urine samples were collected for seven pre-defined intervals, up to 48 hours post-dose, for the two regimens in which HCTZ was administered. Plasma concentrations of eprosartan and HCTZ were

quantified using [redacted] Pharmacokinetic parameters (Cmax, Tmax and AUC(0-t)) were calculated using [redacted] methods. Additionally, the amount of HCTZ excreted in the urine (Ae) and the renal clearance (CLr) were calculated from the urine data.

- ***Statistics:*** Following log-transformation, AUC(0-t) and Cmax of eprosartan and HCTZ were analyzed by analysis of variance (ANOVA), including terms for sequence, subject within sequence, period and regimen. There was additional assessment of first-order carryover. Point estimates and associated 95% confidence intervals were constructed for the differences C-A and C-B. The point and interval estimates on the log-scale were exponentially back-transformed to give estimates for the ratios of C:A and C:B. No adjustment for multiple comparisons was made. Renal clearance of HCTZ for regimens B and C was analyzed in a similar fashion. Tmax of eprosartan and HCTZ was analyzed non-parametrically using the Wilcoxon matched pairs method, The point estimate and 95% confidence interval were constructed for the median difference C-A and C-B.

RESULTS:

- ***Pharmacokinetics:*** Mean concentration-time profiles for eprosartan and HCTZ following administration of regimens A and B are illustrated in the next Figure.



Mean Plasma Eprosartan and HCTZ Concentrations Following A Single Dose of 2 x Eprosartan 400 mg or 2 x Commercial Tablets (–X–) or HCTZ 12.5 mg Commercial Capsule (–▲–) or 2 x Eprosartan 400 mg Commercial Tablets Plus 2 x HCTZ 12.5 mg Capsules (–O–)

The next Table presents the mean (SD) pharmacokinetic values and summary statistics for eprosartan and HCTZ.

Summary of Pharmacokinetic Parameters and Statistics for Eprosartan and HCTZ

EPROSARTAN					
PHARMACOKINETICS			STATISTICS		
Parameter	Eprosartan	Eprosartan + HCTZ	Comparison	Point Estimate**	95% CI
AUC_{0-t} (ng.h/ml)	10567 (4613)	10571 (4881)	C:A	0.97	81-117
C_{max} (ng/ml)	3310 (1873)	3025 (1362)	C:A	0.93	80-109
*T_{max} (hour)	1.00 (1.0 -3.0)	1.00 (1.0 -3.0)	C-A	0.00^	-0.5, 0.25
HYDROCHLOROTHIAZIDE					
PHARMACOKINETICS			STATISTICS		
Parameter	HCTZ	Eprosartan + HCTZ	Comparison	Point Estimate**	95% CI
AUC_{0-t} (ng.h/ml)	1046 (254)	850 (228)	C:B	0.81	72-91
C_{max} (ng/ml)	155 (50)	127 (52)	C:B	0.80	69-92
T_{max} (hour)	1.53 (0.98 -3.0)	1.97 (0.98-2.98)	C-B	0.22^	-0.27, 0.53
CLr (ml/min)	215 (66)	195 (72)	C:B	0.89	76-104

* presented as median (range).
** Point estimate represents the ratio of geometric means.
^ Point estimate represents the median difference.
Regimen A: Eprosartan 800 mg alone (as 2 x 400 mg commercial tablet).
Regimen B: HCTZ 25 mg (as 2 x 12.5 mg capsule).
Regimen C: Eprosartan 800 mg (as 2 x 400 mg commercial tablet) + HCTZ 25 mg (as 2 x12.5 mg capsule).

Eprosartan: The pharmacokinetic parameters AUC(0-t), Cmax and Tmax for eprosartan were similar following administration of eprosartan alone or concomitantly with HCTZ.

The observed within-subject coefficients of variation for AUC(0-t) and Cmax were 25.7% and 22.3% respectively, while the coefficient of variation used in sample size calculations was 29.9%, indicating no inadequacies in terms of sample size. Between subject variability estimates were similar for each regimen (approximately 50% for AUC(0-t) and Cmax).

Hydrochlorothiazide: Following administration of HCTZ alone (25 mg) or concomitantly with eprosartan (800 mg), median Tmax values of 1.53 and 1.97 hour, respectively, were observed. In general, after attaining Cmax, HCTZ plasma concentrations declined over time in an apparent mono or biexponential fashion and were generally quantifiable for 32 to 48 hours. Mean (SD) half-life values were 9.42 (1.34) hours for HCTZ alone and 10.95 (2.97) hours for HCTZ when administered with eprosartan. Administration of HCTZ concomitantly with eprosartan resulted in an approximate decrease in AUC(0-t) and Cmax of 19% and 20%, respectively, compared to administration of HCTZ alone. The mean amount of HCTZ excreted in urine over 48 hours (Ae, as % of dose) was approximately 53% (range 23 to 79%) for HCTZ alone and 37% (range 15 to

53%) for HCTZ when administered with eprosartan.

The observed within-subject coefficients of variation for AUC(0-t) and Cmax were 16.5% and 20.2% respectively, while the coefficient of variation used in sample size calculations was 29.9%, indicating no inadequacies in terms of sample size. Between-subject variability estimates were similar for each regimen (approximately 26% for AUC(0-t) and 34-42% for Cmax).

Safety:

A total of twelve adverse experiences (AEs) were reported for seven subjects following treatment with study medication. Of these AEs, two AEs occurred in two subjects following administration of eprosartan 800 mg, six of the AEs occurred in five subjects following HCTZ 25 mg and four of the AEs occurred in three subjects following eprosartan 800 plus HCTZ 25 mg. All AEs were mild in severity. The most common AE was headache. All of the AEs suspected of being related to study medication resolved without treatment. There were no withdrawals due to AEs, there were no serious, non-fatal AEs and there were no deaths during the study. One subject had a single change in vital signs of potential clinical concern (decreased systolic blood pressure) at 3 hours after administration of eprosartan 800 mg plus HCTZ 25 mg, which was associated with complaints of dizziness and was considered suspected of being related to study medication. There were no clinically significant changes in laboratory values, which were attributed to treatment with study medication.

CONCLUSIONS:

- Eprosartan 800 mg, HCTZ 25 mg and eprosartan 800 mg plus HCTZ 25 mg, given as a single oral dose, were safe and well tolerated in healthy adult male and female volunteers.
- The pharmacokinetics of eprosartan were similar; whether administered alone or concomitantly with HCTZ. There was a slight decrease (approximately 20%) in the AUC(0-t) and Cmax of HCTZ when co-administered with eprosartan as compared to administration of HCTZ alone, which was not clinically significant.
- Renal clearance and Tmax of HCTZ did not appear to be affected by the co-administration of eprosartan.

REVIEWER COMMENTS:

1. *The provided Quality Control data showed adequate assay precision and accuracy for both drugs.*

2. *There was a minor (20%), yet statistically significant, decrease in AUC(0-t) and Cmax for HCTZ after administration of HCTZ and eprosartan. The mechanism for this change is not clear as the renal clearance of HCTZ was not affected by eprosartan administration, although a slight decrease in the total amount excreted of HCTZ was observed with combination dosing (37%) versus HCTZ alone (53%). Additionally, the terminal elimination half-life of HCTZ appeared to be similar, approximately 10 hours, when HCTZ was administered alone or with eprosartan. These results are consistent with a decrease in bioavailability of HCTZ.*

Study Summary

Study No. S1711006

Study Title: A Randomized, Single-Dose, Two-Period, Cross-Over Study to Compare the Bioavailability of One Combination Tablet of Eprosartan 600 mg/Hydrochlorothiazide 25 mg Relative to the Coadministration of One 600-mg Eprosartan Tablet and One 25-mg Hydrochlorothiazide Tablet in Healthy Male and Female Volunteers.

Principal Investigator/Investigation Site:
Investigator: Dr. Lawrence Galitz/ South Florida Bioavailability Clinic, Miami, Florida.

Objectives:
To compare the bioavailability of one eprosartan 600 mg/hydrochlorothiazide (HCTZ) 25 mg combination tablet relative to the coadministration of one 600-mg eprosartan tablet and one 25-mg HCTZ tablet in healthy male and female volunteers.

Study Population:
A total of 36 subjects, consisting of 18 healthy male and 18 healthy female subjects were enrolled and completed the trial as planned. The demographic data for all subjects are presented below :

GROUP	PARAMETER	AGE	WEIGHT	HEIGHT
		(years)	(lb)	(in)
All subjects	n	36	36	36
	Mean	43.2	166.2	66.7
	SEM	1.8	5.0	0.7
	Range	25-56	121-231	60-75

Study Design:
This was a randomized, open-label, balanced, two-period, crossover, single oral dose study in 36 healthy volunteers. Each subject received two treatments in randomized order. Treatment A consisted of a single eprosartan 600 mg/HCTZ 25 mg combination tablet. Treatment B consisted of one 600-mg eprosartan tablet and one 25-mg HCTZ tablet.

Screening assessments were performed within 21 days prior to Day 1 and included physical examination, ECG, vital sign measurements, clinical laboratory determinations, HIV and Hepatitis B/C screening, serum pregnancy test, urine drug screen, blood alcohol test, and medical history. In addition to the routine vital sign schedule, sitting blood pressures and pulse rate were monitored at 1, 2, 4, and 6 hours following the administration of study drug on Day 1 and Day 8.

The subjects were randomly placed into two groups. During each of the two periods of this study, one group received a single eprosartan 600 mg/HCTZ 25 mg combination tablet, while the other group received one 600-mg eprosartan tablet and one 25-mg HCTZ tablet. These two single-dose treatments were separated by a 7-day washout period.

Blood samples for each time point for the determination of eprosartan and HCTZ plasma

concentrations were collected at specified times. The study was completed when subjects had undergone pre-study assessments, two single-dose treatments (Treatments A and B), and post-study assessments, including any possible follow-up assessments. All subjects were included in the safety analysis. Blood samples obtained from subjects who completed both single dose treatments were eligible for pharmacokinetic analysis.

Dosage and Administration

Subjects were administered either one combination tablet eprosartan 600 mg/HCTZ 25 mg or one 600 mg eprosartan tablet and one 25 mg HCTZ tablet with 240 mL of water on the morning of Days 1 and 8 at approximately 8:00 a.m. by medical personnel at the clinical site. Subjects were to receive drug at approximately the same time during each treatment period.

Formulations:

Eprosartan 600 mg/HCTZ 25 mg combination tablets were supplied by Solvay Pharmaceuticals B.V., and eprosartan tablets (600 mg) and HCTZ tablets (25 mg) were obtained commercially by the study site. The formulations, dose units, and Lot numbers of the medications used in the study are presented in the table below.

STUDY DRUGS	APPEARANCE	FORMULATION	DOSE UNIT	LOT NO.	LOT SIZE
Eprosartan mesylate	White, non-scored, capsule-shaped tablets	Tablet	600	NA	NA
Hydrochlorotiazide	White tablets	Tablet	25 mg	NA	NA
Eprosartan plus hydrochlorothiazide	Brick-red, film-coated, capsule-shaped tablet.	Tablet	600/25 mg	00H304	237,700 Tablets

Collection of Samples:

Blood samples (for each time point) for the determination of eprosartan (5-mL sample) and HCTZ (7-mL sample) plasma concentrations were collected into heparinized tubes prior to dosing, and at the following time points after drug administration: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24, and 32 hours. Blood samples collected for quantification of plasma eprosartan and HCTZ concentrations were sent to [redacted] who performed the assays.

Analytical Methods:

Eprosartan and hydrochlorothiazide (HCTZ) were isolated from human plasma[redacted] The lower limits of quantification (LLQ) for eprosartan and HCTZ were [redacted] ng/ml and [redacted] ng/ml, respectively, utilizing [redacted] ml of plasma. HCTZ was isolated from human urine[redacted] The lower limit of quantification (LLQ) for HCTZ was [redacted] µg/ml, utilizing [redacted] µL of urine. Quality control (QC) samples for each assay were analyzed with [redacted] The results of the analysis of the QC samples were used to assess the day-to-day performance of each assay.

DATA ANALYSIS:

- ***Pharmacokinetics:*** Pharmacokinetic parameters for plasma eprosartan and HCTZ concentration-time data were computed by [redacted] methods. The following pharmacokinetic parameters for eprosartan and HCTZ were determined:

$AUC_{(0-t)}$	area under the plasma concentration time curve (0 to last time point)
$AUC_{(0-t')}$	area under the plasma concentration time curve (0 to the time of the last quantifiable concentration in common for all treatments for each subject)
$AUC_{(0-inf)}$	area under the plasma concentration time curve from 0 extrapolated to Infinity
AUMC	area under the moment plasma concentration-time curve
Cmax	maximum observed concentration
T_{max}	time to Cmax
Kel	elimination rate constant, calculated from the log-linear terminal portion of the plasma concentration time curve
MRT	mean residence time, calculated as AUMC/AUC
CL/F	apparent total clearance, CL/F = DOSE/AUC(0-inf)
Vd/F	apparent volume of distribution, Vd/F = ((Dose) / AUC(0-inf)*Kel)
T1/2	apparent elimination half-life, ln 2/kel

- ***Safety:*** Screening assessments included medical history, physical examination, ECG, HIV/Hepatitis B/C screening, vital sign measurements, clinical laboratory determinations, serum pregnancy test (beta-HCG), urinary drug and blood alcohol screen. Final assessments included physical examination, ECG, vital sign measurements, and clinical laboratory determinations. A total of approximately 60 ml whole blood was obtained for clinical laboratory determination. Vital signs and adverse events were monitored throughout the duration of the study. In addition to the routine vital sign schedule, sitting blood pressures and pulse rate were measured at 1,2, 4, and 6 hours after the administration of study drug on Day 1 and Day 8. A serum pregnancy test (beta-HCG), urinary drug and blood alcohol screen was performed on Day -1 and on Day 7, prior to each of the confinement periods.

- ***Statistics:***

  Pharmacokinetics: The primary pharmacokinetic parameters were AUC(0-t') and Cmax of eprosartan and HCTZ. Secondary pharmacokinetic parameters were AUC(0-t), AUC(0-inf), and Tmax of eprosartan and HCTZ. Point estimates and associated 90% confidence intervals (CI) were computed for the ratio of A:B for AUC(0-t) and Cmax of both eprosartan and HCTZ. Equivalence would be demonstrated if the 90% CIs ,were completely contained within the range 80 to 125% for both AUC and Cmax of both eprosartan and HCTZ.

  Following the natural log-transformation, AUC(0-t') and Cmax of eprosartan and HCTZ were analyzed separately with the analysis of variance (ANOVA) model, fitting terms for sequence, subject within sequence, period, and treatment (A and B). Point estimates and associated 90% CIs were calculated for the difference A-B. Analysis of Tmax focused on estimation of the difference between the test formulation A and the reference formulation B. Based on the non-parametric approach, point estimates and associated 90% CIs were constructed for the median difference A-B.

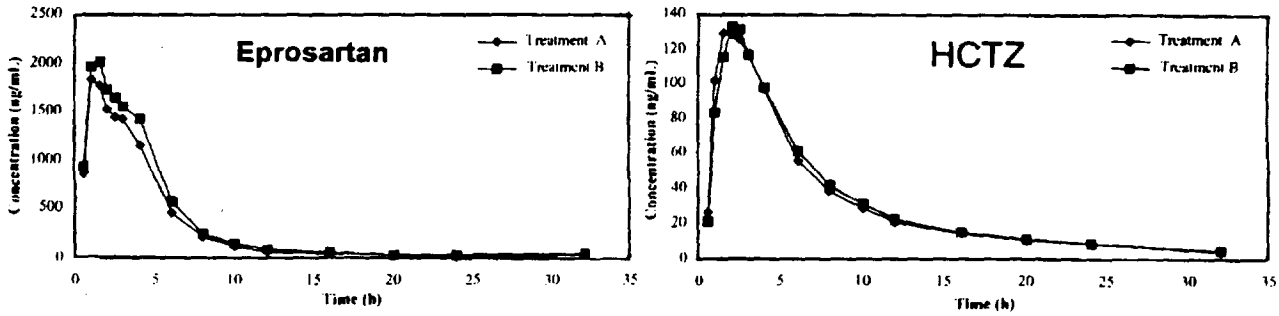
  In addition, an analysis of covariance (ANCOVA) model including gender as a covariate was employed to check the gender effect in the analysis of AUC(0-t') and Cmax of eprosartan and HCTZ. The model included the following factors: gender, sequence, sequence-by-gender,

subject within sequence-by-gender, period, treatment, period-by-gender, and treatment-by-gender.

Safety: Adverse events, physical exam, vital signs, and clinical laboratory data were tabulated and reviewed to evaluate the safety of all randomized subjects. Listings of values for each subject were presented with abnormal or out of range values for vital signs, laboratory assays, and physical examinations. Any clinical abnormalities were described.

RESULTS:

- ***Pharmacokinetics:*** Mean concentration-time profiles for eprosartan and HCTZ following administration of regimens A and B are illustrated in the next Figure.



Mean Plasma Eprosartan and HCTZ Concentration Time Profiles for Treatments A and B

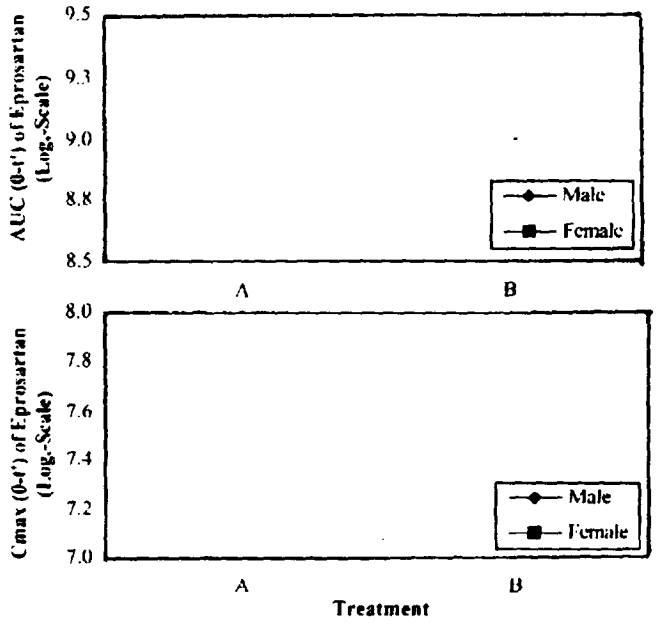
The next Table presents the mean (SD) pharmacokinetic values and summary statistics for eprosartan and HCTZ.

Summary of Pharmacokinetic Parameters and Statistics for Eprosartan and HCTZ

EPROSARTAN					
PHARMACOKINETICS			STATISTICS		
Parameter	Treatment A	Treatment B	Comparison	Point Estimate**	90% CI
AUC_{0-t} (ng.h/ml)	8456 (3920)	9854 (4313)	A:B	0.82	73-93
C_{max} (ng/ml)	2257 (1070)	2566 (1039)	A:B	0.86	77-95
T_{max} (hour)	1.50* (0.5-8.0)	1.50* (0.5-8.0)	A:B	0.00^	-0.5, 0.25
HYDROCHLOROTHIAZIDE					
PHARMACOKINETICS			STATISTICS		
Parameter	Treatment A	Treatment B	Comparison	Point Estimate**	90% CI
AUC_{0-t} (ng.h/ml)	950 (371)	976 (386)	A:B	0.97	91-104
C_{max} (ng/ml)	155 (52)	151 (60)	A:B	1.05	99-113
T_{max} (hour)	2.00* (1.0-6.0)	2.5* (1.0-6.0)	A:B	-0.5^	-0.5, 0

* presented as median (range).
** Point estimate represents the ratio of geometric means (A:B)
^ Point estimate represents the median difference (A-B)
Regimen A: Eprosartan 600 mg/ HCTZ 25 mg (test formulation)
Regimen B: 1 x eprosartan 600 mg + 1 x HCTZ 25 mg (reference formulation)

The study was stratified by gender. The results of the analysis of AUC(0-t') and Cmax of eprosartan by gender are illustrated in the next Figure.



Sequence Analysis for AUC(o-t') and Cmax of Eprosartan

The pharmacokinetic parameters for males and females and the statistical results of the analysis of ANCOVA of AUC and Cmax for eprosartan fitting gender as a covariate are presented below.

Summary by Gender of Pharmacokinetic Parameters and Statistics for Eprosartan

EPROSARTAN					
MALES					
PHARMACOKINETICS*			**STATISTICS**		
Parameter	Treatment A	Treatment B	Comparison	Point Estimate**	90% CI
$AUC_{0-t'}$ (ng.h/ml)	7087 (3078)	9230 (2613)	A:B	0.715	61-83
C_{max} (ng/ml)	1828 (831)	2449 (931)	A:B	0.735	65-84
FEMALES					
PHARMACOKINETICS*			**STATISTICS**		
Parameter	Treatment A	Treatment B	Comparison	Point Estimate**	90% CI
AUC_{0-t} (ng.h/ml)	9825 (4264)	10478 (5536)	A:B	0.947	81-110
C_{max} (ng/ml)	2687 (1129)	2684 (1152)	A:B	0.995	87-113

* Arith Mean (SD)
** Point estimate represents the ratio of geometric means (A:B)
Regimen A: Eprosartan 600 mg/ HCTZ 25 mg (test formulation)
Regimen B: 1 x eprosartan 600 mg + 1 x HCTZ 25 mg (reference formulation)

It appears that the combination formulation has lower bioavailability in males compared to females, therefore, the results showed that bioequivalence of the treatments is influenced by gender. Eprosartan bioequivalence for the two treatments appears to be demonstrated for

females but not for males. However, this observation is based on data from 18 males and females.

DISCUSSION::

Pharmacokinetics:

- The purpose of this study was to assess the bioavailability of the eprosartan 600 mg/HCTZ 25 mg combination tablet relative to the coadministration of one 600-mg eprosartan tablet and one 25-mg HCTZ tablet. Bioequivalence criteria were achieved for AUC(0-t) and Cmax for HCTZ, but they were not achieved for AUC(0-t') and Cmax for eprosartan. For eprosartan, the 90% confidence intervals for AUC(0-t) and Cmax were not completely contained within the equivalence range as the lower bound of the confidence interval was less than 80%, indicating that the two treatments were not equivalent.
- The AUC(0-t') of eprosartan was 18% lower, on average, for the 600/25 mg combination tablet, with 90% confidence intervals ranging from 73% to 93%. The Cmax of eprosartan was 14% lower, on average, for the 600/25 mg combination tablet, with 90% confidence intervals ranging from 77% to 95%. Based on these data and examination of the mean plasma eprosartan concentration-time profiles, it appears that there was a decrease in the extent of absorption but no change in the rate of absorption for the combination tablet (Treatment A) relative to the two tablets given separately (Treatment B).

Safety:

- Adverse events were only reported by four subjects (11.1%). All four subjects were in the Treatment A/Treatment B group. All adverse events were considered mild and none were considered to be related to treatment. No subject with a potentially clinical important out-of-range vital sign reported an adverse event. There were no deaths, serious adverse events, or premature terminations from the study.

CONCLUSIONS:

- Bioequivalence criteria were achieved for the AUC(0-t) and Cmax of HCTZ but not for the eprosartan AUC(0-t) and Cmax for the combination tablet. Thus, the eprosartan 600 mg/HCTZ 25 mg combination tablet was not proven to be bioequivalent to the 600 mg eprosartan tablet and 25 mg HCTZ tablet administered separately.
- The eprosartan 600 mg/HCTZ 25 mg combination tablet was as safe and well-tolerated as the 600 mg eprosartan tablet and 25 mg HCTZ tablet administered separately .

REVIEWER COMMENTS:

- *Bioequivalence could not be shown for eprosartan. The combination and individual tablets were not bioequivalent with respect to eprosartan's Cmax. The 90% CI exceeded the upper bound of the bioequivalence range of 80-125%. With respect to HCTZ, the combination and individual tablets were bioequivalent with respect to all pharmacokinetic variables.*
- *Although the results of this study showed that the combination and individual tablets are not bioequivalent with respect to eprosartan's Cmax, based upon the adequate safety profile of eprosartan at doses up to 1200 mg and high intra-subject variability for Cmax (approximately 40% in this study), it is not expected that the failure to pass the Agency's 80-125% bioequivalence criteria will have any clinical consequences.*

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DISSOLUTION DATA

Dissolution Results:

The dissolution was carried out using the following method.

The dissolution medium is 1000 ml of de-aerated 0.2 M phosphate buffer, pH 7.5. The dissolution is performed with USP apparatus 2 at 100 rpm. A[ ]the percentage of dissolved eprosartan and HCTZ. at :

Batch number: U98250 Eprosartan/hydrochlorothiazide 300mg/6.25mg tablets				
Sampling point:	**Dissolution of eprosartan in % Relative to Label Claim:**	**Mean in %RLC**	**Dissolution of hydrochlorothiazide in % Relative to Label Claim**	**Mean in %RLC**
15 minutes	[illegible]	100	[illegible]	102
30 minutes	[illegible]	100	[illegible]	102
45 minutes	[illegible]	100	[illegible]	101
60 minutes	[illegible]	101	[illegible]	102

Batch number: U98200 Eprosartan/hydrochlorothiazide 600mg/12.5mg tablets				
Sampling point:	**Dissolution of eprosartan in % Relative to Label Claim:**	**Mean in %RLC**	**Dissolution of hydrochlorothiazide in % Relative to Label Claim**	**Mean in %RLC**
15 minutes	[illegible]	82	[illegible]	79
30 minutes	[illegible]	91	[illegible]	88
45 minutes	[illegible]	94	[illegible]	90
60 minutes	[illegible]	96	[illegible]	92

Batch number: 00H304 Eprosartan/hydrochlorothiazide 600mg/25mg tablets				
Sampling point:	**Dissolution of eprosartan in % Relative to Label Claim:**	**Mean in %RLC**	**Dissolution of hydrochlorothiazide in % Relative to Label Claim**	**Mean in %RLC**
15 minutes	[redacted]	82	[redacted]	82
30 minutes	[redacted]	91	[redacted]	93
45 minutes	[redacted]	95	[redacted]	92
60 minutes	[redacted]	96	[redacted]	93

* This value could not be explained post analysis. This is probably caused by an air bubble in the tubing.

APPEARS THIS WAY
ON ORIGINAL

Attachment II

Includes

NDA 21-268

Proposed Labeling for Teveten® [redacted] Tablets

21 pages redacted from this section of the approval package consisted of draft labeling