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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-387/S-013, 015 & 027

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA: 20-387/SE1-027

Submission Dates: 9/24/2002 and 3/17/2003

Drug Name: Hyzaar (losartan potassium/HCTZ) Tablets, 50-12.5 and 100-25 mg

Applicant: Merck & Co, Inc.

Submission: Supplemental NDA

Reviewer: Elena V. Mishina, Ph.D.

1 EXECUTIVE SUMMARY

This supplemental NDA review evaluates whether the sponsor has made adequate changes to the labeling of Hyzaar to the hypertensive patients with renal impairment.

The sponsor has submitted this efficacy supplement for a new indication for the use of Hyzaar for the initial treatment of severe hypertension (SiDBP> 110 mmHg). The sponsor has also submitted the draft of the manuscript for the publication based on the two studies which evaluated the pharmacokinetic, efficacy and safety of Hyzaar in patients with mild to moderate renal impairment. The Agency requested the study report for the pharmacokinetic study (Protocol 088) for review. The results of this study were used to update the labeling for Hyzaar with respect to the patients with renal impairment.

HYZAAR 50-12.5 mg (losartan potassium-hydrochlorothiazide) and HYZAAR 100-25 mg (losartan potassium-hydrochlorothiazide) combine an angiotensin II receptor (type AT1) antagonist and a diuretic, hydrochlorothiazide.
OCPB finds the submitted data in NDA 20-387/027 to be acceptable in meeting the OCPB requirements, however, the recommendations for the use of HYZAAR in renally impaired patients should be changed following labeling revisions.
HYZAAR is not recommended to the patients with moderately and severe impaired renal function (creatinine clearance <50 mL/min).

2 RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation I finds the information included in the NDA 20-387/027 for HYZAAR 50-12.5 mg and 100-25 mg (losartan potassium-hydrochlorothiazide) acceptable. The Office of Clinical Pharmacology and Biopharmaceutics recommends changes in the labeling with regard to the use of HYZAAR in renally impaired patients.

Please forward the Comments to the sponsor.

/S/

Date_____

Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

/S/

Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

CPB Briefing was held on April 10, 2003.
Attendees: Drs. M. Mehta, C. Sahajwalla, P. Marroum, A. Bhattaram, R. Ramchandani.

cc list: NDA 20,386, MehulM, MarroumP, MishinaE, HFD 110 BIOPHARM

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4 SUMMARY OF CPB FINDINGS

4.1 Background:

HYZAAR 50-12.5 and 100-25 (losartan potassium-hydrochlorothiazide) combine an angiotensin II receptor (type AT1) antagonist and a diuretic, hydrochlorothiazide.

Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT1 receptor and have much greater affinity (about 1000-fold) for the AT1 receptor than for the AT2 receptor. In vitro binding studies indicate that losartan is a reversible, competitive inhibitor of the AT1 receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT1 receptor. Neither losartan nor its active metabolite inhibits ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin); nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide

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 potassium loss associated with these diuretics. The mechanism of the antihypertensive effect of thiazides is unknown.

After oral dose, losartan is converted, in part (about 14%), to an active carboxylic acid metabolite. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily dosing.

Following oral administration, losartan is well absorbed (based on absorption of radiolabeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of losartan. A meal slows absorption of losartan and decreases its Cmax but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2%, respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution of losartan is about 34 liters and of the active metabolite is about 12 liters. Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively.

When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral 14 C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of 14 C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

4.2 Current Submission:

In this Application the sponsor determined the effect of renal impairment in hypertensive patients on the pharmacokinetics of losartan, its active metabolite, and

hydrochlorothiazide (HCTZ) following chronic doses of the combination tablet of losartan/HCTZ 50 mg/12.5 mg. The main purpose of this study was to make changes to the Package Insert regarding the use of HYZAAR in hypertesive patients with renal impairment. In this study, the sponsor enrolled three groups of patients: Group I with normal renal function (N=14), Group IIa with mild (N=6), and Group IIb - with moderate renal impairment (N=6). The data for the severely impaired patients already existed in the label. However, the sponsor pooled the data for both groups of patients with renal impairment together for the data analysis. None of the statistical tests were performed. Although the data submitted by the sponsor are valuable, the data analysis submitted by the sponsor with the study Protocol 088 report in the HYZAAR NDA **20-387/SE1-027** was not adequate.
The data analysis using the sponsor's data was performed by the Agency. The results of this analysis were used to make changes in the Package Insert regarding the use of HYZAAR in hypertesive patients with renal impairment.

The analytical methods were found to be acceptable.

4.3 Summary of the CPB Findings:

When HYZAAR 50/12.5 mg daily dose was administered for 7 days to the hypertensive patients, losartan AUC increased from 520 ng/mL/hr (normal renal function) to 780 ng/mL/hr (mild renal impairment) and 930 ng/mL/hr (moderate renal impairment). In the same studied groups of patients, the renal clearance values of losartan decreased from 53 mL/min to 25 mL/min and 7 mL/min, respectively. The renal clearance values of losartan metabolite decreased from 20 mL/min to 8 mL/min and 4 mL/min respectively. The AUC values of losartan metabolite increased 2-fold in patients with moderate renal impairment compared to patients with normal kidneys.
In the same study, hydrochlorothiazide AUC increased from 492 ng/mL/hr (normal renal function) to 821 ng/mL/hr (mild renal impairment) and 3426 ng/mL/hr (moderate renal impairment). In the same studied groups of patients, renal clearance of HCTZ decreased from 261 mL/min to 143 mL/min and 41 mL/min (respectively).

Losartan
The exposure (AUC) to losartan was higher in the patients with mild and moderate renal impairment in comparison to the patients with normal renal function and the differences were marginally significant ($p=0.043$ and $p=0.038$). Renal excretion in the patients with renal impairment was significantly reduced ($p=0.004$, mild vs. normal and $p<0.0001$, moderate vs. normal).

Losartan metabolite
The exposure (AUC) to losartan metabolite was higher in the patients with mild and moderate renal impairment in comparison to the patients with normal renal function. The differences were not significant for mild impairment vs. normal, and they were marginally significant ($p=0.035$) for moderate vs. normal group. Renal excretion in the patients with renal impairment was significantly reduced ($p<0.0001$, both comparisons).

HCTZ

The exposure (AUC) to HCTZ was higher in the patients with mild and moderate renal impairment in comparison to the patients with normal renal function and the differences were significant (p=0.021, mild vs. normal) and marginally significant (p=0.038 moderate vs. normal). Renal excretion in the patients with renal impairment was significantly reduced (p<0.001, both comparisons).

5 REVIEWER COMMENTS

GENERAL

1. The data provided in the submission for HYZAAR labeling changes for renally impaired patients meets the OCPB requirements.

COMMENTS TO THE MEDICAL OFFICER

2. According to the Guidance for industry for the pharmacokinetic studies with renally impaired patients, the sponsor enrolled three groups of patients: Group I with normal renal function, Group IIa with mild, and Group IIb - with moderate renal impairment (the data for the severely impaired patients already existed in the label). However, for the data analysis, the sponsor combined groups IIa and IIb, defined as patients with moderate renal impairment and compared them to the patients from Group I. None of the statistical tests were performed.

3. From the values of descriptive statistics performed on the pharmacokinetic parameters, the sponsor concluded that the pharmacokinetic of losartan, its metabolite, and HCTZ in hypertensive patients with moderate renal impairment following 7 daily doses of 50 mg losartan/ 12.5 mg HCTZ combination tablets were higher (1.7, 1.6, and 3.1 fold, respectively) compared to patients with normal renal function. This conclusion was not reflected properly in the Package Insert: the sponsor claimed that plasma concentrations of losartan and its metabolite were not altered in the patients with creatinine clearance > 30 mL/min (severely impaired renal function).

4. There is no information in the Package insert about the changes in the pharmacokinetics of HCTZ in renally impaired patients. However, in the Package insert for hydrochlorothiazide, there is a warning that the drug may precipitate azotemia and cumulative effects may develop in patients with impaired renal function. If progressive renal impairment becomes evident, therapy with HCTZ should be discontinued.

5. The changes in the Package insert should properly describe the finding of the present study. HYZAAR should not be recommended to patients with creatinine clearance <50 mL/min (moderate renal impairment).

LABELING COMMENTS:

[redacted]

Hydrochlorothiazide
Renal Insufficiency:

[redacted]

2. **WARNINGS:**

[redacted]

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

6 APPENDIX

6.1 Individual Study Review

6.1.1 An Open, Multicenter Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Losartan in Combination with Hydrochlorothiazide (HCTZ) After Chronic Dosing in Hypertensive Patients with Renal Impairment

Primary Investigators: Dr. Raij, Dr. Blum, Dr. Kunau, Dr. Levine, and Dr. Marbury
Sites: Veterans Administration Medical Center, Minneapolis, MN (Raij)
Millard Filmore Hospital, Buffalo, NY (Blum)
Dallas Nephrology Associates, Dallas, TX (Kunau)
Veterans Administration Medical Center, Los Angeles, CA (Levine)
Orlando Clinic Research Center, Orlando, FL (Marbury)
Clinical Monitor:

Bioanalysts:

Pharmacokineticist:
Date of completion: October 31, 1995.

Objectives:

To determine the effect of renal impairment on the pharmacokinetics of losartan, HCTZ and losartan metabolite (E-3174) following chronic doses of the combination tablet of losartan/HCTZ 50 mg/12.5 mg;

To investigate, in hypertensive patients with renal impairment, the effects of chronic doses of the losartan/HCTZ 50 mg/12.5 mg combination on blood pressure and pulse;

To investigate the safety and tolerability of multiple doses of the losartan/HCTZ combination in patients with renal impairment.
This report addresses Objective #1.

Study Design:

This was an open, multicenter, multiple daily dose study to evaluate the effects of renal impairment on the pharmacokinetics of losartan 50 mg and HCTZ 12.5 mg in a fixed combination tablet in mild to moderate hypertensive patients. Following a 10-14-day predose washout period, patients were given the combination tablet once a day for seven days. During the washout period, two creatinine clearance (CLcr) determinations were done. The second determination was used to classify the patients into the following groups:

Group I: CLcr values ≥75 mUmin/1.73 m^2,
Group IIa: CLcr values between 50 and 74 mUmin/1.73 m^2,

Group IIb: CLcr values between 30 and 49 mUmin/1.73 m^2.

There were eight males and six females in Group I, three males and three females in Group IIa, and three males and three females in Group IIb. Patient #432 in Group IIb had a baseline CLcr value of 24, and she was enrolled into the study. Her CLcr value went back up to 32 on Dose 7. The CLcr values of female Patients #431 and #631 (Group IIb) went down from >30 to 21 and 20 on Dose 7, respectively. Demographics described in Table 1.

Group	I	AGE	WT	SEX	CLr_1	clR_2	clR_7	CLcr ml/min
	111 Caucasian	35	196	M	85.4	97.3	92.4	108
	112 Caucasian	57	0.226	M	97.6	103.8	98.5	123
	113 Caucasian	36	151	M	129	136.4	132.5	139
	114 Caucasian	62	189	M	102.8	83.9	95.2	97
	211 Caucasian	37	198	M	98.5	100	118.6	144
	213 Caucasian	56	238	M	115.5	124.8	133.6	167
	214 Caucasian	36	191	M	101.3	115.9	137.1	160
	215 Caucasian	36	200	M	127.1	102.4	145.6	177
	212 Black	43	174	F	120.8	135.9	99.4	116
	216 Caucasian	43	172	F	133.1	124.8	102.3	116
	217 Caucasian	59	161	F	173.7	104.4	126.3	127
	218 Caucasian	42	183	F	104.1	94.1	84.9	93
	219 Caucasian	45	128	F	126.2	123.6	117.7	105
	220 Caucasian	60	161	F	123.7	109.7	74.1	78
Mean		46.2	183.4		117.1	111.2	111.3	125
S.D.		10.3	28.9		21.8	16	21.8	29
	IIA							
	421 Oriental	48	155	M	46	54	51	50
	521 Black	66	190	M	78	74	62	72
	623 Caucasian	30	201	M	64	57	61	63
	522 Caucasian	65	116	F	62	63	61	54
	621 Caucasian	57	191	F	75	67	72	75
	622 Caucasian	48	130	F	83	68	54	49
Mean		52	164		68	64	60	61
SD		13	36		13	7	7	11
	IIB							
	131 Caucasian	46	210	M	40.6	44.9	47.2	58
	531 Caucasian	61	152	M	56	49	49	49
	532 Black	55	195	M	38	41	34	38
	431 Caucasian	52	143	F	39	32	21	26
	432 Caucasian	37	192	F	29	24	32	39
	631 Caucasian	55	182	F	26	33	20	20
Mean		51	179		38	37	34	38
SD		8	26		11	9	12	14
Group II mean		51.7	171.4		53.1	50.6	47	49
SD	II	10.7	30.8		19.4	16	16.8	17

Prior to the first dose, control blood and urine blanks were drawn. On the morning of the sixth dose, trough plasma samples were taken. On the morning of the seventh dose, blood samples were collected in heparinized tubes at 0, 15, 30 and 45 minutes, and at 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10,12,18, 24, 30, 36 and 48 hours post dose for the determination of losartan and E-3174 plasma concentrations, and at 0 and 30 minutes, and 1, 1.5,2, 3, 4, 6, 8, 10, 12, 18, 24, 30, 36 and 48 hours for HCTZ plasma

concentrations. Total urine voided over 24 hours after the seventh dose was collected at the following intervals: 0-2, 2-4, 4-6, 6-8, 8-12, 12-18 and 18-24 hours. Patients were fasted overnight prior to taking Dose 1 and Dose 7.

Formulation

The dosage formulation No 0954AFCT008B002 (DuPont Merck Lot 921640, Batch Size

Bioanalitical Methods

A. Losartan and E-3174

The samples were analyzed using HPLC

A standard curve of losartan and E-3174 in human control plasma or urine was prepared daily with study samples. The concentration of losartan is expressed as losartan potassium, and E-3174 as the free acid. The range of concentrations in the daily standard curve was 5-1000 ng/mL in plasma for both components. For the urine assay, the range of the standard curve was 10-2000 ng/mL for E-3174, and 20-2000 ng/mL for losartan. Losartan and E-3174 concentrations in study samples were calculated from the daily least-squares linear regression of peak height ratios of an analyte to the internal standard versus standard amounts, with reciprocal weighting on the amounts. When a calculated amount exceeded the standard curve range, the sample was diluted and reanalyzed.

Reproducibility.

Intraday Variation

Prior to the analysis of clinical samples, losartan and E-3174 were added to blank plasma or urine, and five replicate standards were assayed to assess within-day variability. The peak height ratio was used to calculate the intraday coefficient of variation. Intraday reproducibility data at low concentration (losartan, CV , E-3174, CV) and at high concentration (losartan, CV , E-3174, CV , in the daily standard curve are satisfactory.

Interday Variation.

Quality control (QC) standards of losartan and E-3174 at low, medium and high concentrations were prepared prior to study sample analysis, and were analyzed daily in duplicate with the study samples to assess the acceptability of the daily run and interday variability. Interday values of the QC standards in plasma are satisfactory: at low concentration (losartan, CV E-3174, CV) and at high concentration (losartan, CV , E-3174, CV).

Sensitivity.

The limit of quantification was ng/mL in plasma for both components, ng E-3174 per mL of urine, and ng losartan per mL of urine.

Specificity.

Representative chromatograms in plasma and urine are shown. There was no interference at the retention time of losartan, E-3174 or the internal standard.

Extraction Recovery.

The recovery of the analytes from plasma was for losartan and E-3174, respectively, while the recovery from urine was for losartan and E-3174, respectively. The recovery was determined across the range of the standard curve by

comparing peak areas after direct injections of standards with those of extracted standards at each concentration.

B. Hydrochlorothiazide (HCTZ)

Plasma and urine samples were prepared via , respectively, and were analyzed using HPLC

A standard curve of HCTZ in human control plasma or urine was prepared daily with study samples. The range of concentration in the daily standard curve was 2-100 ng/mL in plasma and 0.1-20 ng/mL in urine. HCTZ concentrations in study samples were calculated from the daily least-squares linear regression of peak height ratios versus standard amounts, with reciprocal weighting on the amounts. When a calculated amount exceeded the standard curve range, the sample was diluted and reanalyzed.

Reproducibility:

Intraday Variation –

Prior to the analysis of clinical samples, HCTZ and internal standard were added to blank plasma and urine, and five replicate standards were assayed to assess within-day variability. Intraday reproducibility data at low concentration (CV , reproducibility, CV) and at high concentration (, reproducibility,) in the daily standard curve are satisfactory. Interday reproducibility data at low concentration (CV and at high concentration (CV) in the daily standard curve are satisfactory.

Sensitivity.

The limit of quantification (LOQ) was ng/mL in plasma and mcg/mL in urine. Plasma concentration levels below LOQ (-10%) are reported as 0.

Specificity.

Representative chromatograms of HCTZ in plasma and urine are shown. There was no interference at the retention time of HCTZ or the internal standard.

Pharmacokinetics

Plasma AUC up to the last measured time point (AUCT) for losartan, and AUC_{t-24} for E-3174 and HCTZ were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. AUC_{t-24} for losartan was estimated by summing AUCT and AUC_{t-24}, after obtaining the C_{24} value by extrapolation using lambda, which is the terminal disposition rate constant (estimated by regression of the terminal log-linear plasma concentration time points). Terminal plasma half-life was calculated as the quotient of the natural log of 2 and lambda. Harmonic mean half-lives and their pseudo standard deviations were calculated according to the method of Lam et al. (J. Pharm. Sci. 74: 229-231, 1985).

Percent recovery of losartan, E-3174 and HCTZ in urine was calculated from urinary recovery from 0 to 24 hours and the actual assayed contents of the formulations. For E-3174, the amount excreted in urine was expressed as percent of losartan dose after correction, using the molecular weights 436.905 for E-3174 and 461.015 for losartan. Renal clearance (CLr) was calculated as the quotient of the amount excreted in urine and the corresponding plasma AUC.

Results

The sponsor presented individual and mean plasma and urine losartan, E-3174, and HCTZ profiles vs. time as tables and graphics. The mean (SD) of all calculated pharmacokinetic parameters for each entity was calculated to compare groups of normal subjects vs. the subjects with a mean creatinine clearance of 49 mL/min (ranged from 20 to 75 mL/min) and stratified by gender.

Figure 1 shows mean plasma concentrations (ng/mL) of losartan, E-3174 and HCTZ following multiple doses of 50 mg losartan/12.5-mg HCTZ tablets in hypertensive patients with normal renal function (circles) and with renal impairment (squares).

The sponsor concluded that pharmacokinetic of losartan, E-3174 and HCTZ in hypertensive patients with moderate renal impairment following 7 daily doses of 50 mg losartan/ 12.5 mg HCTZ combination tablets were higher (1.7, 1.6, and 3.1 fold, respectively) compared to patients with normal renal function.

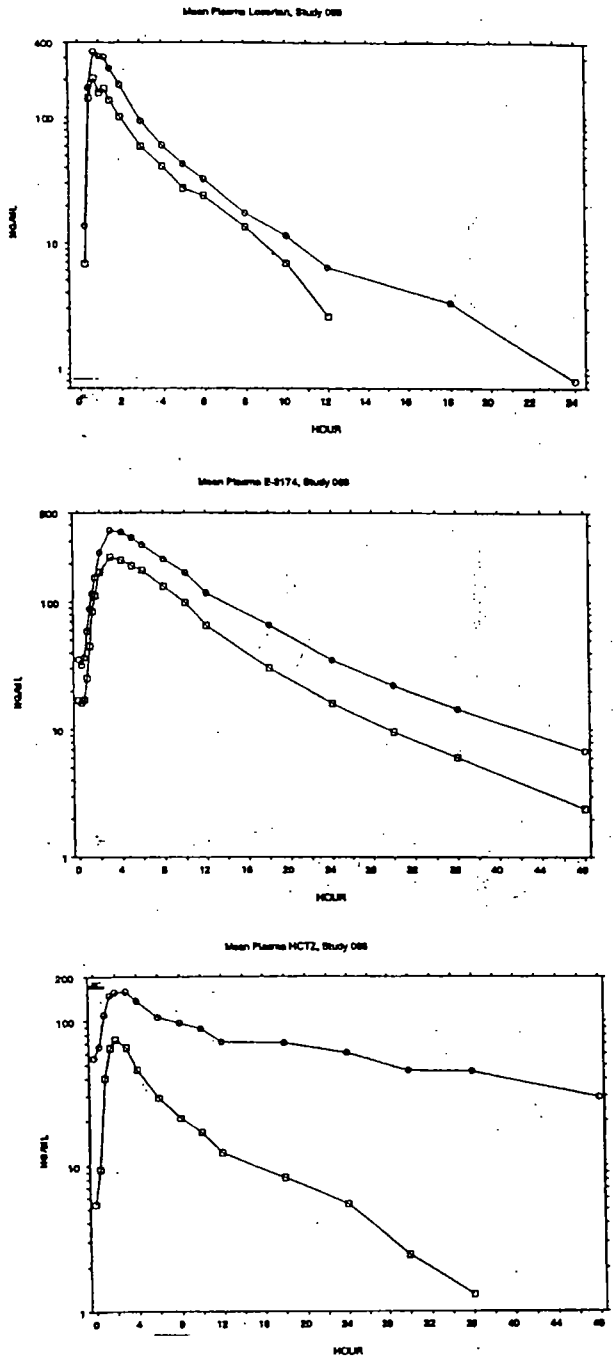


Figure 1.

Data Analysis Performed by the FDA Reviewer

The FDA reviewer performed two sample t-test assuming unequal variances to compare the following groups of patients:

Group I	normal renal function (mean CLcr > 120 mL/min)
Group IIa	mild renal impairment (50 mL min<CLcr<70 mL/min)
Group IIb	moderate renal impairment (30 mL/min<CLcr<50 mL/min).

The following pharmacokinetic parameters were compared for losartan, its metabolite, and HCTZ: Cmax, AUC.

Tables 1-3 show the results of the statistical tests. Results are discussed briefly below.

For losartan, the difference between all groups was not statistically significant when Cmax values were compared. The difference between losartan' AUC values for all comparisons was marginal (Group IIa vs. Group I, p=0.043, and Group IIb vs. Group I, p=0.038). The CLr values were statistically significantly different when Group IIa (p=0.004) and Group IIb (p<0.0001) were compared to Group I.

The losartan metabolite' Cmax values did not differ significantly between all groups. The AUC values for Group IIb were different from Group I (p=0.035), while Groups I and IIa differ insignificantly (p=0.136). The differences between CLr values for all comparisons were statistically significantly (p<0.0001).

For HCTZ the difference for all parameters and all groups was statistically significant except for Cmax, Group IIa vs. Group I, p= 0.122. The other comparisons: Cmax, Group IIb vs. Group I, p= 0.034; AUC, Group IIa vs. Group I p=0.021, Group IIb vs. Group I p=0.048; CLr, Group IIa vs. Group I p<0.00014, Group IIb vs. Group I p=<0.0001).

Table 1. Losartan Pharmacokinetic Parameters

t-Test: Two-Sample Assuming Unequal Variances

	Cmax 1 vs 2		Cmax 1 vs 3	
	Variable 1	Variable 2	Variable 1	Variable 2
Mean	333.414	510.300	333.414	493.200
Variance	44618.563	37734.220	44618.563	59266.396
Observations	14	6	14	6
Hypothesized Mean Difference	0.000		0.000	
df	10.000		8.000	
t Stat	-1.817		-1.398	
P(T<=t) one-tail	0.050		0.100	
t Critical one-tail	1.812		1.860	
P(T<=t) two-tail	0.099		0.200	
t Critical two-tail	2.228		2.306	

	AUC 1 vs 2		AUC 1 vs 3	
	Variable 1	Variable 2	Variable 1	Variable 2
Mean	520.366	789.632	520.366	930.205
Variance	57339.068	56578.915	57339.068	131041.898
Observations	14	6	14	6
Hypothesized Mean Difference	0.000		0.000	
df	10.000		7.000	
t Stat	-2.315		-2.545	
P(T<=t) one-tail	0.022		0.019	
t Critical one-tail	1.812		1.895	
P(T<=t) two-tail	0.043		0.038	
t Critical two-tail	2.228		2.365	

	CLr 1 vs 2		CLr 1 vs 3	
	Variable 1	Variable 2	Variable 1	Variable 2
Mean	52.557	24.585	52.557	6.805
Variance	114.891	224.806	114.891	13.945
Observations	14	6	14	6
Hypothesized Mean Difference	0.000		0.000	
df	7.000		18.000	
t Stat	4.139		14.099	
P(T<=t) one-tail	0.002		1.80893E-11	
t Critical one-tail	1.895		1.734	
P(T<=t) two-tail	0.004		3.61785E-11	
t Critical two-tail	2.365		2.101	

Table 2. Losartan Metabolite Pharmacokinetic Parameters

t-Test: Two-Sample Assuming Unequal Variances

	Cmax 1 vs 2		Cmax 1 vs 3	
	Variable 1	*Variable 2*	*Variable 1*	*Variable 2*
Mean	248.307	344.283	248.307	418.833
Variance	9026.282	17924.638	9026.282	62893.831
Observations	14	6	14	6
Hypothesized Mean Difference	0		0	
df	7		6	
t Stat	-1.593		-1.617	
P(T<=t) one-tail	0.078		0.079	
t Critical one-tail	1.895		1.943	
P(T<=t) two-tail	0.155		0.157	
t Critical two-tail	2.365		2.447	

	AUC 1 vs 2		AUC 1 vs 3	
	Variable 1	*Variable 2*	*Variable 1*	*Variable 2*
Mean	2045.944	2887.750	2045.944	4068.945
Variance	378756.353	1269268.722	378756.353	3173223.032
Observations	14	6	14	6
Hypothesized Mean Difference	0		0	
df	6		6	
t Stat	-1.723		-2.713	
P(T<=t) one-tail	0.068		0.017	
t Critical one-tail	1.943		1.943	
P(T<=t) two-tail	0.136		0.035	
t Critical two-tail	2.447		2.447	

CLr 1 vs 2

	Variable 1	*Variable 2*	*Variable 1*	*Variable 2*
Mean	20.455	8.273	20.455	3.930
Variance	30.344	4.865	30.344	4.355
Observations	14	6	14	6
Hypothesized Mean Difference	0		0	
df	18		18	
t Stat	7.059		9.715	
P(T<=t) one-tail	6.9423E-07		6.95386E-09	
t Critical one-tail	1.734		1.734	
P(T<=t) two-tail	1.3885E-06		1.39077E-08	
t Critical two-tail	2.101		2.101	

Table 3. HCTZ Pharmacokinetic Parameters
T-Test: Two-Sample Assuming Unequal Variances

	Cmax 1 vs 2		Cmax 1 vs 3	
	Variable 1	*Variable 2*	*Variable 1*	*Variable 2*
Mean	77.332	105.702	77.332	238.547
Variance	525.207	1336.840	525.207	18389.495
Observations	14	6	14	6
Hypothesized Mean Difference	0		0	
df	7		5	
t Stat	-1.758		-2.894	
P(T<=t) one-tail	0.061		0.017	
t Critical one-tail	1.895		2.015	
P(T<=t) two-tail	0.122		0.034	
t Critical two-tail	2.365		2.571	

	AUC 1 vs 2		AUC 1 vs 3	
	Variable 1	*Variable 2*	*Variable 1*	*Variable 2*
Mean	492.176	821.262	492.176	3426.203
Variance	18826.25	59226.12	18826.25	7581992.849
Observations	14	6	14	6
Hypothesized Mean Difference	0		0	
df	6		5	
t Stat	-3.107		-2.609	
P(T<=t) one-tail	0.010		0.024	
t Critical one-tail	1.943		2.015	
P(T<=t) two-tail	0.021		0.048	
t Critical two-tail	2.447		2.571	

	CLr 1 vs 2		CLr 1 vs 3	
	Variable 1	*Variable 2*	*Variable 1*	*Variable 2*
Mean	261.651	143.798	261.651	41.26
Variance	6130.668	951.40774	6130.668	940.66796
Observations	14	6	14	6
Hypothesized Mean Difference	0		0	
df	18		18	
t Stat	4.826		9.038	
P(T<=t) one-tail	6.78E-05		2.07E-08	
t Critical one-tail	1.734063		1.734063	
P(T<=t) two-tail	0.000136		4.14E-08	
t Critical two-tail	2.101		2.101	

The AUC and CLr values for the three Groups of patient were compared graphically. Figure 1 compares these parameters for losartan, Figure 2 shows metabolite parameters, and Figure 3 shows the same for HCTZ.

Figure 1. AUC (upper panel) and CLr (lower panel) of losartan vs. Creatinine Clearance (circles are for the patients with normal renal function, triangles for the patients with mild renal impairment, and squares for the patients with moderate renal impairment)

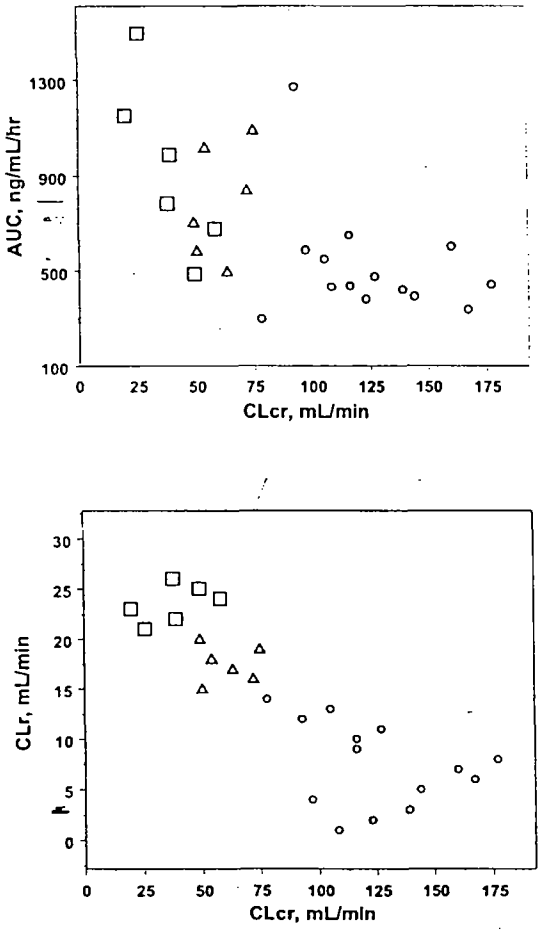


Figure 2. AUC (upper panel) and CLr (lower panel) of losartan metabolite vs. Creatinine Clearance (circles are for the patients with normal renal function, triangles for the patients with mild renal impairment, and squares for the patients with moderate renal impairment)

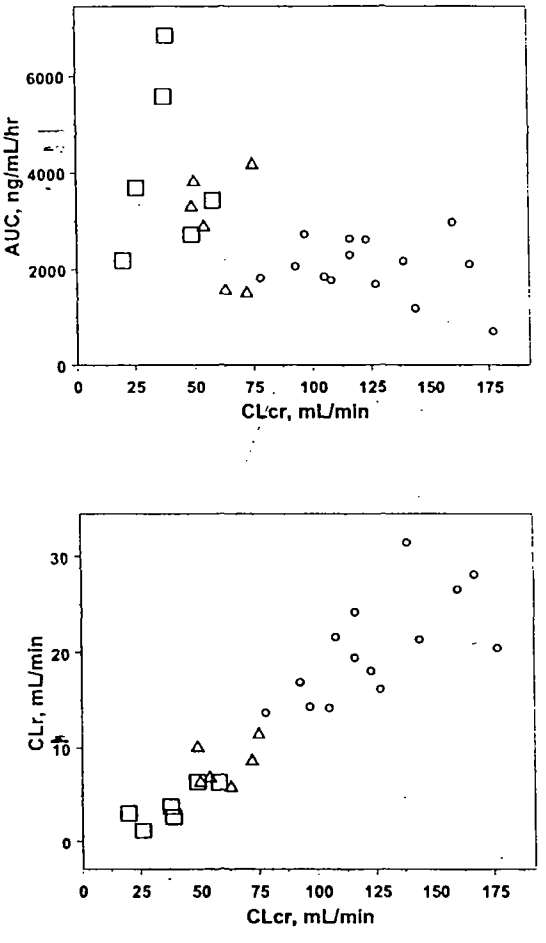
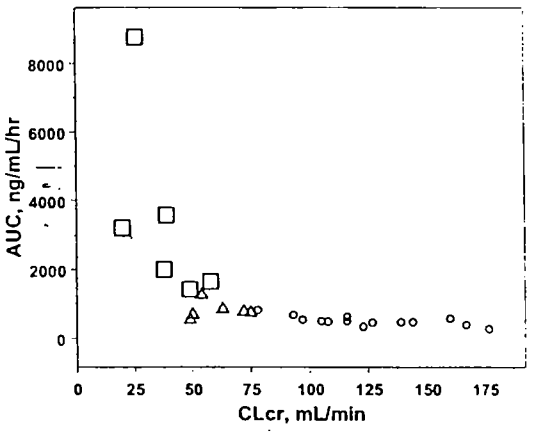
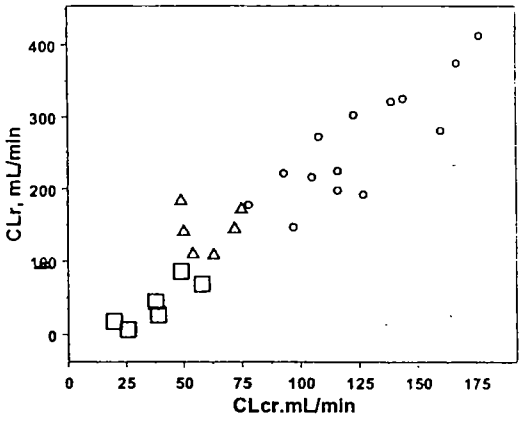


Figure 3. AUC (upper panel) and CLr (lower panel) of HTCZ vs. Creatinine Clearance (circles are for the patients with normal renal function, triangles for the patients with mild renal impairment, and squares for the patients with moderate renal impairment)





Conclusions:

Losartan

The exposure (AUC) to losartan was higher in the patients with mild and moderate renal impairment in comparison to the patients with normal renal function and the differences were marginally significant ($p=0.043$ and $p=0.038$). Renal excretion in the patients with renal impairment was significantly reduced ($p=0.004$, mild vs. normal and $p<0.0001$, moderate vs. normal).

Losartan metabolite

The exposure (AUC) to losartan metabolite was higher in the patients with mild and moderate renal impairment in comparison to the patients with normal renal function. The

differences were not significant for mild impairment vs. normal, and they were marginally significant (p=0.035) for moderate vs. normal group. Renal excretion in the patients with renal impairment was significantly reduced (p<0.0001, both comparisons).

HCTZ

The exposure (AUC) to HCTZ was higher in the patients with mild and moderate renal impairment in comparison to the patients with normal renal function and the differences were significant (p=0.021, mild vs. normal) and marginally significant (p=0.038 moderate vs. normal). Renal excretion in the patients with renal impairment was significantly reduced (p<0.001, both comparisons).

Comment:

1. *According to the Guidance for the industry for the pharmacokinetic studies with renally impaired patients, the sponsor enrolled three groups of patients: Group I with normal renal function, Group IIa with mild, and Group IIb - with moderate renal impairment (the data for the severely impaired patients already exists in the label). However, for the data analysis, the sponsor combined groups IIa and IIb, defined as patients with moderate renal impairment and compared them to the patients from Group I. None of the statistical tests were performed.*
2. *From the values of descriptive statistics performed on the pharmacokinetic parameters, the sponsor concluded that the pharmacokinetic of losartan, E-3174 and HCTZ in hypertensive patients with moderate renal impairment following 7 daily doses of 50 mg losartan/ 12.5 mg HCTZ combination tablets were higher (1.7, 1.6, and 3.1 fold, respectively) compared to patients with normal renal function. This conclusion was not reflected properly in the Package Insert: the sponsor claimed, that plasma concentrations of losartan and its metabolite were not altered in the patients with creatinine clearance > 30 mL/min (severely impaired renal function).*
3. *There is no information in the Package insert about the changes in the pharmacokinetic of HCTZ in renally impaired patients. However, in the Package insert for hydrochlorothiazide, there is a warning that the drug may precipitate azotemia and cumulative effects may develop in patients with impaired renal function. If progressive renal impairment becomes evident, therapy with HCTZ should be discontinued.*
4. *The changes in the Package insert should properly describe the finding of the present study. HYZAAR should not be recommended to the patients with creatinine clearance <50 mL/min (moderate renal impairment).*

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

6.3 Filing Memo Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	20-387/S-027	Brand Name	Hyzaar
OCPB Division (I, II, III)	DIV-1	Generic Name	Losartan potassium/HCTZ
Medical Division	CARDIORENAL	Drug Class	angiotensin II antagonist
OCPB Reviewer	ELENA MISHINA	Indication(s)	Severe hypertension
OCPB Team Leader	Patrick Marroum	Dosage Form	50-12.5 mg and 100-25 mg (Losartan Potassium-Hydrochlorothiazide Tablets)
		Dosing Regimen	The starting dose is one tablet of HYZAAR 50-12.5 mg QD with possible increase to one tablet of HYZAAR 100-25.
Date of Submission	9/27/2002	Route of Administration	ORAL
Estimated Due Date of OCPB Review	MARCH, 2003		Merck Pharmaceutical Group
PDUFA Due Date	JULY 2003	Priority Classification	S
Division Due Date	MAY, 2003		

Clin. Pharm. and Biopharm. Information	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	2		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	X	2		
hepatic impairment:				
PD:				

Phase 2:				
Phase 3:				
PK/PD:	X	2		
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	2		
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	1			

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)	Are the labeling changes for the use of Hyzaar in the hypertensive patients with renal impairment adequate?	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 20,387, HFD-850(Lee), HFD-860(Marroum, Mehta, Mishina), Biopharm (CDER)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Elena Mishina
4/10/03 03:30:11 PM
BIOPHARMACEUTICS

Patrick Marroum
4/10/03 03:43:44 PM
BIOPHARMACEUTICS