

## CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

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**NDA:** 19,851 SE5 028 **Submission Dates:** April 28 2003  
**Drug Name:** Lotensin (benazepril hydrochloride) tablets  
**Applicant:** Novartis  
**Submission:** Pediatric Supplement  
**Reviewer:** Elena V. Mishina, Ph.D.

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### 2 RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation I has reviewed the information included in the sNDA 21,437. The Office of Clinical Pharmacology and Biopharmaceutics recommends adopting the proposed language for the labeling.

\_\_\_\_\_  
Elena Mishina, Ph. D.  
Clinical Pharmacology Reviewer

Date \_\_\_\_\_

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

CPB Briefing was held on October 9, 2003

Attendees:

cc list: NDA 21,437, MehulM, MarroumP, MishinaE, HFD 110 BIOPHARM

### 3 EXECUTIVE SUMMARY

#### 3.1 Background

NDA 19,581 for Lotensin (benazepril hydrochloride) tablets was approved in 1991. Benazepril and benazeprilat (active metabolite) inhibit angiotensin-converting enzyme (ACE). ACE inhibitors such as captopril and enalapril are widely used in clinical practice to treat children with hypertension. ACE inhibitors have become primary agents for pharmacologic therapy of hypertension because they reduce blood pressure (BP) and have a favorable hemodynamic profile. Lotensin® (benazepril hydrochloride) has been approved for the treatment of hypertension in the adult human population.

The applicant is seeking to obtain Pediatric Exclusivity for Lotensin, to evaluate the efficacy (b) (4) of benazepril in pediatric population, and to provide the labeling changes related to the benazepril use in children. The recommended starting dose of Lotensin (benazepril HCl) in children is 0.2 mg/kg (b) (4) once daily. Dosage should be adjusted according to blood pressure response.

#### 3.2 Current Submission

With this Application, NDA 19,851 SE5-028, the sponsor included 4 studies. These were:

Study Protocol US02 “A Pharmacokinetic Study to Assess the Comparative Bioavailability of a Pediatric Formulation of Lotensin (10 mg oral suspension) vs Lotensin (10 mg) Tablets”,

Study Protocol US03A1 “A single center, single dose, open-label study to evaluate the pharmacokinetics of benazepril in pediatric subjects”,

Study Protocol US03 “A multicenter open-label, steady state study to evaluate the pharmacokinetics of benazepril in pediatric subjects”, and

Study Protocol US01 “A multicenter study to evaluate the pharmacokinetics, dose-response, efficacy, and safety of benazepril in pediatric subjects”.

Study US02 compared a pediatric formulation of benazepril with the currently marketed tablet formulation in healthy adults. Lotensin ® (10 mg) administered orally as an extemporaneously compounded suspension was compared to Lotensin ® (10 mg) administered in tablet formulation. For benazepril, the 90% CI for the ratio of C<sub>max</sub>, AUC(0-t), and AUC(0-inf) were 86.72%- 111.95%, 84.38%-101.84%, and 81.48%-99.55%, respectively. For benazeprilat, the 90% CI for the ratio of C<sub>max</sub>, AUC(0-t), and AUC(0-inf) were 88.94%-112.49%, 90.8%-106.49%, and 89.69%-104.47%, respectively. Therefore, the 90% CI for geometric mean ratios of natural-log transformed C<sub>max</sub>, AUC(0-t), and AUC(0-inf) were all within the 80%-125% range and the test and reference formulations were found to be bioequivalent with respect to both benazepril and benazeprilat.

The pharmacokinetics of benazepril and its active metabolite benazeprilat was determined following the administration of a single oral dose of benazepril hydrochloride in pediatric subjects (Study US03a1). Healthy subjects received the dose of Lotensin as a suspension (age range from 0.7 to 5.5 years) or a 5 or 10 mg tablet (age range from 6.5 to 16.9 years). The dose was individualized in the range of 0.1-0.5 mg/kg. The mean CL values of benazepril for all four pediatric groups were: 2.1, 3.8, 2.1, and 2.9 L/hr/kg respectively. These CL values were larger but of the same order of magnitude as calculated for adults after a 10 mg of Lotensin, Study US02 (1.45 L/hr/kg). The mean CL values for benazeprilat for all four pediatric groups were: 0.284, 0.364, 0.258, and 0.169 L/hr/kg. These CL values were larger than calculated for adults (0.132 L/hr/kg). The group of school age children had benazeprilat clearance twice faster than adults and adolescents' clearance values were 27% larger than the adults' clearance values. Study US03 determined the pharmacokinetic of benazepril in pediatric patients at steady state. Four plasma samples were taken per patient at the specified time window of 4 hours covering the interval of 24 hours after dosing at Day 5. Population modeling was performed on the sparse plasma concentrations data separately for benazepril and benazeprilat. The sponsor concluded that the only significant covariate affecting clearance for both benazepril and benazeprilat is age. The model development is lacking the important part of model validation: after covariate adding one by one into the model, the sponsor did not perform deletion of the covariates from the model which was assumed to be final. Therefore, the appropriateness of the final model is not convincing. The graphic exploration of the data by the reviewer indicates that clearance depends on body weight. Body weight corrected clearance of benazepril was 10.7, 9.3, 6.3, and 3.4 L/hr/kg for each of four pediatric groups respectively. These values are higher than the same values calculated for the healthy children and for adults and are in agreement with the lower plasma concentrations profiles of benazepril found in the pediatric patients in comparison with healthy children. Therefore, the same dose of Lotensin produced lower exposure to benazepril in pediatric patients compared to healthy children and adults. Given the wide therapeutic index of benazepril, there will be no safety concern to use this drug in pediatric patients. Body weight corrected clearance of benazeprilat was 0.209, 0.363, 0.351, and 0.166 L/hr/kg for each of four pediatric groups respectively. These values were comparable with the same for healthy children. The plasma benazeprilat profiles were similar for both studies in pediatric patients and healthy children. The exposure to benazeprilat is about 10 times larger than the exposure to benazepril. Additionally, benazeprilat is much more potent ACE inhibitor benazepril. Therefore, although the exposure to benazepril was found to be smaller in pediatric patients, it might not compromise the efficacy of Lotensin. The efficacy of Lotensin issue will be assessed by the MO. The report of Study US01 did not include any of the pharmacokinetic data because the sponsor was not able to collect plasma samples from the patients in this study.

## 4 QUESTION BASED REVIEW

### 4.1 General Attributes

*Was the pediatric exclusivity granted for this sNDA?*

Yes. This sNDA was performed in agreement with the guidelines for clinical investigations in pediatric subjects. This submission fulfills the requirements described in the Written Request and the pediatric exclusivity was granted to the sponsor.

*What is the proposed mechanism of action and therapeutic indication?*

Benazepril (Lotensin®) is an angiotensin converting enzyme inhibitor (ACE inhibitor). ACE inhibitors act by selectively inhibiting the conversion of angiotensin I to angiotensin II by inhibition of angiotensin converting enzyme. The effects of decreased levels of angiotensin II include vasodilation and decreased retention of sodium and water. Lotensin® is marketed in the US for the treatment of hypertension in adults.

*What are the general pharmacokinetic properties of Lotensin?*

In adults, approximately 37% of orally administered benazepril is rapidly absorbed and subsequently metabolized in the liver to its active form, benazeprilat. Both benazepril and benazeprilat are glucuronidated and excreted in the urine and bile. Peak concentrations of benazeprilat are observed approximately one to two hours following drug administration, with the plasma half-life being 10–11 hours. Only trace amounts of an administered dose of Lotensin can be recovered in the urine as unchanged benazepril, while about 20% of the dose is excreted as benazeprilat, 4% as benazepril glucuronide, and 8% as benazeprilat glucuronide.

The serum protein binding of benazepril is about 96.7% and that of benazeprilat about 95.3%, as measured by equilibrium dialysis; on the basis of in vitro studies, the degree of protein binding should be unaffected by age, hepatic dysfunction, or concentration (over the concentration range of 0.24–23.6 µmol/L).

*What is the approved dosage and administration?*

Benazepril is currently available in 5, 10, 20, and 40 mg tablet form. Common adult dosages of Lotensin range from 5 to 80 mg daily (single or divided dosage). The recommended initial dose for patients not receiving a diuretic is 10 mg QD. The usual maintenance dosage range is 20–40 mg per day administered as a single dose or in two equally divided doses.

## 4.2 Pharmacokinetic Studies in Pediatric Patients

*Were there the correct moieties identified and measured to assess clinical pharmacology?*

Yes. Benazepril and benazeprilat concentrations were quantified in plasma using electro-spray ionization (ESP-HPLC/MS/MS) method.

Within-study assay validation was performed by analysis of QC samples together with the study samples. The limit of quantitation for both benazepril and benazeprilat was 0.5 ng/mL. The inter-day and intra-day variability were satisfactory, chromatograms were shown.

*What are the exposure-response relationships for efficacy and safety?*

The following pharmacodynamic (PD) parameters were measured at baseline and after drug administration in children: systolic and diastolic blood pressure, its difference, and heart rate. However, the sponsor did not seek to establish any relationship between benazepril and benazeprilat plasma concentrations and response.

*Are the pharmacokinetics of benazepril and benazeprilat in children and adults similar?*

The pharmacokinetics of benazepril and its active metabolite benazeprilat was determined following the administration of a single oral dose of benazepril hydrochloride in pediatric subjects (Study US03a1). Healthy subjects received Lotensin as a suspension (age range from 0.7 to 5.5 years) or a 5 or 10 mg tablet (age range from 6.5 to 16.9 years). The dose was individualized and ranged from 0.1 to 0.5 mg/kg. The mean CL values of benazepril for all four pediatric groups were: 2.1, 3.8, 2.1, and 2.9 L/hr/kg respectively (Table 1). These CL values were larger but of the same order of magnitude as calculated for adults after a dose of 10 mg of Lotensin (Study US02, 1.45 L/hr/kg).

Table 1. Comparison of CL values from Studies US02, US03, and US03a1

Parameter	Infants and toddlers (1 to 24 months)	Pre-school Children (>2 to 6 years)	School-age children (>6 to 12 years)	Adolescent (>12 to 16 years)	Adults (32±7 years)
Benazepril					
BW-corrected CL* (L/h/kg) <sup>a</sup>	10.7 ± 3.5	9.3 ± 3.2	6.3 ± 2.8	3.4 ± 0.8	1.45 <sup>c</sup>
BW-corrected CL* (L/h/kg) <sup>b</sup>	2.1 ± 3.9	3.8 ± 1.3	2.2 ± 0.7	2.9 ± 2.1	
Benazeprilat					
BW-corrected CL* (L/h/kg) <sup>a</sup>	0.209 ± 0.188	0.363 ± 0.107	0.351 ± 0.203	0.166 ± 0.05	0.132 <sup>c</sup>
BW-corrected CL* (L/h/kg) <sup>b</sup>	0.284 ± 0.114	0.365 ± 0.078	0.258 ± 0.073	0.169 ± 0.057	

\*body weight-corrected CL, calculated as CL/BW (L/h/kg)

<sup>a</sup>study US03

<sup>b</sup>study US03A1

<sup>c</sup>study US02

The mean CL values for benazeprilat for all four pediatric groups were: 0.284, 0.364, 0.258, and 0.169 L/hr/kg, respectively. These CL values were larger than calculated for adults (0.132 L/hr/kg). The group of school age children had benazepril clearance twice faster than adults and adolescents' clearance values were 27% larger than adults' clearance values.

Body weight corrected clearance of benazepril in pediatric patients (Study US03) estimated with NONMEM was 10.7, 9.3, 6.3, and 3.4 L/hr/kg for each of the four pediatric groups respectively. These values are higher than the same values calculated for the healthy children and for adults and are in agreement with the slightly lower plasma concentrations profiles of benazepril found in the patients in comparison with healthy children.

Body weight corrected clearance of benazeprilat (Study US03) was 0.209, 0.363, 0.351, and 0.166 L/hr/kg for each of the four pediatric groups respectively. These values were comparable with the same for healthy children. The plasma benazeprilat profiles were similar for both studies in pediatric patients and healthy children.

*Were the plasma profiles for benazepril and benazeprilat comparable for pediatric patients and healthy children?*

Figures 1 and 2 represent benazepril plasma concentrations measured after a single dose in healthy children, and at steady state in pediatric patients (6 to 16 years of age), respectively. The doses (calculated in mg/kg of BW) used in these studies were similar. The patients had higher body weight than healthy subjects. Additionally, one could expect a slight ( $R=1.19$ ) accumulation of benazepril after multiple dosing. Nevertheless, the plasma profiles of benazepril look similar although slightly higher in Figure 1 (in accordance with lower clearance values obtained for the healthy children).

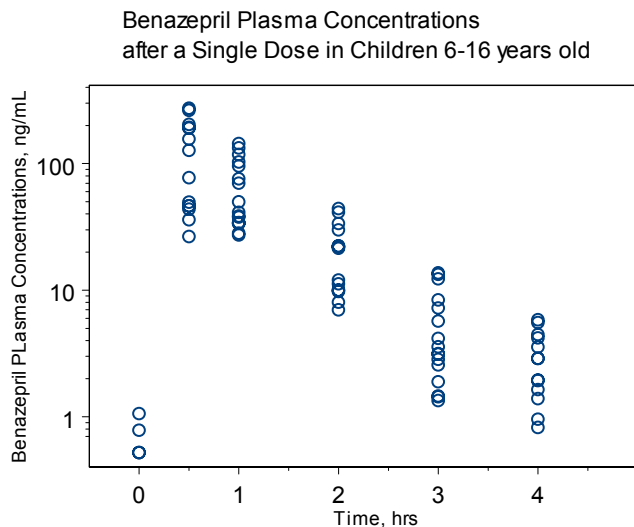


Figure 1.

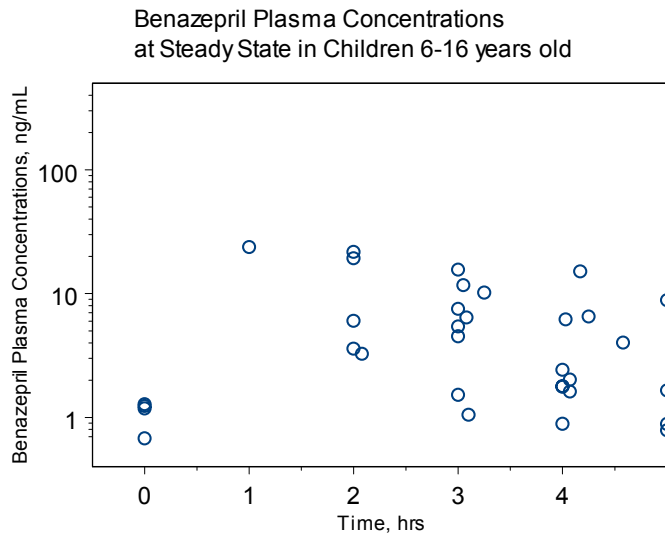


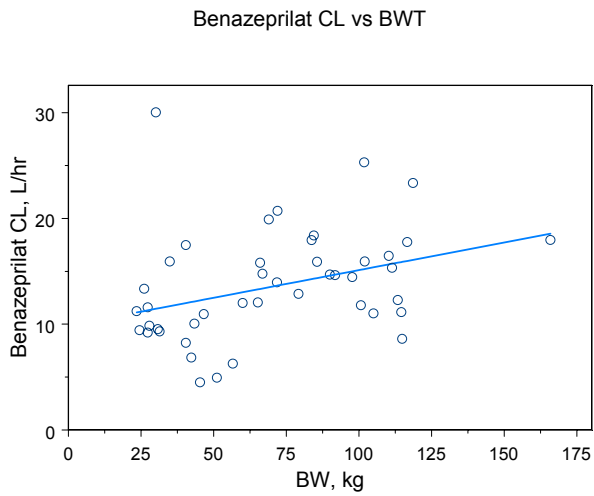
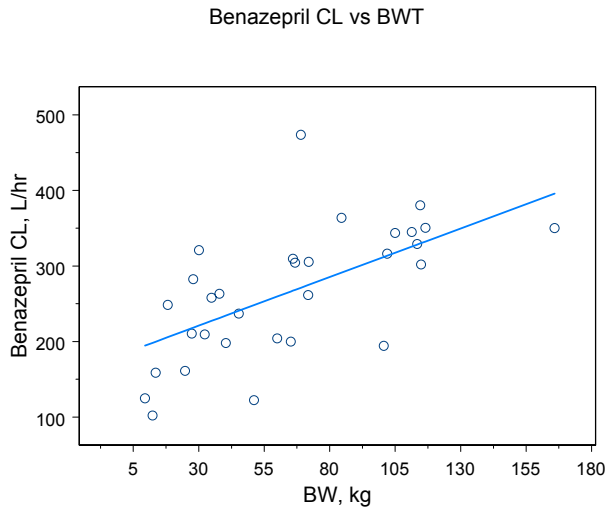
Figure 2.

Therefore, the same dose of Lotensin produced slightly lower exposure in pediatric patients to benazepril than healthy children and adults. After the dosing with Lotensin, the exposure to benazeprilat is about 10 times larger than the exposure to benazepril. Additionally, benazeprilat is much more potent ACE inhibitor than benazepril. Therefore, although the exposure to benazepril was found to be smaller in pediatric patients, it might not compromise the efficacy of Lotensin.

*Were the population pharmacokinetic data analyses for benazepril and benazeprilat performed appropriately?*

No. Study US03 determined the pharmacokinetic of benazepril in pediatric patients at steady state. Four plasma samples were taken per patient at the specified time window of 4 hours covering the interval of 24 hours after the dose on Day 5. Population modeling was performed on the sparse plasma concentrations data separately for benazepril and benazeprilat. The sponsor concluded that the only significant covariate affecting clearance for both benazepril and benazeprilat is age. The model development is lacking the important part of model validation: after covariate adding one by one into the model, the sponsor did not perform deletion of the covariates from the model which was assumed to be final. Therefore, the appropriateness of the final model was not convincing.





The graphic exploration of the data by the reviewer indicates that clearance depends on the body weight.

*What dosage regimen is recommended based on the data obtained for the pediatric population?*

The sponsor recommended a starting dose [REDACTED] <sup>(b) (4)</sup> for hypertensive patients aged 6 to 16 years based on the placebo-controlled double-blind clinical study.

## 5 COMMENTS

### *GENERAL*

1. The Agency considered that the information provided in the Supplement No. SE5 030 to NDA 19,581 dated April 28, 2003 for Lotensin (benazepril) was appropriate to fulfill the pediatric exclusivity requirements described in the FDA Written Request and Written Agreement letters. The Agency granted an additional six months of marketing exclusivity.

### *LABELING COMMENTS:*

1. CLINICAL PHARMACOLOGY Section,  
Clinical Pharmacology in Pediatric Patients. The FDA suggested labeling is as follows:

(b) (4)



2. PRECAUTIONS

Pediatric Use. The FDA suggested labeling is as follows:

(b) (4)



3. DOSING RECOMMENDATIONS:

Pediatric Patients. The FDA suggested labeling is as follows:

(b) (4)



(b) (4)



For pediatric patients who cannot swallow tablets, or for whom the calculated dosage (mg/kg) does not correspond to the available tablet strengths for Lotensin, follow the suspension preparation instructions below to administer benazepril HCL as a suspension.

## 6 APPENDIX

### 6.1 Review of Individual Studies

#### 6.1.1 A Pharmacokinetic Study to Assess the Comparative Bioavailability of a Pediatric Formulation of Lotensin (10 mg oral suspension) vs Lotensin (10 mg) Tablets (US02)

**Investigator(s):** Magdy Shenouda, MD, MDS Pharma Services, 105 Neptune Blvd., Neptune, New Jersey 07754

**Study period:** First subject dosed 07-Dec-01  
Last subject completed 17-Dec-01

**Objectives:** To assess the bioavailability of an extemporaneously compounded suspension of Lotensin compared with Lotensin tablets following a single 10 mg dose, administered in the fasted state.

**Design:** This was a single dose, randomized, open-label, two-way crossover study. For the first study period, the subjects were randomly assigned to receive a single 10 mg dose of Lotensin (either two 5 mg tablets or 5 mL of an oral suspension (2 mg/mL) formulation) after an overnight fast. The alternate product was administered during the subsequent study period. Dosing for each study period was separated by a minimum seven-day washout interval.

**Sampling:** A total of 14 blood samples were collected through the 72-hour postdose interval during each study period. A total of 28 blood samples (56 mL of blood) were drawn during the study for Lotensin analysis. The subjects were confined to the clinic during each study period through collection of the 24-hour postdose blood collection and returned for events as scheduled through 72 hours.

**Number of subjects:** A total of 30 subjects were enrolled in and completed the study.

**Treatments Administered:**

*Investigational drug:* 5 mL Lotensin ® oral suspension (2 mg/mL) prepared from five Lotensin ® 20 mg tablets (Novartis), Mfg. Code: 201E1307, Expiration date: Sep 2006; Ora-Sweet TM, (Paddock Labs, Inc., Minneapolis, MN) Lot No. 182963, Expiration date: April 2003; and Ora-Plus TM solution (Paddock Labs, Inc., Minneapolis, MN), Lot No. 193011, Expiration date: April 2003.

*Comparator Drug:* Lotensin ® 5 mg tablets (Novartis Pharmaceuticals), Mfg. Ref. Code: 112E7963, Expiration date: March 2004.

**Preparation of Suspension** (for 150 mL of a 2.0 mg/mL suspension)

Add 75 mL of Ora-Plus®\* oral suspending vehicle to a polyethylene terephthalate (PET) bottle containing fifteen Lotensin® 20 mg tablets, and shake for at least 2 minutes. Allow the suspension to stand for a minimum of 1 hour. After the standing time, shake the suspension for a minimum of 1 additional minute. Add 75 mL of Ora-Sweet®\* oral syrup vehicle to the bottle and shake the suspension to disperse the ingredients. The suspension should be refrigerated at 2-8 °C (36-46 °F) and can be stored for up to 30 days in the PET bottle with a child-resistant screw-cap closure. Shake the suspension before each use.

**Duration of treatment:** For the first study period, the subjects were randomly assigned to receive a single 10 mg dose of Lotensin (either two 5 mg tablets or 5 mL of an oral suspension (2 mg/mL) formulation) after an overnight fast. The alternate product was administered during the subsequent study period. Dosing for each study period was separated by a minimum seven-day washout interval. All investigational drug supplies were stored in a secured and temperature-controlled area that had restricted access. The clinical site was responsible for study drug administration and inventory.

**Pharmacokinetic evaluations:** The pharmacokinetics of benazepril and benazeprilat were assessed by measuring serial plasma concentrations following the test and reference treatments.

The following pharmacokinetic parameters were calculated from the concentration-time data for benazepril and benazeprilat for all subjects.

$AUC(0-\infty) = AUC(0-t) + C_t/K_{el}$ , where  $K_{el}$  is the terminal elimination rate constant.

$AUC(0-t) / AUC(0-\infty)$  Ratio of  $AUC(0-t)$  to  $AUC(0-\infty)$ . Also referred to as AUCR.

$C_{max}$  Maximum observed drug concentration.

$T_{max}$  Time of the maximum drug concentration (obtained without interpolation).

$K_{el}$  Terminal elimination rate constant calculated by linear regression of the terminal linear portion of the  $\ln$  concentration vs. time curve.

$T_{1/2}$  Elimination half-life calculated as  $\ln(2)/K_{el}$ .

Relative bioavailability was evaluated based on 90% confidence intervals (CI) of the ratio of product means for  $\ln(C_{max})$ ,  $\ln[AUC(0-t)]$ , and  $\ln[AUC(0-\infty)]$  being within the range of 80 to 125%.

**Statistical methods:** Descriptive statistics were computed for the pharmacokinetic parameters and concentration data. Pharmacokinetic parameters  $AUC(0-\infty)$ ,  $AUC(0-t)$ ,  $C_{max}$ , and  $T_{max}$  were compared between the test treatment (5 mL Lotensin oral suspension 2 mg/mL, Treatment A) and the reference treatment (2 x 5 mg Lotensin tablets, Treatment B). With the exception of  $T_{max}$ , the statistical analysis using ANOVA was based on natural log-transformed pharmacokinetic parameters. The analysis model contained sequence, formulation, and period as fixed factors and subject (nested in sequence) as a random factor. The ratio of treatment means on the original scale was estimated, along with its 90% confidence interval (CI), by the anti-log of the difference in least squares means on the log scale for  $AUC(0-t)$ ,  $AUC(0-\infty)$ , and  $C_{max}$ . For  $T_{max}$ , the ratio of treatment means and 90% CI were estimated on the original scale. Relative

bioavailability of the test formulation was evaluated based on the 90% CI of AUC(0-t), AUC(0-inf), and Cmax being within the 80% to 125% range.

**Results:**

Four subjects in this trial were female and the remaining 26 subjects were male. Of these 30 subjects, 21 subjects were Black, six were Caucasian, and three were Hispanic. Three subjects had a large body frame size, 23 subjects had a medium frame size, and four subjects had a small frame size. Demographic and baseline characteristics are shown in Table 3.

Table 3. Demographic and Baseline Characteristics

	<b>Age (years)</b>	<b>Weight (lb)</b>	<b>Height (in)</b>
Mean ± SD	32.07 ± 7.34	167.24 ± 22.17	70.37 ± 3.22
Range	20–44	113.00–201.00	64.00–77.00

**Bioanalytical assay**

Within-study assay validation was performed by analysis of QC samples together with the study samples. The limit of quantitation was 0.5 ng/mL.

**Benazepril**

High range: The mean value for all calibration standards met the guideline for accuracy + 15%, ranging from 98.3% at 100 ng/ml, to 103% at 25.0 ng/ml. The precision, expressed as the Relative Standard Error (%RSD), ranged from 4.43% at 300 ng/ml, to 9.32% at 100 ng/ml was also within industry + 15% guideline for precision. The mean correlation coefficient was found to be 0.9960.

Low range: The mean value for all calibration standards met the guideline for accuracy + 15%, ranging from 94.6% at 25.0 ng/ml, to 105% at 2.50 and 5.00 ng/ml. The precision, expressed as the Relative Standard Error (%RSD), ranged from 4.59% at 1.00 ng/ml, to 8.13% at 0.500 ng/ml was also within industry + 15% guideline for precision. The mean correlation coefficient was found to be 0.9954.

**Benazeprilat**

High range: The mean value for all calibration standards were found to have accuracy, ranging from 96.1% at 300 ng/ml, to 107% at 100 ng/ml. The precision, expressed as the Relative Standard Error (%RSD), ranged from 6.89% at 100 ng/ml, to 9.55% at 25.0 ng/ml was also within industry + 15% guideline for precision.

Low range: The mean value for all calibration standards were found to have accuracy, ranging from 96.4% at 0.500 ng/ml, to 104% at 10.0 ng/ml. The precision, expressed as the Relative Standard Error (%RSD), ranged from 6.91% at 5.00 ng/ml, to 10.8% at 0.500 ng/ml was also within industry + 15% guideline for precision.

Table 2. Inter-Day Accuracy and Precision Measurements for Benazepril

Mean (ng/mL)	32.7	148	225
STDev	2.73	12.8	46.2
% RSD	8.33	8.62	20.6
% Accuracy	109	98.7	89.8
Mean (ng/mL)	1.53	7.09	14.8
STDev	0.3373	0.878	1.72
% RSD	22.1	12.4	11.6
% Accuracy	102	94.6	98.6

Table 3. Inter-Day Accuracy and Precision Measurements for Benazeprilat

Mean (ng/mL)	32.1	160	273
STDev	4.76	31.8	33.6
% RSD	14.8	19.9	12.3
% Accuracy	107	106	109
Mean (ng/mL)	1.39	7.65	14.3
STDev	0.203	1.41	2.53
% RSD	14.6	18.4	17.7
% Accuracy	92.4	102	95.1

Pharmacokinetic Results:

The mean plasma benazepril concentrations for Treatments A and B are presented in Figure 1.

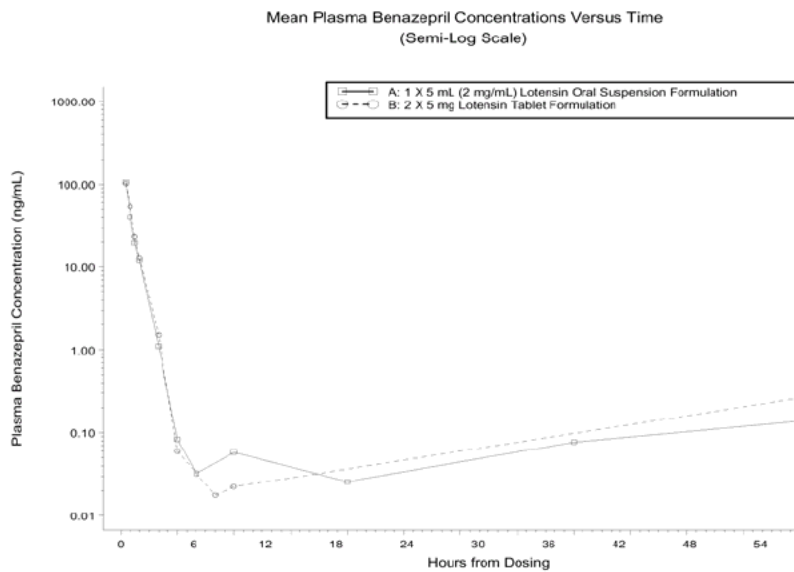
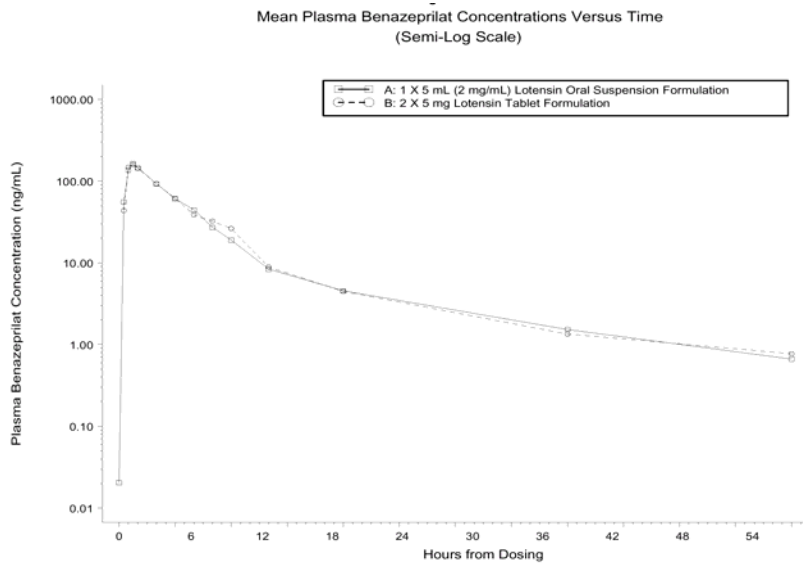


Figure 1.



Pharmacokinetics:

The arithmetic means and standard deviations of benazepril pharmacokinetic parameters and statistical comparisons of Tmax and ln-transformed parameters Cmax, AUC(0-t), and AUC(0-inf) following Treatments A and B are summarized in the following Table 4.

Table 4.

Summary of the pharmacokinetic parameters of plasma benazepril Treatments A versus B

Pharmacokinetic Parameters	Plasma Benazepril		Plasma Benazepril		90% CI	% Mean Ratio
	Treatment A	Treatment B	Treatment A	Treatment B		
	Arithmetic Mean	SD	Arithmetic Mean	SD		
Cmax(ng/mL)	106.45	43.12	110.97	47.15		
Tmax (hr)	0.517	0.0913	0.651	0.297	63.85–94.86	79.39
AUC(0-t) (ng*hr/mL)	97.75	37.28	106.5	42.15	-	.
AUC(0-inf) (ng*hr/mL)	97.71	36.46	110.1	41.48	-	.
T1/2 (hr)	0.648	0.178	0.629	0.166	-	.
Kel (1/hr)	1.16	0.392	1.19	0.353	-	.
ln(Cmax)	4.599	0.3694	4.614	0.4647	86.72–111.95	98.53
ln[AUC(0-t)]	4.519	0.3572	4.595	0.3872	84.38–101.84	92.70
ln[AUC(0-inf)]	4.522	0.3475	4.636	0.3667	81.48–99.55	90.06

Treatment A = 1 X 5 mL (2 mg/mL) Lotensin® Oral Suspension Formulation: test

Treatment B = 2 X 5 mg Lotensin® Tablet Formulation: reference

The geometric mean ratios of AUC(0-t) and AUC(0-inf) were 92.70% and 90.06%, respectively, indicating that benazepril from the oral suspension had similar extent of absorption compared to the reference tablet formulation. The geometric mean ratio of Tmax was 79.39%, with 90% CI of 63.85% - 94.86%, indicating marginally faster



achievement of peak plasma concentrations for the suspension; however, at a geometric mean ratio of 98.53% for Cmax the peak benazepril concentrations were practically identical between the two formulations. The 90% CI for the ratio of Cmax, AUC(0-t), and AUC(0-inf) were 86.72%- 111.95%, 84.38%-101.84%, and 81.48%-99.55%, respectively, and therefore were all within the 80% to 125% range required for the conclusion of equivalent bioavailability.

Therefore, benazepril has a very similar pharmacokinetic profile when administered as an oral suspension compared to when administered as an oral tablet. Benazepril from an oral suspension had similar extent of absorption compared to the reference tablet formulation. Despite the shorter time to reach maximum benazepril concentrations, peak benazepril concentrations were practically identical between the two formulations. The 90% CI for the ratio of Cmax, AUC(0-t), and AUC(0-inf) were within the 80% to 125% range required for the conclusion of equivalent bioavailability.

The arithmetic means and standard deviations of benazeprilat pharmacokinetic parameters and statistical comparisons of Tmax and ln-transformed parameters Cmax, AUC(0-t), and AUC(0-inf) following Treatments A and B are summarized in the following Table 5.

Table 5.

**Summary of the pharmacokinetic parameters of plasma benazeprilat for Treatments A versus B**

Pharmacokinetic Parameters	Plasma Benazeprilat				90% CI	% Mean Ratio
	Treatment A		Treatment B			
	Arithmetic Mean	SD	Arithmetic Mean	SD		
Cmax (ng/mL)	180.24	56.28	180.25	56.40		
Tmax (hr)	1.90	1.35	1.57	0.774	92.82-149.87	121.35
AUC(0-t) (ng*hr/mL)	979.2	313.9	1001	358.2	-	.
AUC(0-inf) (ng*hr/mL)	1042	256.5	1102	367.8	-	.
T1/2(hr)	17.3	9.59	15.5	9.07	-	.
Kel(1/hr)	0.0617	0.0545	0.0704	0.0548	-	.
ln(Cmax)	5.136	0.3667	5.136	0.3696	88.94-112.49	100.00
ln[AUC(0-t)]	6.831	0.3528	6.849	0.3524	90.80-106.22	98.20
ln[AUC(0-inf)]	6.921	0.2400	6.954	0.3213	89.69-104.47	96.80

Treatment A = 1 X 5 mL (2 mg/mL) Lotensin® Oral Suspension Formulation: test

Treatment B = 2 X 5 mg Lotensin® Tablet Formulation: reference

The geometric mean ratios of benazeprilat Cmax, AUC(0-t), and AUC(0-inf) were 100.0%, 98.20%, and 96.80%, respectively, indicating that formation of benazeprilat following benazepril administration as an oral suspension occurred at a similar rate and similar extent compared to that following the reference tablet formulation. The 90% CI for the ratio of Cmax, AUC(0-t), and AUC(0-inf) were 88.94%-112.49%, 90.8%-106.22%, and 89.69%-104.47%, respectively, and therefore were all within the 80% to 125% range required for the conclusion of equivalent bioavailability. The geometric mean ratio of benazeprilat Tmax was 121.35%; however, the 90% CI was 92.82% -

149.87% indicating that the slight prolongation in time to peak was not statistically significant.

Therefore, formation of benazeprilat following benazepril administration as an oral suspension occurred at a similar rate and similar extent compared to that following reference tablet formulation. The 90% CI for the ratio of C<sub>max</sub>, AUC(0-t), and AUC(0-inf) were 88.94%-112.49%, 90.8%-106.49%, and 89.69%-104.47%, respectively, and therefore were all within the 80% to 125% range required for the conclusion of equivalent bioavailability.

**Conclusions:** Lotensin® (10 mg) administered orally as an extemporaneously compounded suspension appeared to be safe and well tolerated by this normal healthy population compared to Lotensin® (10 mg) administered in a tablet formulation. The test and reference formulations have been shown to exhibit similar bioavailability with respect to both benazepril and benazeprilat. The 90% CI for geometric mean ratios of natural-log transformed C<sub>max</sub>, AUC(0-t), and AUC(0-inf) were all within the 80%-125% range required for the conclusion of equivalent bioavailability. Although T<sub>max</sub> values were different between the 2 formulations, the temporal differences were very small for benazepril, and not statistically significant for benazeprilat.

**Comments:**

1. The sponsor has adequately performed a study to compare the Lotensin® (10 mg) administered orally as an extemporaneously compounded suspension with Lotensin® (10 mg) administered in tablet formulation. These formulations were bioequivalent both with respect to AUC and C<sub>max</sub> of benazepril (parent drug) and benazeprilat (active metabolite). This formulation appeared to be plausible to use in children and other patients who are unable to swallow the tablet.

### **6.1.2 A single center, single dose, open- label study to evaluate the pharmacokinetics of benazepril in pediatric subjects (US03a1)**

**Investigators:** Samuel W. Boellner, MD

**Study center:** Clinical Study Centers, 9601 Lile Drive, Little Rock, Arkansas

**Study period:** First patient enrolled: 09 Sept. 2002 Last patient completed: 29 Sept. 2002

**Objectives:** To determine the pharmacokinetics of benazepril and its active metabolite benazeprilat following the administration of a single oral dose of benazepril hydrochloride in pediatric subjects.

**Study Design:** This single center, open- label, single- dose study consisted of a screening visit, a baseline visit and a 24- hour pharmacokinetic sampling period. The study included 6 infants/ toddlers (1 to 24 months), 8 pre-school children (> 2 to 6 years), 8 school-age children (> 6 to 12 years), and 8 adolescents (> 12 to 16 years). At the screening visit (Visit 1) each subject had a medical history taken, a physical examination was performed that included assessment of vital signs, the use of prescription and over-the-counter medications was assessed, specimens were collected (non- fasting) for laboratory evaluations (hematology, chemistry, urinalysis) and urine drug and alcohol screens, an electrocardiogram (ECG) was performed, and had a pregnancy test, if indicated. Following review of the results of the screening evaluations, an eligible subject returned for the baseline visit. At this visit, the subject was re- evaluated using the study inclusion/ exclusion criteria, vital signs were taken, specimens were obtained for urine drug and alcohol screens, an ECG was performed, and a pregnancy test was performed, if indicated. Following an overnight fast, each subject received a single dose of benazepril. Immediately before dosing and at 0.5, 1, 2, 3, 4, 8, 12, and 24 hours after dosing the subject provided 1.0 mL blood samples which were analyzed for benazepril and benazeprilat. Subjects continued to fast for 2 hours after dosing. Vital signs were measured at each sampling time. After the 12-hour assessments, subjects could be discharged to local accommodations. Each subject was evaluated at the study site at 24 hours post dose and had a physical examination that included assessment of vital signs, provided a blood sample for laboratory evaluations, and had an ECG performed.

**Number of patients:** Planned, 30. Recruited, 30. Analyzed: 30 (infants/ toddlers 6; pre-school children 8; school- age children 8, adolescents 8).

**Investigational drug:** Benazepril tablets (Lotensin ® for oral administration: 5 mg tablet, lot number 0083005930, batch number 119G8953; 10 mg tablet, lot number 0083006330, batch number 028G4621; 20 mg tablet, lot number 0083007930, batch number 038G4601). For subjects 6 years of age the dose was 0.2 – 0.5 mg/ kg administered as a suspension prepared from the 20 mg tablets, and for subjects > 6 to 16 years of age the dose was 0.1 - 0.5 mg/ kg (administered as a 5 mg or 10 mg tablet).

The dose of benazepril was 0.2 to 0.5 mg/ kg for subjects younger than 6 years of age and was 0.1 to 0.5 mg/ kg for subjects over 6 years of age (Table 1).

Table 1. Benazepril dosage by age group

Age Group	Dose of Benazepril
Infants and toddlers (1 to ≤ 24 months)	0.2 – 0.5 mg/kg (administered as a suspension) <sup>a</sup>
Pre-school children (> 2 to ≤ 6 years)	0.2 – 0.5 mg/kg (administered as a suspension) <sup>a</sup>
School-age children (> 6 to ≤ 12 years)	0.1 – 0.5 mg/kg (administered as a 5 or 10 mg tablet)
Adolescents (> 12 to ≤ 16 years)	0.1 – 0.5 mg/kg (administered as a 5 or 10 mg tablet)

**Reference therapy:** None

**Duration of treatment:** Single oral dose of benazepril followed by a 24-hour assessment period.

**Statistical methods:** Background and demographic variables were summarized using descriptive statistics for each age group and for all age groups combined. For benazepril and benazeprilat, the following pharmacokinetic parameters were estimated from the concentration- time data over the 24- hour post- dose period for each age group and for all age groups combined: AUC<sub>0- 24</sub> (area under the plasma concentration- time curve from 0 to 24 hours), AUC<sub>0- inf</sub> (area under the plasma concentration- time curve from time zero to infinity), C<sub>max</sub> (observed maximum plasma concentration), T<sub>max</sub> (time to maximum plasma concentration), k<sub>e</sub> (elimination rate constant), t<sub>1/ 2</sub> (terminal half- life), CL/ F (apparent clearance), and CL/ F/ wt (apparent clearance normalized for body weight). For each parameter except T<sub>max</sub>, descriptive statistics were calculated (arithmetic mean, standard deviation, geometric mean, minimum, median, and maximum) and 90% confidence intervals. For T<sub>max</sub>, only the median and range were computed. For each pharmacokinetic parameter except T<sub>max</sub>, 90% confidence intervals for the differences between age groups were computed.

## RESULTS

### Demographics:

The demographic characteristics of subjects in each age group are summarized in Table 2. The mean age, height, and weight of subjects increased across age groups. The majority of subjects were Caucasian (90%) and male (56.7%).

Table 2. Demographic and background characteristics by age group, safety population

	Age Group				
	Infants/ Toddlers (N = 6)	Pre-School (N = 8)	School Age (N = 8)	Adolescents (N = 8)	All (N = 30)
<b>Age (years)</b>					
Mean	1.3	3.8	8.3	14.3	7.3
Standard deviation	0.51	1.2	2.1	1.5	5.2
Range	0.7 – 1.9	2.5 – 5.5	6.5 – 11.9	12.7 – 16.9	0.7 – 16.9
<b>Sex - n (%)</b>					
Male	2 (33.3)	7 (87.5)	3 (37.5)	5 (62.5)	17 (56.7)
Female	4 (66.7)	1 (12.5)	5 (62.5)	3 (37.5)	13 (43.3)
<b>Race – n (%)</b>					
Caucasian	4 (66.7)	7 (87.5)	8 (100.0)	8 (100.0)	27 (90.0)
Black	2 (33.3)	1 (12.5)	0 (0.0)	0 (0.0)	3 (10.0)
<b>Weight (kg)</b>					
Mean	10.1	16.3	29.5	59.6	30.1
Standard deviation	1.3	3.6	9.9	13.4	21.1
Range	8.4 – 11.6	12.0 – 21.3	20.6 – 48.6	42.9 – 80.0	8.4 – 80.0
<b>Height (cm)</b>					
Mean	77.7	102.5	129.6	164.0	121.2
Standard deviation	4.6	10.3	16.0	10.3	33.6
Range	71 – 84	90 – 113	110 – 159	150 – 178	71 – 178

**Pharmacokinetics:**

**Benazepril**

The estimates of the benazepril pharmacokinetic parameters derived from the plasma concentration vs. time values for each age group are given in Table 3.

Table 3. Mean (standard deviation) of benazepril pharmacokinetic parameters by age group

Pharmacokinetic Parameter	Age Group				
	Infants/ Toddlers	Pre-School	School Age	Adolescents	All
AUC <sub>0-24</sub> (ng·h/mL)	106.4 (71.7)	113.4 (43.1)	138.2 (44.7)	137.1 (64.4)	125.6 (54.1)
AUC <sub>0-∞</sub> (ng·h/mL)	105.1 (72.5)	99.8 (27.8)	136.5 (44.5)	148.5 (71.9)	126.4 (57.1)
Dose Normalized AUC <sub>0-∞</sub> (h·ng/mL/mg·kg)	300.4 (207.0)	285.0 (79.4)	490.8 (142.6)	501.3 (286.3)	416.4 (209.7)
C <sub>max</sub> (ng/mL)	95.7 (62.4)	99.2 (63.6)	141.4 (75.8)	118.1 (88.1)	115.4 (72.7)
T <sub>max</sub> (h)*	0.53 (0.43 – 1.17)	0.58 (0.38 – 1.92)	0.54 (0.43 – 1.02)	0.73 (0.47 – 2.00)	0.55 (0.38 – 2.00)
k <sub>e</sub> (1/h)	1.063 (0.405)	1.249 (0.421)	1.419 (0.381)	0.670 (0.421)	1.117 (0.457)
CL/F/wt (mL/h/kg)	2126.5 (3883.1)	3786.7 (1347.5)	2199.5 (660.1)	2936.9 (2116.4)	3141.7 (1727.5)
t <sub>1/2</sub> (h)	0.76 (0.37)	0.64 (0.32)	0.52 (0.14)	1.44 (0.86)	0.82 (0.60)

A scatterplot of the weight normalized oral clearance values for each subject in each age group are given in Figure 1.

Figure 1. Scatter plot of weight normalized benazepril oral clearance (CL/ F/ wt) versus age

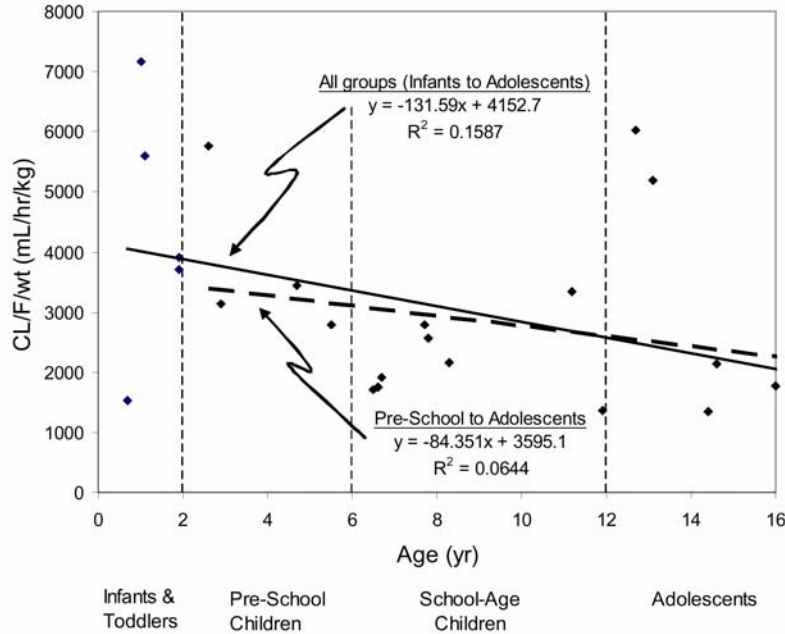


Table 4 demonstrates the comparison of pharmacokinetic parameters estimated for each age group of children with calculation of the 90% confidence intervals.

Table 4. Age group comparisons of benazepril pharmacokinetic parameters

Pharmacokinetic Parameter	90% Confidence Intervals					
	Adolescents-Toddlers/Infants	Adolescents – Pre-school Children	Adolescents – School-age Children	School-age Children – Infants/Toddlers	School-age Children – Pre-school Children	Pre-school Children – Infants/Toddlers
Ln AUC <sub>(0-24)</sub> (ng h/mL)	(48.3, 113.5)	(59.5, 125.9)	(72.3, 152.9)	(4539, 107.9)	(56.6, 119.7)	(55.8, 131.1)
Ln AUC <sub>(0-∞)</sub> (ng h/mL)	(41.4, 111.9)	(42.9, 123.6)	(62.4, 151.4)	(43.9, 111.9)	(45.3, 123.8)	(54.0, 162.3)
Ln Dose Normalized AUC <sub>(0-∞)</sub> (h·ng h/mL/mg·kg)	(36.3, 103.5)	(37.5, 114.5)	(70.6, 179.5)	(33.3, 89.2)	(34.3, 98.9)	(52.4, 167.1)
Ln C <sub>max</sub> (ng/mL)	(46.9, 182.5)	(53.7, 176.8)	(75.8, 249.8)	(34.1, 132.7)	(39.0, 128.5)	(48.1, 187.4)
CL/F/wt (mL/h/kg)	(96.6, 275.2)	(87.3, 266.6)	(55.7, 141.7)	(112.1, 300.4)	(101.1, 291.5)	(59.8, 190.9)
Ln t <sub>1/2</sub> (h)	(35.6, 91.3)	(29.2, 79.5)	(27.1, 62.7)	(88.9, 215.6)	(72.6, 118.1)	(70.4, 199.5)

A plot of plasma concentrations of benazepril vs time in children 6 to 16 years of age is shown below.

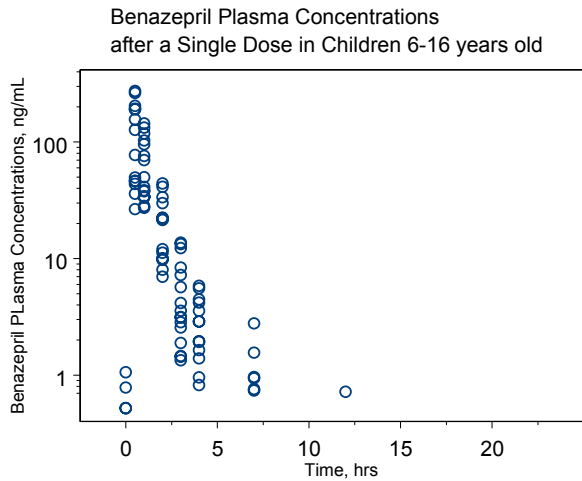


Figure 2. Benazepril plasma concentrations vs time in healthy children of 6 to 16 years of age.

In all four age groups, maximum concentrations of benazepril were achieved rapidly, with median  $T_{max}$  values ranging from 0.53 to 0.73 hours (overall mean of 0.55 hours), indicating rapid absorption and/ or metabolism of benazepril. Similar values of 0.5 to 1 hours have been reported in adults.

Mean terminal half-life values of benazepril were small in all four age- groups, ranging from 0.4 to 1.4 hours (overall mean, 0.82 hours), suggesting rapid elimination. Similar values of 0.8 hours have been reported in adults. Mean oral clearance values of benazepril were 4.38, 3.79, 2.20, and 2.94 L/h/kg for the infant/ toddler, preschool, school-age and adolescent groups, respectively.

#### BENAZEPRILAT

The estimates of the benazeprilat pharmacokinetic parameters derived from the plasma concentration- time values for each age group are given in Table 5 below for all pharmacokinetic variables.

Table 5. Mean (standard deviation) of benazeprilat pharmacokinetic parameters by age group

Pharmacokinetic Parameter	Age Group				
	Infants/ Toddlers	Pre-School	School Age	Adolescents	All
AUC <sub>(0-24)</sub> (ng·h/mL)	1416.1 (693.1)	964.3 (200.8)	1086.1 (296.9)	1861.2 (638.8)	1323.2 (583.0)
AUC <sub>(0-∞)</sub> (ng·h/mL)	1444.8 (704.7)	997.1 (211.3)	1084.1 (311.4)	1908.9 (644.0)	1372.8 (608.8)
Dose Normalized AUC <sub>(0-∞)</sub> (h·ng/mL/mg·kg)	4127.9 (2013.5)	2849.0 (603.8)	4176.3 (1316.2)	6592.3 (2432.3)	4359.1 (2198.8)
C <sub>max</sub> (ng/mL)	291.4 (104.8)	206.4 (56.7)	225.6 (47.8)	318.6 (151.2)	257.3 (104.7)
T <sub>max</sub> (h)*	1.00 (0.58 – 2.00)	2.01 (1.00 – 3.00)	1.95 (0.92 – 2.92)	1.97 (0.47 – 2.92)	1.95 (0.47 – 3.00)
CL/F/wt (mL/h/kg)	283.7 (113.9)	364.9 (77.5)	258.5 (72.8)	169.3 (56.9)	264.3 (105.2)
k <sub>e</sub> (1/h)	0.144 (0.026)	0.130 (0.026)	0.129 (0.028)	0.147 (0.015)	0.137 (0.024)
t <sub>1/2</sub> (h)	4.96 (0.90)	5.55 (1.23)	5.58 (1.18)	4.77 (0.52)	5.22 (1.00)

A plot of plasma concentrations of benazeprilat vs time in children 6 to 16 years of age is shown below.

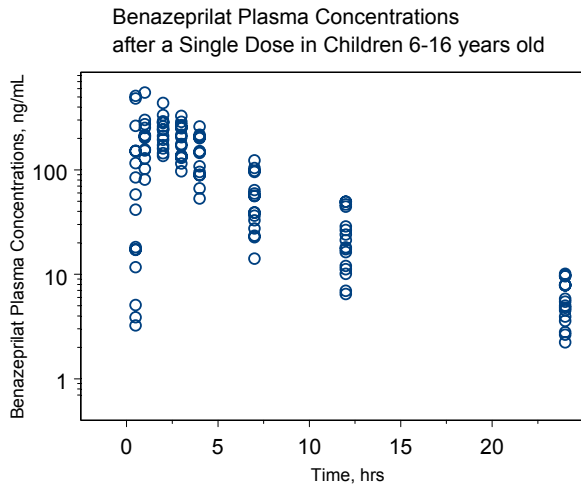


Figure 2. Benazeprilat plasma concentrations vs time for children of 6 to 16 years of age.

A scatter plot of the weight normalized oral clearance values for each subject in each age group are given in Figure 3.



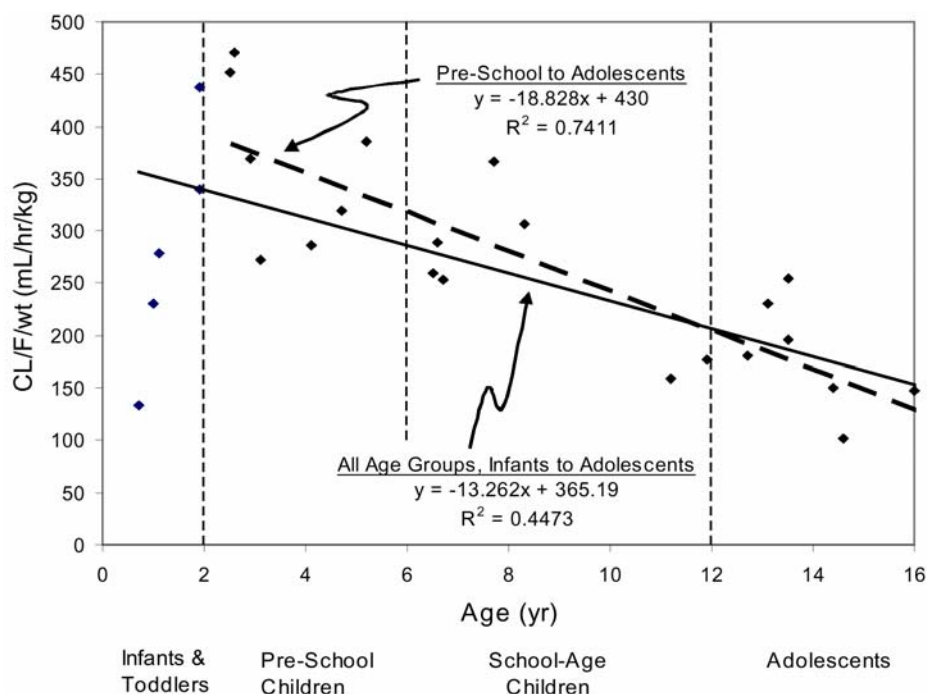


Figure 3. Scatter plot of weight normalized benazeprilat oral clearance (CL/ F/ wt) versus age

Table 6. Age group comparisons of benazeprilat pharmacokinetic parameters

Pharmacokinetic Parameter	90 % Confidence Intervals					
	Adolescents-Toddlers/Infants	Adolescents – Pre-school Children	Adolescents – School-age Children	School-age Children – Infants/Toddlers	School-age Children – Pre-school Children	Pre-school Children – Infants/Toddlers
Ln AUC <sub>(0-24)</sub> (ng h/mL)	(53.4, 104.3)	(40.4, 72.8)	(44.6, 80.3)	(89.1, 174.1)	(67.5, 121.5)	(98.4, 192.3)
Ln AUC <sub>(0-∞)</sub> (ng h/mL)	(52.7, 104.1)	(40.0, 74.3)	(42.6, 79.1)	(89.9, 180.9)	(68.3, 129.2)	(95.7, 192.7)
Ln Dose Normalized AUC <sub>(0-∞)</sub> (h-ng h/mL/mg-kg)	(44.1, 84.1)	(33.5, 60.1)	(48.1, 86.3)	(67.9, 131.7)	(51.5, 94.2)	(97.5, 189.1)
Ln C <sub>max</sub> (ng/mL)	(68.2, 135.7)	(51.4, 94.0)	(56.8, 103.9)	(88.8, 176.8)	(66.9, 122.4)	(98.1, 195.4)
CL/F/wt (mL/h/kg)	(118.9, 226.6)	(166.4, 298.7)	(115.8, 208.0)	(76.0, 147.3)	(106.2, 194.3)	(52.9, 102.5)
Ln t <sub>1/2</sub> (h)	(86.3, 123.1)	(97.7, 134.9)	(98.2, 135.5)	(74.5, 107.2)	(84.3, 117.5)	(74.8, 107.7)

In all four age groups the maximum concentrations of benazeprilat were achieved rapidly (median T<sub>max</sub> values ranging from 1 to 2 hours for the four age groups), with similar values reported in adults (1 to 2 hours). The mean terminal half-life (t<sub>1/2</sub>) values ranged from 4.8 to 5.6 hours, approximately two- fold less than values reported in adults (10 to 11 hours). Mean oral clearance values of benazeprilat were 0.284, 0.65, 0.259, and 0.169 L/h/kg in the infant/ toddler, preschool, school-age, and adolescent groups, respectively. The confidence intervals for the differences between all age group pairs were wide and outside the 80 to 125% limit for equivalence for all pharmacokinetic parameters (including C<sub>max</sub>, dose- normalized AUC, CL/F/wt and t<sub>1/2</sub>) of both benazepril and benazeprilat. Therefore, it cannot be concluded that the C<sub>max</sub>, AUC, oral clearance or

terminal half- life values are equivalent between any age- group pair for both benazepril and benazeprilat. This inability to demonstrate equivalency is possibly due to the low number of subjects studied coupled with the large variability in the data. There was a slight trend noted toward lower clearance (and greater AUC<sub>0-inf</sub>) of benazeprilat with increasing age. For example, mean apparent clearance values decreased with increase in age from 284, 365, 258, to 169 mL/h/kg for infant/ toddler, preschool, school and adolescent age- groups, respectively. Mean dose- normalized AUC<sub>0-inf</sub> values increased with increase in age from 4128, 2849, 4176 to 6592 ng·h/mL/mg·kg for infant, toddler, preschool, school age and adolescent groups, respectively. Previous studies in adults have found higher dose-normalized AUC<sub>0-inf</sub> values of approximately 10,000 ng·h/mL/mg·kg for benazeprilat, which is consistent with this trend. Potential reasons for this trend could be age-related differences in absorption, metabolism, distribution or elimination. It cannot be concluded that the C<sub>max</sub>, AUC, oral clearance or terminal half- life values are similar between any age-group pair for both benazepril and benazeprilat due to the wide confidence intervals. There was a slight trend noted toward lower clearance (and greater AUC<sub>0-inf</sub>) of benazeprilat with increasing age.

**Comments:**

1. A single dose pharmacokinetic study was conducted in normal pediatric volunteers aged from 0.7 to <16 years following daily oral administration of 0.1 to 0.5 mg/kg benazepril HCL.
2. The mean CL values of benazepril for school age children (6 to 12 years old) and adolescents (12 to 16 years old) were: 2.1 and 2.9 L/hr/kg respectively. These CL values were larger than calculated for adults after a dose of 10 mg of Lotensin (1.5 L/h/kg). The mean CL values for benazeprilat for all two pediatric groups were: 0.258 and 0.169 L/hr/kg, respectively. These CL values were larger than calculated for adults (0.132 L/hr/kg). The group of school age children had benazeprilat clearance twice faster than adults and the adolescents' clearance values were 27% larger than the adults' clearance values.
3. The sponsor concludes that the conducted study may not give a full explanation of the observed trends in apparent clearance and AUC found with age and further studies would be needed to determine the statistical validity and reasons for these trends.

**6.1.3 A multicenter open- label, steady state study to evaluate the pharmacokinetics of benazepril in pediatric subjects (US03)**

**Investigators:** Carolyn Abitbol, MD et al.

**Study center(s):** Subjects enrolled at 20 centers in the United States.

**Study period:** First subject enrolled: 23 July 2002  
Last subject completed: 03 December 2002

**Development phase:** IV

**Objectives:** To define appropriate dosing information in the pediatric age group. The study was to determine the pharmacokinetics of benazepril after a minimum of 5 days at steady state in pediatric subjects.

**Study Design:** This multicenter, open- label study consisted of a screening visit, a baseline visit and a 4- hour pharmacokinetic sampling period at least 5 days after the baseline visit. The study was to include 16 subjects in each of the following age groups: infants/ toddlers (1 to 24 months), pre- school children (> 2 to 6 years), school- age children (> 6 to 12 years), and adolescents (> 12 to 16 years). At the baseline visit subjects were randomized to one of four 4- hour collection schedules for blood sampling (1 mL) for pharmacokinetic analysis: 1, 2, 3, and 4 hours post dose; 5, 6, 7, and 8 hours post dose; 12, 13, 14, and 15 hours post dose; or 21, 22, 23, and 24 hours post dose. Four subjects in each age group were randomized to each of the four collection schedules.

**Number of subjects:** Planned, 64 (16 in each of the 4 age groups). Recruited, 57. Analyzed: 3, infants/ toddlers; 9, pre- school children; 19, school- age children; 26, adolescents.

**Investigational drug:** Benazepril tablets

(Lotensin ® for oral administration:

5 mg tablet, lot number 0083005930, batch number 119G8953;

10 mg tablet, lot number 0083006330, batch number 028G4621;

20 mg tablet, lot number 0083007930, batch number 038G4601).

For subjects 6 years of age the dose was 0.2 to 0.5 mg/ kg administered as a suspension prepared from the 20 mg tablets, and for subjects > 6 to 16 years of age the dose was 0.1 to 0.5 mg/kg (5 mg or 10 mg tablet).

**Treatment assignment:**

All subjects received orally administered benazepril. The dose received depended on the subject's age and weight (Table 1).

Table 1. Benazepril dosage by age group

Age Group	Dose of Benazepril
Infants and toddlers (1 – ≤ 24 months)	0.2 – 0.5 mg/kg (administered as a suspension) <sup>a</sup>
Pre-school children (> 2 – ≤ 6 years)	0.2 – 0.5 mg/kg (administered as a suspension) <sup>a</sup>
School-age children (> 6 – ≤ 12 years)	0.1 – 0.5 mg/kg (administered as a 5 or 10 mg tablet)
Adolescents (> 12 – ≤ 16 years)	0.1 – 0.5 mg/kg (administered as a 5 or 10 mg tablet)

### Sampling

At the baseline visit (Visit 2), subjects who were eligible to continue in the study were to be randomly assigned to one of the following four collection schedules for blood samples for pharmacokinetic analysis:

- 1, 2, 3, and 4 hours post dose
- 5, 6, 7, and 8 hours post dose
- 12, 13, 14, and 15 hours post dose
- 21, 22, 23, and 24 hours post dose.

For each eligible subject, the investigator called a central randomization center to have the subject assigned to one of the collection schedules. The randomization was balanced so that for each age group, four subjects were randomly assigned to each of the four collection schedules.

Subjects were to be dosed with benazepril at the same time each day (2 hours). The time of dosing was one that would allow the subject to return to the clinic for Visit 3 at a convenient time to have blood samples drawn for pharmacokinetic analysis at the times determined by the collection schedule for the subject.

### Pharmacokinetics:

Steady- state benazepril and benazeprilat pharmacokinetic parameters were determined from the plasma concentration-time data over a 24-hour post-dose period.

### Statistical methods:

Background and demographic variables were summarized using descriptive statistics for each age group and for all age groups combined.

The pharmacokinetic analyses of benazepril and benazeprilat plasma concentrations were performed using population pharmacokinetic analysis methods. The analyses were conducted to identify important demographic variables, concomitant medications, and disease conditions that could influence the pharmacokinetics of benazepril and benazeprilat. The effect of age on the pharmacokinetics of benazepril and benazeprilat was evaluated for the purpose of developing appropriate dose recommendations for pediatric subjects. The population pharmacokinetic analyses were performed in three

steps: population pharmacokinetic model building, evaluation of potential covariates and model validation. Population pharmacokinetic models were developed using the NONMEM (Nonlinear Mixed- Effect Model) software. The pharmacokinetic model was chosen based on goodness- of- fit criteria including diagnostic scatter plots, decreases in inter-subject variances, and the value of the objective function. Models were built in a stepwise manner with incremental covariate factors. The objective function was used for hypothesis testing to discriminate among alternative hierarchical models. Demographic variables such as age, gender, race, height, and body weight were evaluated as potential covariates. Once the basic population pharmacokinetic model was developed, Bayesian estimates of individual parameters were calculated using the POSTHOC method in NONMEM. The performance of the final optimal population pharmacokinetic model was tested using bootstrapping. The validity of the model was assessed by bootstrapping and by examination of the diagnostic plots.

## RESULTS

Table 2. Demographic and background characteristics by age group, safety population

	Age Group				
	Infants/ Toddlers (N = 3)	Pre-School (N = 9)	School Age (N = 19)	Adolescents (N = 26)	All (N = 57)
<b>Age (years)</b>					
Mean	1.3	4.2	8.5	14.9	10.4
Standard deviation	0.5	1.4	1.8	1.2	4.8
Range	0.9 – 1.9	2.1 – 5.8	6.1 – 11.9	12.6 – 16.9	0.9 – 16.9
<b>Sex – n (%)</b>					
Male	3 (100.0)	4 (44.4)	9 (47.4)	15 (57.7)	31 (54.4)
Female	0 (0.0)	5 (55.6)	10 (52.6)	11 (42.3)	26 (45.6)
<b>Race – n (%)</b>					
Caucasian	2 (66.7)	5 (55.6)	14 (73.7)	11 (42.3)	32 (56.1)
Black	0 (0.0)	4 (44.4)	3 (15.8)	12 (46.2)	19 (33.3)
Other	1 (33.3)	0 (0.0)	2 (10.5)	3 (11.5)	6 (10.5)
<b>Weight (kg)</b>					
Mean	10.9	20.4	37.8	93.2	58.9
Standard deviation	1.5	8.5	13.1	25.8	37.7
Range	9.5 – 12.4	11.0 – 37.9	23.5 – 69.0	42.3 – 165.9	9.5 – 165.9
<b>Height (cm)</b>					
Mean	78.3	103.2	133.3	163.5	139.4
Standard deviation	5.7	15.4	11.6	25.0	32.4
Range	72 – 83	77 – 124	118 – 164	50 – 190	50 – 190

The sponsor's plots of benazepril and benazeprilat plasma- concentration- versus- time for all pediatric subjects are shown in Figures 1.1 and 1.2.

Figure 1.1 Scatter plot of benazepril plasma concentrations versus time for all the pediatric subjects  
(symbol '1': age 1 - ≤ 24 months; symbol '2': age > 2 - ≤ 6 years; symbol '3': age > 6 - ≤ 12 years; symbol '4': age > 12 - ≤ 16 years)

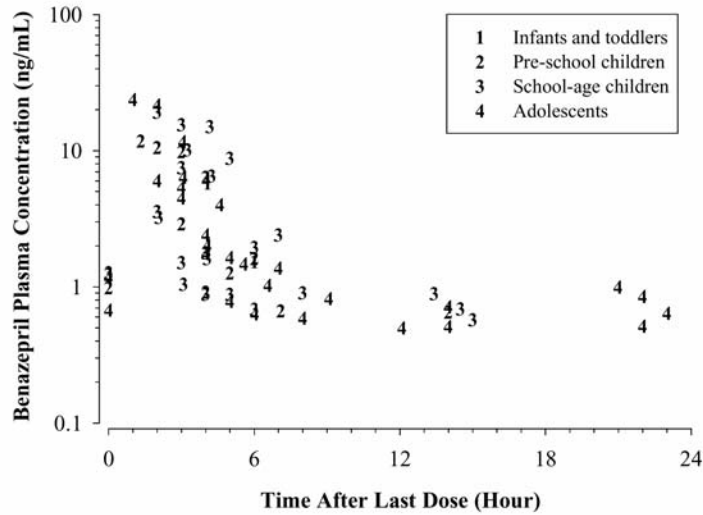
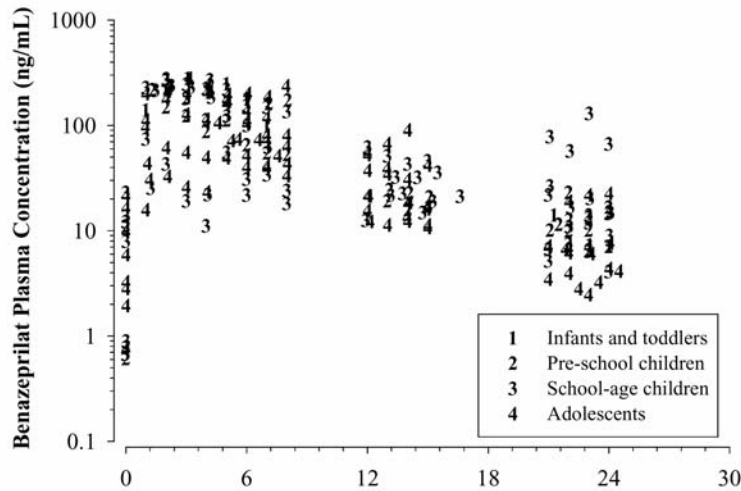


Figure 1.2 Scatter plot of benazeprilat plasma concentrations versus time for all the pediatric subjects  
(symbol '1': age 1 - ≤ 24 months; symbol '2': age > 2 - ≤ 6 years; symbol '3': age > 6 - ≤ 12 years; symbol '4': age > 12 - ≤ 16 years)



## BENAZEPRIL PHARMACOKINETICS

Plasma samples (n = 281) were assayed for benazepril concentrations in 57 pediatric subjects (age: 0.91 to 16.9 years). Of these 281 concentrations, sixty-seven were above the limit of quantitation from 31 pediatric subjects (age: 0.91 to 16.9 years).

A summary of baseline demographic continuous data for subjects included in the NONMEM analysis is illustrated in Table 3 below.

Table 3. Characteristics of the pediatric subjects for benazepril (N = 31)

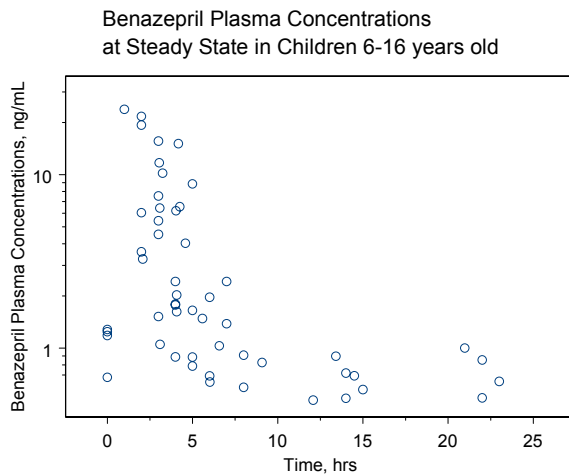
Characteristic	Mean ± Standard Deviation	Median (Minimum – Maximum)
Age (year)	10.6 ± 4.9	11.9 (0.91 – 16.9)
Weight (kg)	64.7 ± 39.7	65.2 (9.5 – 165.9)
Height (cm)	143 ± 31.0	146 (72 – 190)
Dose (mg/day)	13.4 ± 8.1	10 (4, 30)
Dose (mg/kg/day)	0.269 ± 0.209	0.196 (0.083, 1.10)

Characteristic	Number (%) of Subjects
Gender	
Female	17 (55%)
Male	14 (45%)
Ethnic Origin	
Caucasian	16 (52%)
Black	12 (39%)
Other	3 (9%)
Disease	
Other medical conditions (proteinuria)	3 (10%)
Hypertension	28 (90%)

### Base Population Pharmacokinetic Model Development

A one-compartment pharmacokinetic model was chosen over a two-compartment pharmacokinetic model for fitting of benazepril plasma concentration- time data. The Figure 1.1 compares benazepril plasma concentration profiles for 4 studied groups of children. The figure below compares benazepril plasma concentration profiles for school-age children and adolescents (6 to 16 years of age). Visual inspection suggests the plausibility of one-compartmental model proposed by the sponsor.



If consider only pediatric patients who had the efficacy and safety data in this clinical study (aged from 6 to 16 years), this plot contains only 53 data points from 27 patients.

Table below refers to the data obtained in Study US02 for adults.

ADULTS Study US01			
Benazepril	AUC	AUCinf	Cmax
Mean	102.1	103.8	108.7
SD	39.7	39.1	44.9

Plasma concentrations in adults were higher on average than the same for pediatric patients.

Several error models were also tested for describing residual error during the population modeling process. A heteroscedastic model (consisting of a proportional term and an additive term) was found to best describe the residual variability in concentrations of benazepril. All tested intermediate models for benazepril are listed in Table 4.

Table 4. Listing of the intermediate models for benazepril.

Test Model	Reference Model	Objective function Value (OFV)	Change in OFV	Description of the model	Comment
1	-	-	-	2-CPT, Exponential error model	Prematurely terminated
2	-	210.5	-	2-CPT, Proportional/Additive error model	-
3	-	-	-	2-CPT, Proportional error model	Prematurely terminated
4	-	190.6	-	2-CPT, Additive error model	-
5	-	-	-	1-CPT, Proportional/Additive error model, ETAs for CL, V, ka	Rounding error
6	-	135.9	-	1-CPT, Proportional/Additive error model, ETAs for CL, V	-
7	-	175.5	-	1-CPT, Exponential error model, ETA for CL	-
8	-	142.9	-	1-CPT, Exponential error model, ETA for V	-
9	-	-	-	1-CPT, Exponential error model, ETA for ka	Error 65: floating invalid
<b>10</b>	-	<b>133.47</b>	-	1-CPT, Proportional/Additive error model, ETA for CL, Base Model	-

The parameter estimates for the base one- compartment model along with the inter-subject variability parameter associated with oral clearance (CL), apparent volume of distribution (V) and absorption rate constant (ka) are shown in Table 5.

Table 5. Parameter estimates from the base model for benazepril.

Parameter	Units	Symbol	Estimate	SE of Estimate
CL	L/h	$\theta_1$	243	41.4
V	L	$\theta_2$	191	81.4
ka	1/h	$\theta_5$	0.866	0.390
Variance on CL	--	$\omega_{CL}^2$	0.165	0.087
Proportional error term	--	$\theta_4$	0.303	0.042
Additive error term	--	$\theta_5$	0.773	0.062



The residual variability on clearance was about 40%

### Covariate Population Pharmacokinetic Model Development

The covariate model building steps are shown in Table 6.

Table 6. Covariate model building steps.

Test Model	Reference Model	Objective function Value (OFV)	Change in OFV	Description of the model	Comment
<b>10</b>	-	<b>133.47</b>	-	1-CPT, Proportional/Additive error model, ETA for CL, Base Model	
11	10	126.8	-6.67	CL vs. AGE (exponential)	NS
12	10	127.8	-5.67	CL vs. AGE ('Emax')	NS
13	10	130.8	-2.67	CL vs. BW (exponential)	NS
14	10	130.1	-3.37	CL vs. BW ('Emax')	NS
15	10	130.6	-2.87	CL vs. SEX	NS
16	10	130.6	-2.87	CL vs. RACE (RACE = 1)	NS
17	10	314.7	+181.2	CL vs. RACE (RACE = 2)	Rounding error

Test Model	Reference Model	Objective function Value (OFV)	Change in OFV	Description of the model	Comment
18	10	130.6	-2.87	CL vs. RACE (RACE = 4)	NS
19	10	127.1	-6.37	CL vs. HT (exponential)	NS
20	10	124.3	-9.17	CL vs. HT ('Emax')	Rounding error
21	10	129.2	-4.27	CL vs. BW (linear)	NS
22	10	124.0	-9.47	CL vs. HT (linear)	SIG
<b>23</b>	<b>10</b>	<b>125.56</b>	<b>-7.91</b>	<b>CL vs. AGE (linear)</b> <b>Final Model</b>	<b>SIG</b>
24	23	124.0	-1.56	CL vs. AGE (linear) + CL vs. HT (linear)	NS

None of body weight, sex, and race was found to be a significant covariate on oral clearance of benazepril. The sponsor concluded that age and body height were identified as significant covariates on benazepril oral clearance. Age was highly correlated with body height (HT). Since age is a more meaningful parameter than HT, the sponsor selected Model 23 as the final covariate model.

The final model for benazepril is shown in Table 7. The differences in the objective function with the inclusion of age was small although significant with the level of sensitivity as  $p=0.05$  ( $\Delta$ OFV 3.8).

The sponsor has not performed the significance testing of the covariates at the higher level of sensitivity by removing them from the model one by one. The difference in OFV

of 7.91 would be insignificant for the level of sensitivity as  $p=0.001$  ( $\Delta\text{OFV}$  10.83). Therefore, the conclusion on the effect of age on clearance cannot be made. An attempt was made to test the effect of these covariates on volume of distribution and absorption rate. However, it was not successful because the model did not converge.

Table 7. Covariate assessment during covariate model development for benazepril

Model Description*	Covariate Model	$\Delta\text{OFV}$
Base Model (Model 10)		
Model 23**		
Age on oral clearance (CL)	$\text{TVCL} = \theta_1 + (\text{AGE}-0.91) \times \theta_6$	-7.9 <sup>a</sup> ( $\text{OFV}_{\text{Model23}} - \text{OFV}_{\text{Base Model}}$ ) $p < 0.005$
Model 22		
Body Height (HT) on oral clearance (CL)	$\text{TVCL} = \theta_1 + (\text{HT}-72) \times \theta_6$	-9.5 <sup>b</sup> ( $\text{OFV}_{\text{Model23}} - \text{OFV}_{\text{Base Model}}$ ) $p < 0.005$
Model 24		
Age on oral clearance (CL)	$\text{TVCL} = \theta_1 + (\text{AGE}-0.91) \times \theta_6$	-1.6 <sup>c</sup>
HT on oral clearance (CL)	$\text{TVCL} = \theta_1 + (\text{HT}-72) \times \theta_7$	( $\text{OFV}_{\text{Model24}} - \text{OFV}_{\text{Model23}}$ ) $p > 0.05$ , Not Significant

### Model Validation

The final population pharmacokinetic model 23 for benazepril was fitted to 4000 bootstrapped runs to evaluate its stability and performance. The values of all parameter estimates (20<sup>th</sup> and 80<sup>th</sup> percentiles) obtained by bootstrapping are summarized in Table 8 along with the parameter estimates of the final model.

Table 8. The twentieth and eightieth percentiles of the parameter estimates for benazepril by 4000 bootstrapping runs and typical population parameter estimates of the final model

Parameter	Units	Symbol	20 <sup>th</sup> Percentile	80 <sup>th</sup> Percentile	Typical Value $\pm$ SE
CL	L/h	$\theta_1$	93.9	155	$129 \pm 30.0$
V	L	$\theta_2$	97.6	327	$203 \pm 69.9$
$k_a$	1/h	$\theta_3$	0.52	1.58	$0.88 \pm 0.34$
Variance on CL	--	$\omega^2_{\text{CL}}$	0.21	0.35	$0.11 \pm 0.05$
Age on CL	--	$\theta_6$	8.6	15.8	$13.9 \pm 4.79$
Proportional error term	--	$\theta_4$	0.22	0.39	$0.30 \pm 0.038$
Additive error term	--	$\theta_5$	0.70	0.84	$0.75 \pm 0.06$

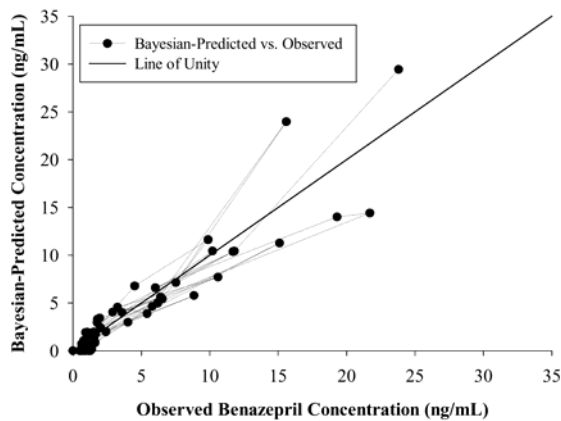
All of the typical values of the parameter estimates, except for  $\omega^2_{\text{CL}}$ , of the final model all fell within the 20<sup>th</sup> and 80<sup>th</sup> percentiles of the respective ones by bootstrapping, indicating that the performance and stability of the final population pharmacokinetic model of benazepril was adequate.

Based on the final model, the following population pharmacokinetic parameters (typical value  $\pm$  SE) were estimated for benazepril: oral clearance (CL:  $129 \pm 30.0$  L/h), apparent volume of distribution (V:  $203 \pm 69.9$  L) and first-order absorption rate constant ( $k_a$ :  $0.88 \pm 0.34$  1/h). Inter-individual variability of the pharmacokinetic parameter was 33.2% for CL. Residual variability consisted of a combined additive (0.75 ng/mL) and a proportional error (54.8%) term.

The plot of Bayesian- predicted benazepril concentrations versus observed concentrations is shown in Figure 2.1.

Figure 2.1.

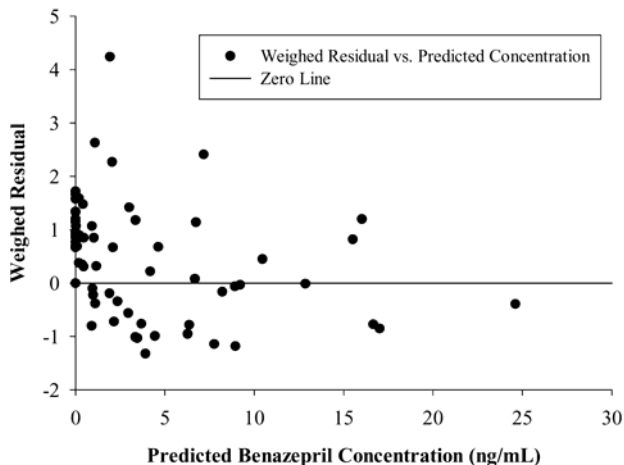
Bayesian-predicted versus observed benazepril concentrations by the final covariate model



Although the predicted vs observed values are distributed around the line of identity, the conclusion on the improvement of the final model with inclusion of covariate cannot be made because the sponsor did not submit the same plot for the base model. The plot of weighted residuals versus predicted benazepril concentrations is shown in Figure 2.2.

Figure 2.2.

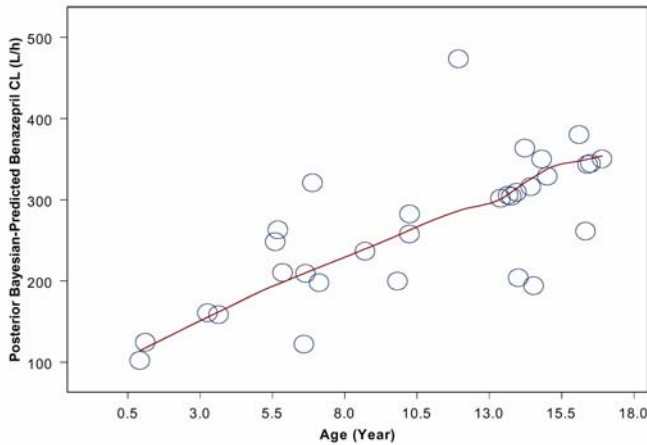
Weighted residuals versus population predicted benazepril concentrations by the final covariate model



The sponsor concluded that no apparent bias was observed in both plots. However, at low plasma concentrations the WRES values are shifted to the positive side.

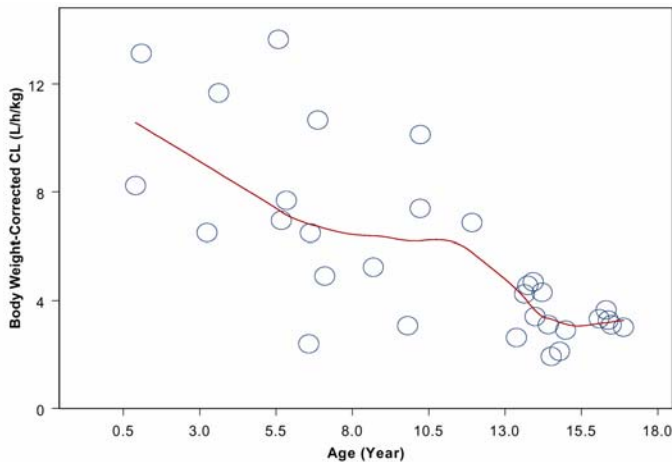
Age was reported as an important covariate on oral clearance of benazepril in these pediatric subjects. The relationship between posterior Bayesian- predicted individual oral clearance of benazepril and corresponding age is depicted in Figure 2.3. A positive correlation between posterior Bayesian- predicted oral clearance of benazepril and age was apparent.

Figure 2.3. Relationship between posterior Bayesian- predicted oral clearance of benazepril and corresponding age (solid line: loess smoothing line)



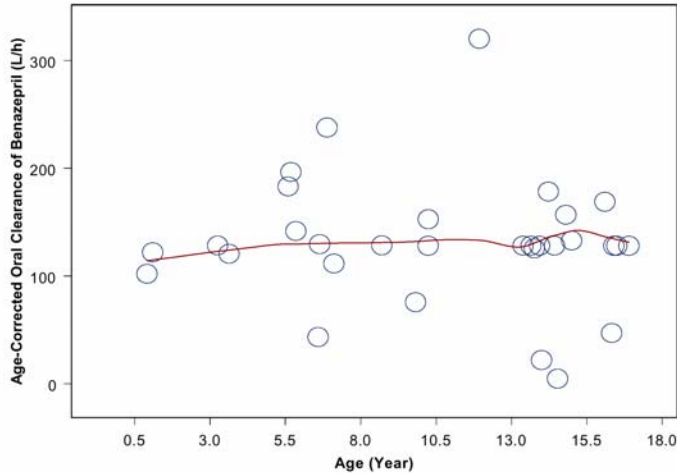
The relationship between body weight- corrected oral clearance of benazepril and age is presented in Figure 2.4. There was a negative trend between body weight- corrected benazepril oral clearance and age in these pediatric subjects.

Figure 2.4. Relationship between body weight- corrected posterior Bayesian- predicted oral clearance of benazepril and corresponding age (solid line: loess smoothing line)



If the individual posterior Bayesian- predicted oral clearance (CL) values are corrected by the following equation derived from the final population pharmacokinetic model (Model 23) for benazepril [ $\text{Age- corrected CL} = \text{CL} - (\text{Age} - 0.9) \times 6 = \text{CL} - (\text{Age} - 0.9) \times 13.9$  (L/ h)] correlation between individual age- corrected clearance and age no longer became apparent, as shown in Figure 2.5.

Figure 2.5. Relationship between age- corrected posterior Bayesian- predicted oral clearance of benazepril and corresponding age (solid line: loess smoothing line)



Nevertheless, substantial inter-subject variability was reported. The summary of the Bayesian- estimated individual oral clearance, body weight- corrected oral clearance and age- corrected oral clearance is presented in Table 9.

Table 9. Summary (mean  $\pm$  SD) of Bayesian- estimated individual oral clearance, body weight- corrected oral clearance and age-corrected oral clearance by age group

Parameter	Infants/Toddlers (1 to $\leq$ 24 months) (N = 2)	Pre-school Children ( $>2$ to $\leq$ 6 years) (N = 5)	School-age Children ( $>6$ to $\leq$ 12 years) (N = 9)	Adolescent ( $>12$ to $\leq$ 16 years) (N = 15)
CL (L/h)	113 $\pm$ 16.0	208 $\pm$ 48.3	256 $\pm$ 99.5	311 $\pm$ 54.0
BW-corrected CL* (L/h/kg)	10.7 $\pm$ 3.5	9.3 $\pm$ 3.2	6.3 $\pm$ 2.8	3.4 $\pm$ 0.8
Age-corrected CL** (L/h)	112 $\pm$ 14.2	154 $\pm$ 33.9	148 $\pm$ 83.9	116 $\pm$ 50.5

After age correction, the mean CL of benazepril appeared to be comparable among age groups.

If consider only pediatric patients who had the efficacy and safety data in this clinical study, this plot contains only 53 data points from 27 patients. Due to the small sample size of the two youngest age groups, their parameter estimations cannot be considered as

reliable results. Figure 2-6 shows the relationship of benazepril clearance and body weight for patients of 6 to 16 years of age.

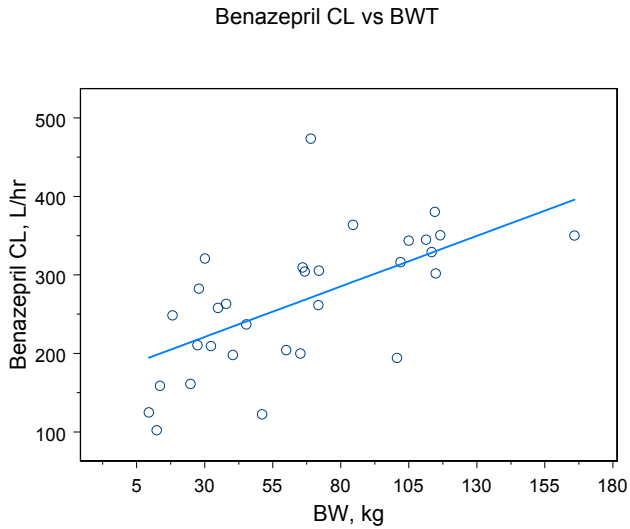


Figure 2-6. Benazepril clearance vs body weight for patients of 6 to 16 years of age.

**BENAZEPRILAT PHARMACOKINETICS**

**Base Population Pharmacokinetic Model Development**

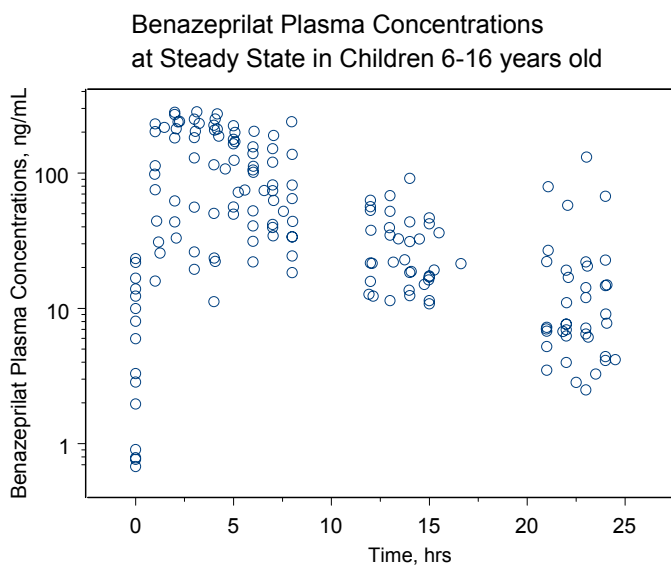
Plasma samples (n = 281) were assayed for benazeprilat concentrations in 57 pediatric subjects (age: 0.91 to 16.9 years). Of these 281 concentrations, two hundred and nine were greater than the limit of quantitation from 56 pediatric subjects (age: 0.91 to 16.9 years). A summary of baseline demographic continuous data for subjects included in the NONMEM analysis is illustrated in Table 10.

Table 10. Characteristics of the pediatric subjects (continuous data) included in the NONMEM analysis for benazeprilat (N = 56)

<b>Characteristic</b>	<b>Mean ± Standard Deviation</b>	<b>Median (Minimum – Maximum)</b>
Age (year)	10.4 ± 4.8	10.8 (0.91 – 16.9)
Weight (kg)	59.4 ± 37.9	48.9 (9.5 – 165.9)
Height (cm)	141 ± 30.3	146 (72 – 190)
Dose (mg/day)	13.5 ± 12.0	10 (2.2, 80)
Dose (mg/kg/day)	0.295 ± 0.260	0.210 (0.083, 1.63)

Characteristic	Number (%) of Subjects
Gender	
Female	30 (54%)
Male	26 (46%)
Ethnic Origin	
Caucasian	32 (57%)
Black	19 (34%)
Other	5 (9%)
Disease	
Other Medical Conditions (proteinuria)	7 (12.5%)
Hypertension	49 (87.5%)

A one-compartment pharmacokinetic model was chosen over a two-compartment pharmacokinetic model for fitting of benazeprilat plasma concentration-time data. The benazeprilat plasma concentrations in the four studied groups of patients are shown in the Figure 1-2. The benazeprilat plasma concentrations vs time in the pediatric patients of 6 to 16 years of age are shown in Figure below.



The C<sub>max</sub> values in pediatric patients were similar to the same calculated for adults (Study US02) as shown in the Table 11.

Table 11. Mean pharmacokinetic parameters of benazeprilat in adults (Study US02).

Benazeprilat	AUC	AUC <sub>inf</sub>	C <sub>max</sub>
Mean	990.2	1072.4	180.2
SD	334.1	316.1	55.9

Several error models, i. e., additive, proportional, exponential, and heteroscedastic error models, were tested for describing residual error during the population modeling process.

An exponential model was found to best describe the residual variability in plasma concentrations of benazeprilat.

All tested intermediate models for benazeprilat are listed in Table 12.

The parameter estimates from the base one- compartment model of benazeprilat along with the inter- subject variability parameters associated with the apparent clearance (CL), apparent volume of distribution (V) and absorption rate constant are shown in Table 12.

Table 12.

Test Model	Reference Model	Objective function value (OFV)	Change in OFV	Description of the model	Comment
1	-	1873.6	-	2-CPT, Exponential error model	-
2	-	1821.9	-	2-CPT, Proportional/Additive error model	-
3	-	1874.0	-	2-CPT, Proportional error model	-
4	-	2006	-	2-CPT, Additive error model	-
5	-	1544.7	-	1-CPT, Proportional/Additive error model, ETAs for CL, V	-
6	-	-	-	1-CPT, Additive error model, ETAs for CL, V	Prematurely terminated
7	-	1497.1	-	1-CPT, Proportional model, ETAs for CL, V	-
8	-	1497.1	-	1-CPT, Exponential model, ETAs for CL, V	Base Model

Table 13. Parameter estimates from the base population pharmacokinetic model for benazeprilat (Model 8) in 56 pediatric subjects

Parameter	Units	Symbol	Estimate	SE of Estimate
CL	L/h	$\theta_1$	10.8	1.43
V	L	$\theta_2$	87.9	22.9
$k_a$	1/h	$\theta_3$	0.701	0.128
Variance on CL	--	$\omega^2_{CL}$	0.406	0.113
Variance on V	--	$\omega^2_V$	1.12	0.487
Residual variance	--	$\sigma_1^2$	0.105	0.0172

For the base model, the inter-individual variability was very high (for CL 63.7%, and for V 105%).

#### Covariate Population Pharmacokinetic Model Development

Table 14 shows the steps of including the covariates into the model.

Table 14.

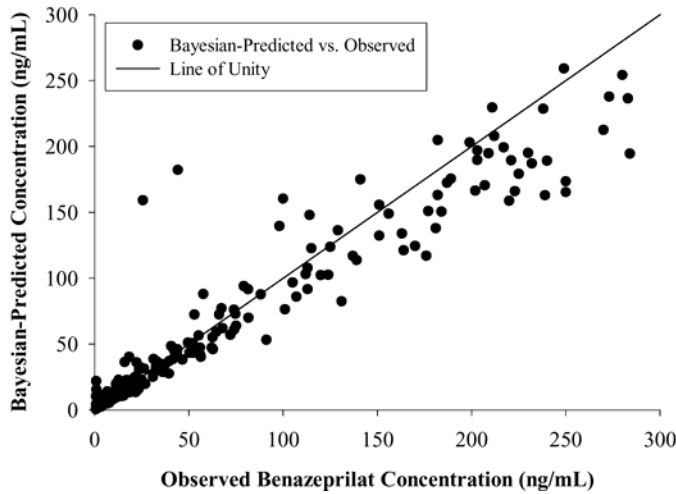


Test Model	Reference Model	Objective function value (OFV)	Change in OFV	Description of the model	Comment
9	8	1570.7	+73.6	CL vs. AGE (exponential)	NS
10	8	1481.8	-15.3	CL vs. BW (exponential)	Rounding error
11	8	1487.6	-9.5	CL vs. BW ('Emax')	Rounding error
12	8	-	-	CL vs. BW (Linear)	Prematurely terminated
13	8	1496.2	-0.9	CL vs. SEX	NS
14	8	1520.9	+23.8	CL vs. RACE (RACE = 1 )	Rounding error
Test Model	Reference Model	Objective function value (OFV)	Change in OFV	Description of the model	Comment
15	8	1491.8	-5.3	CL vs. RACE (RACE = 2 )	Rounding error
16	8	-	-	CL vs. AGE (linear)	Prematurely terminated
17	8	1497.8	+0.7	CL vs. RACE (RACE = 4)	NS
18	8	1494.8	-2.3	CL vs. HT (exponential)	Rounding error
19	8	1479.3	-17.8	CL vs. HT ('Emax')	Covariance aborted
20	8	1468.2	-28.9	CL vs. AGE ('Emax') Final Model	SIG
21	8	1641.3	+144.2	V vs. AGE (exponential)	NS
22	8	-	-	V vs. BW (exponential)	Prematurely terminated
23	8	1489.2	-7.9	V vs. AGE ('Emax')	Covariance aborted
24	8	1562.9	+65.8	V vs. BW ('Emax')	NS
25	8	1520.7	+23.6	V vs. RACE (RACE = 1)	NS
26	8	1495.8	-1.3	V vs. RACE (RACE = 2)	NS
27	8	1570.4	+73.3	V vs. RACE (RACE = 4)	Rounding error
28	8	1478.7	-18.4	V vs. SEX	SIG
29	8	-	-	V vs. HT (exponential)	Prematurely terminated
30	8	1512.8	+15.7	V vs. HT ('Emax')	Rounding error
31	20	1466.6	-1.6	V vs. SEX + CL vs. AGE ('Emax')	NS

From all tested covariates only age influenced significantly clearance and sex the volume of distribution. Figure 3.1 shows the plot of predicted with the final model vs observed plasma concentrations of benazeprilat. It is not clear, if these are individual predictions or population predictions. Nevertheless, the plot is skewed at high plasma concentration values, therefore, the model underpredicts the benazeprilat plasma concentrations.

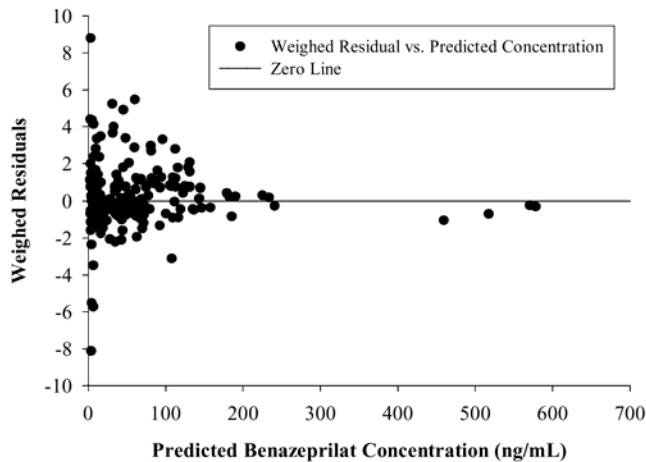
The sponsor did not show graphically how inclusion of these covariates improved the fit. Only final proposed model results were explored graphically.

Figure 3.1 Bayesian-predicted versus observed benazeprilat concentrations by the final covariate model



The plot of weighted residuals versus predicted benazeprilat concentrations is shown in Figure 3.2.

Figure 3.2 Weighted residuals versus population predicted benazeprilat concentrations by the final covariate model



For the final model, the sponsor selected the only covariate age for CL with the explanation as follows:  
“The one- compartment population pharmacokinetic model (Model 20) with covariate of age on apparent clearance was identified as the final model because it had the largest decrease in OFV “.

### Effect of Age on Apparent Clearance of Benazeprilat

Age was reported by the sponsor as an important covariate on apparent clearance of benazeprilat in these pediatric subjects. Figure 3.3 shows the relationship between the predicted individual apparent clearance of benazeprilat and age. The relationship between body weight- corrected apparent clearance of benazeprilat and age is presented in Figure 3.4. After the apparent clearance of benazeprilat was corrected by body weight, the relationship between body weight- corrected benazeprilat apparent clearance and age in these pediatric subjects became less apparent.

Figure 3.3 Relationship between posterior Bayesian-predicted oral clearance of benazeprilat and corresponding age (solid line: loess smoothing line)

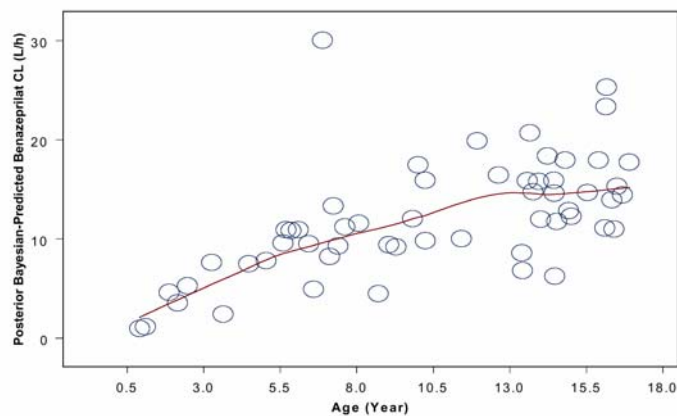
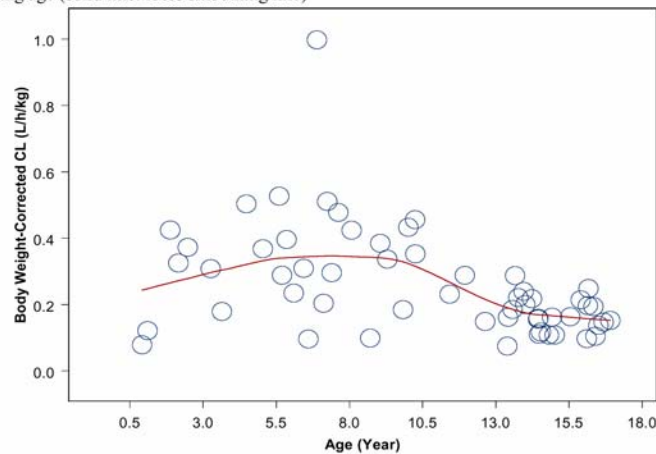


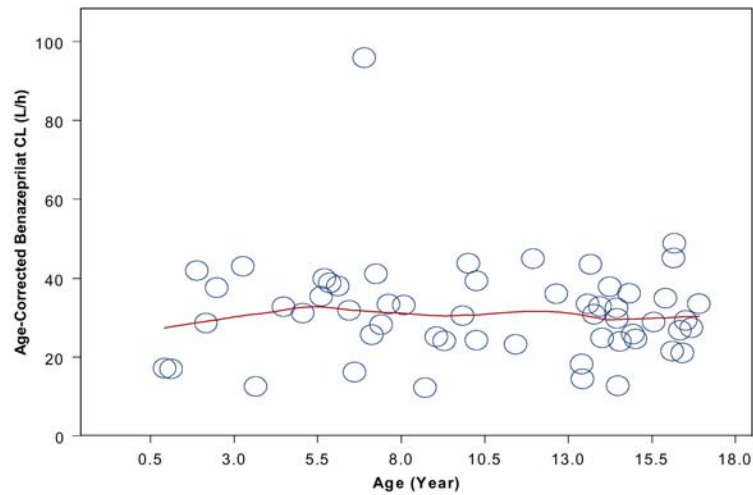
Figure 3.4 Relationship between body weight-corrected posterior Bayesian-predicted apparent clearance of benazeprilat and corresponding age (solid line: loess smoothing line)



If the individual posterior Bayesian- predicted apparent clearance (CL) values are corrected by the following equation derived from the final population pharmacokinetic model (Model 20) for benazeprilat, correlation between individual age- corrected clearance and age no longer became apparent, as shown in Figure 3.5.

$$\text{Age corrected CL} = \text{CL} \times (\text{Age} + 4) / \text{Age} = \text{CL} \times (\text{Age} + 15.1) / \text{Age} \text{ (L/h)}$$

Figure 3.5 Relationship between age-corrected posterior Bayesian-predicted apparent clearance of benazeprilat and corresponding age (solid line: loess smoothing line)



The sponsor did not mention if the inter-subject variability decreased after the incorporation of age into the model. However, substantial inter-subject variability was noted in the final model.

The summary of the Bayesian-estimated individual apparent clearance, body weight-corrected apparent clearance and age-corrected apparent clearance for benazeprilat is presented in Table 15.

Table 15. Summary (mean  $\pm$  SD) of Bayesian-estimated individual apparent clearance, body weight-corrected and age-corrected apparent clearance for benazeprilat by age group

Parameter	Infants/Toddlers (1 to $\leq$ 24 months) (N = 3)	Pre-school Children ( $>2$ to $\leq$ 6 years) (N = 9)	School-age Children ( $>6$ to $\leq$ 12 years) (N = 18)	Adolescent ( $>12$ to $\leq$ 16 years) (N = 26)
CL (L/h)	2.3 $\pm$ 2.1	7.3 $\pm$ 3.0	12.1 $\pm$ 5.9	14.8 $\pm$ 4.5
BW-corrected CL* (L/h/kg)	0.209 $\pm$ 0.188	0.363 $\pm$ 0.107	0.351 $\pm$ 0.203	0.166 $\pm$ 0.05
Age-corrected CL** (L/h)	25.4 $\pm$ 14.3	33.4 $\pm$ 9.0	34.0 $\pm$ 17.9	29.9 $\pm$ 8.8

### Model Validation (Bootstrapping)

The final population pharmacokinetic model for benazeprilat was fitted to the 4000 bootstrapped samples to evaluate its stability and performance. The values of all parameter estimates (20<sup>th</sup> and 80<sup>th</sup> percentiles) obtained by bootstrapping are summarized in Table 16 along with the parameter estimates of the final model.

Table 16. The twentieth and eightieth percentiles of the parameter estimates for benazeprilat by 4000 bootstrapping runs and typical population parameter estimates of the final model

Parameter	Units	Symbol	20 <sup>th</sup> Percentile	80 <sup>th</sup> Percentile	Typical Value $\pm$ SE
CL	L/h	$\theta_1$	21.5	115	30.3 $\pm$ 12.2
V	L	$\theta_2$	82.8	114	90.4 $\pm$ 20.2
k <sub>a</sub>	1/h	$\theta_3$	0.76	3.59	0.755 $\pm$ 0.157
Age on CL	--	$\theta_4$	14.0	157	15.1 $\pm$ 9.59
Inter-subject variance on CL	--	$\omega^2_{CL}$	0.44	0.67	0.22 $\pm$ 0.06
Inter-subject variance on V	--	$\omega^2_V$	0.77	1.55	0.74 $\pm$ 0.39
Residual variance	--	$\sigma_1^2$	0.27	0.36	0.11 $\pm$ 0.02

The typical value of the parameter estimates (except  $\omega^2_{CL}$ ,  $\omega^2_V$  and  $\sigma_1^2$ ) of the final model all fell within the 20 th and 80 th percentiles of the respective ones by bootstrapping.

The following population pharmacokinetic parameters (typical value  $\pm$  SE) were estimated for benazeprilat: apparent clearance (CL: 30.3  $\pm$  12.2 L/ h), apparent volume of distribution (V: 90.4  $\pm$  20.2 L) and first-order metabolic conversion/ absorption rate constant (k<sub>a</sub>: 0.76  $\pm$  0.16 1/ h). Inter- individual variability of the benazeprilat pharmacokinetic parameters was 46.9% for CL and 86.0% for V. Residual variability was estimated to be 33.2%.

#### Effect of Sex on Apparent Volume of Distribution for Benazeprilat

Sex was also identified as significant covariate on the apparent volume of distribution of benazeprilat in these pediatric subjects. The box plot of posterior Bayesian- predicted apparent volume of distribution of benazeprilat versus sex (1 for male and 2 for female) is shown in Figure 3.6.

Females appeared to have smaller apparent volume of distribution for benazeprilat than males in these pediatric subjects. However, when both age and sex were included in the final model, the change in the objective function was only 1.6 units. The sponsor rejected the hypothesis of the influence of sex on V and concluded that the clinical relevance of gender influence on V is not anticipated to be significant.

The sponsor concluded that only age influenced significantly clearance. The covariates were not tested with the model reducing technique using more sensitive approach ( $p < 0.005$ ), therefore, the conclusion on the significance of the chosen covariates has not been proven by the sponsor.

The Figure 3.7 shows the relationship between benazeprilat clearance and body weight.

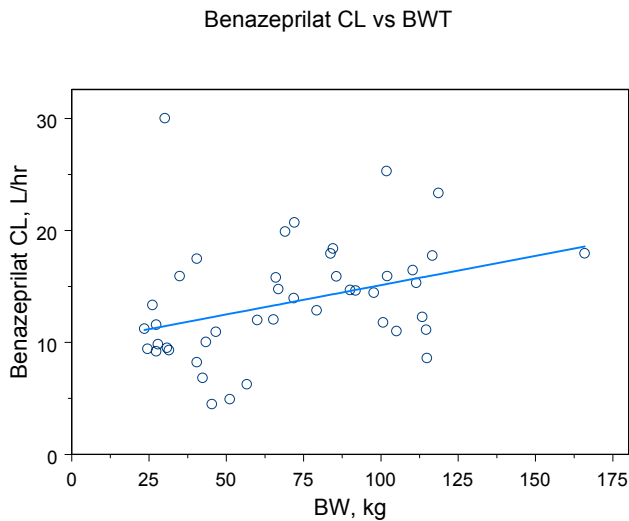


Figure 3.7. Benazeprilat clearance values vs body weight in pediatric patients of 6 to 16 years of age.

COMMENTS:

1. A multiple dose pharmacokinetic study was conducted in 57 hypertensive male and female pediatric patients aged 1 to <16 years following daily oral administration of 0.1 to 0.5 mg/kg benazepril HCL.
2. The sponsor used the data from all patients to develop a population model. The base model development was performed satisfactorily for both benazepril and benazeprilat. The sponsor may consider modeling the pharmacokinetic of parent drug and metabolite simultaneously.
3. The covariate model development is lacking the important part of model validation: after covariate adding one by one into the model, the sponsor did not perform deletion of the covariates from the model which was assumed to be final. The sponsor concluded that the only significant covariate affecting clearance for both benazepril and benazeprilat is age. The appropriateness of the final model is not convincing. The graphic exploration of the data by the reviewer indicates that clearances of both benazepril and benazeprilat depend on body weight.
4. Body weight corrected benazepril clearance in pediatric patients was 6.3 and 3.4 L/hr/kg for school age children (6 to 12 years old) and adolescents (12 to 16 years old) respectively. These values are higher than the same values calculated for the healthy children (2.2 and 2.9 L/hr/kg) and for adults (1.45 L/hr/kg) and are in agreement with the slightly lower plasma concentrations profiles of benazepril found in the patients in comparison with healthy children.
5. Body weight corrected benazeprilat clearance was 0.351, and 0.166 L/hr/kg for two pediatric groups respectively. These values were comparable with the

same for healthy children (0.258 and 0.169 L/hr/kg) and adults (0.132 L/hr/kg). The plasma benazeprilat profiles were similar for both studies in pediatric patients and healthy children.



## 6.2 Proposed Package Insert

6.2.1.1.1  NOVARTIS

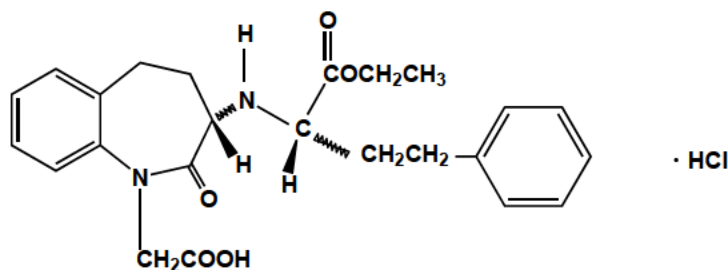
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~~89008505~~

**LOTENSIN<sup>®</sup>**  
**benazepril hydrochloride**  
**Tablets**  
**Rx only**  
**Prescribing Information**

**Use in Pregnancy** When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Lotensin should be discontinued as soon as possible. See **WARNINGS, Fetal/Neonatal Morbidity and Mortality.**

### DESCRIPTION

Benazepril hydrochloride is a white to off-white crystalline powder, soluble (>100 mg/mL) in water, in ethanol, and in methanol. Benazepril's chemical name is 3-[[1-(ethoxy-carbonyl)-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-(3S)-benzazepine-1-acetic acid monohydrochloride; its structural formula is



Its empirical formula is  $C_{24}H_{28}N_2O_5 \cdot HCl$ , and its molecular weight is 460.96.

Benazeprilat, the active metabolite of benazepril, is a non-sulphydryl angiotensin-converting enzyme inhibitor. Benazepril is converted to benazeprilat by hepatic cleavage of the ester group.

Lotensin is supplied as tablets containing 5 mg, 10 mg, 20 mg, and 40 mg of benazepril hydrochloride for oral administration. The inactive ingredients are cellulose compounds, colloidal silicon dioxide, crospovidone, hydrogenated castor oil (5-mg, 10-mg, and 20-mg tablets), iron oxides, lactose, magnesium stearate (40-mg tablets),

### 6.3 Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
General Information About the Submission				
	Information			Information
NDA Number	19,851 SE5 028	Brand Name		Lotensin
OCPB Division (I, II, III)	DIV-1	Generic Name		Benazepril HCL
Medical Division	CARDIORENAL	Drug Class		ACE inhibitor
OCPB Reviewer	ELENA MISHINA	Indication(s)		HYpertension
OCPB Team Leader	P. Marroum	Dosage Form		5, 10, 20, and 40mg tablets
		Dosing Regimen		0.2 mg/kg <sup>(b) (4)</sup> once daily
Date of Submission	April 25, 2003	Route of Administration		ORAL
Estimated Due Date of OCPB Review		Sponsor		NOVARTIS
PDUFA Due Date		Priority Classification		Standard
Division Due Date				
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) -				
<i>Healthy Volunteers-</i>				
single dose:	X	2		
multiple dose:				
<i>Patients-</i>				
single dose:	X	1		
multiple dose:	X	1		
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:	X	2		
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:	X	1		Safety evaluation
Population Analyses -				
Data rich:	X	1		
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	X	1		
solution as reference:				
alternate formulation as reference:	X	1		
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		
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	4			
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 pediatric patients adequate?			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 19-851, HFD-850(Lee), HFD-860(Marroum, Mehta, Mishina), Biopharm (CDER)

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

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Elena Mishina  
10/16/03 02:19:40 PM  
BIOPHARMACEUTICS

Patrick Marroum  
10/16/03 02:42:44 PM  
BIOPHARMACEUTICS