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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-386/S-019 and 029

**Clinical Pharmacology and Biopharmaceutics
Review**

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA: 20,386 SE5 029
Submission Dates: December 21, 2001, March 13 and 26, June 28 and 19, 2002
Drug Name: Cozaar (losartan potassium) tablets
Applicant: Merck Pharmaceutical Group
Submission: Supplemental NDA, pediatric exclusivity
Reviewer: Elena V. Mishina, Ph.D.

EXECUTIVE SUMMARY

This NDA review evaluates whether the sponsor has adequately characterized the pharmacokinetics of COZAAR™ (losartan potassium) in the pediatric patients, whether the pharmacokinetics of losartan in children and in adults is similar, and therefore, whether the sponsor made proper changes in the Package Insert for the pediatric patients. Losartan was the first angiotensin II antagonist approved for the treatment of hypertension in adults. Prior to the data reported in this submission, there were no data from prospective, controlled, adequately sized studies with an angiotensin II antagonist in pediatric patients. NDA 20,386 SE5-029 describes the results of 2 studies conducted in pediatric patients: an open-label study to investigate the pharmacokinetics of losartan in hypertensive children and infants (Protocol 225); and a double-blind, randomized dose-response study of losartan in children with hypertension (Protocol 227). This submission also provides information concerning preparation of a suspension formulation of losartan, and data from an open-labeled, 2-period crossover study conducted in healthy adults to determine the relative bioavailability of the losartan suspension 50 mg and marketed COZAAR™ 50-mg tablets (Protocol 216).

The study (Protocol 216) compared the pharmacokinetic profiles of losartan and its active metabolite (5-carboxy-derivative) following single-dose oral administration of the losartan 50-mg suspension and the losartan 50-mg tablet. Losartan tablet was bioequivalent to the suspension formulation by exposure (AUC) but not by C_{max}. C_{max} values obtained for the treatment with the losartan suspension were about 20% higher than the same values for losartan tablet, and the difference was statistically significant. Losartan tablet was bioequivalent to the suspension formulation in respect to its active metabolite both by AUC and C_{max}. The medical reviewer should assess if the 20% higher will pose additional safety concerns.

The study (Protocol 225) estimated plasma and urine pharmacokinetic parameters of losartan and its metabolite in infants and toddlers, preschool children, school-age children, and adolescents and investigated the safety and tolerability of losartan in children. The dose of losartan suspension used in this study was 0.7 mg/kg, to a maximum of 50 mg, equivalent to the adult starting dose (50 mg in a 70-kg adult = 0.7

mg/kg). The sponsor performed a non-compartmental data analysis. The reviewer applied a two-stage population approach to those results. The pharmacokinetic parameters of losartan (C_{max} , $AUC_{0-\infty}$, AUC_{0-t} , CL/F , V/F) estimated for children older than 6 and younger than 16 years old were similar to the same parameters reported for adults in the same submission (Study 216). Geometric mean C_{max} values of losartan and metabolite in adults were 174 and 218 ng/mL, and in children ranged from about 91 to 140 and about 128 to 251 ng/mL, respectively. Geometric mean AUC_{0-24} values of losartan and metabolite were 388 and 1814 ng·hr/mL in adults, and in children ranged from about 233 to 405 and about 933 to 2186 ng·hr/mL, respectively. Mean renal clearance values reported in the Package Insert for losartan and its metabolite were 75 and 25 mL/min in adults. Mean renal clearance for losartan in children ranged from 45 to 56 mL/min/1.73 m² and for metabolite ranged from 16 to 18 mL/min/1.73 m². Importantly, exposures were not higher in children of any age group compared to similar values in adults when given according to mg/kg dosing. Mean apparent total clearance and volume of distribution values for losartan estimated in adults (Study 216) were 120 L/hr and 443 L and in children population prediction values were 101 L/hr and 416 L. In the current Package Insert, losartan clearance and volume of distribution, upon administration of IV losartan, are 36 L/hr (600 mL/min) and 34 L, and for metabolite 3 L/hr (50 mL/min) and 12 L when the metabolite was given IV, respectively.

The study 227 was designed as safety and effectiveness study to assess whether losartan lowered blood pressure in a dose-dependent manner. Plasma samples were not obtained during this study and only dose-response relationship was evaluated. The data demonstrated that increasing doses of losartan resulted in greater reductions in blood pressure. When part of the patients were withdrawn to placebo, the overall mean increase of sitting diastolic blood pressure was 4.40 mm Hg (statistically significant, $p=0.0046$). Considering the fact that the confounding contributions of the free parent and metabolite concentrations to the overall reduction in blood pressure will limit the interpretability, the reviewer did not conduct any additional PK/PD modeling. no .

RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation I has reviewed the pediatric information included in the Supplement SE5 029 to NDA 20,386. The Office of Clinical Pharmacology and Biopharmaceutics recommends adopting the proposed language for the labeling. The recommended starting dose of 25 mg (slightly less than 0.7 mg/kg) once daily for an average 45 kg child appears to be adequate and comparable with the recommended starting dose of 50 mg for an average 70 kg adult. The pharmacokinetic parameters of losartan and its metabolite in children and adults have moderately high variability. This variability (the range of the estimated parameters) should be reported in the Package Insert. Additionally, the label should include the values and range of peak plasma concentrations and exposures (AUCs) for losartan and its active metabolite. The updated PI should include corrected values for the pharmacokinetic parameters.

/s/

Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

Date _____

/s/

Joga Gobburu, Ph. D.
Pharmacometrics Team Leader

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

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| <u>Study 216</u> . An Open-Labeled, Randomized, Two-Period, Crossover Study to Determine the Relative Bioavailability of Losartan 50-mg Suspension and Losartan 50-mg Tablet Administered Orally as Single Doses. | |
| <u>Study 225</u> An Open-Label Study To Investigate The Pharmacokinetics Of Losartan In Hypertensive Children And Infants. | |
| <u>Study 227</u> A Double-Blind, Randomized Dose-Response Study Of Losartan In Children With Hypertension. | |

SUMMARY OF CPB FINDINGS

Background:

Merck Pharmaceutical Group is seeking approval of COZAAR (losartan potassium) in pediatric population and is requesting an additional six months of marketing exclusivity based on submission of the information in the supplemental NDA 20,386. COZAAR (losartan potassium), the first of a new class of antihypertensives, is an angiotensin II receptor (type AT1) antagonist, which is approved for use in adults in the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. The usual starting dose of COZAAR in adults is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume.

Losartan and its principal active metabolite (5-carboxy- derivative) 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 than losartan and appears to be a reversible, non-competitive inhibitor of the AT1 receptor.

Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes (14% of an orally administered dose of losartan is converted to the active metabolite). The half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours with linear pharmacokinetics after oral losartan once-daily doses up to 200 mg and no accumulation in plasma. The systemic bioavailability of losartan is about 33%. Both losartan and its active metabolite are highly bound to plasma proteins, (free fractions of 1.3% and 0.2%).

The volume of distribution of losartan reported for adults is about 34 L and of the active metabolite is about 12 L. Total plasma clearance of losartan and the active metabolite is about 36 L/hr and 3 L/hr, with renal clearance of about 4.5 L/hr and 1.5 L/hr, respectively.

About 14% of an orally administered dose of losartan converts to the active metabolite. 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. 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. Therefore, relative exposure to losartan is approximately ten-fold larger than the exposure to its metabolite. The active metabolite is 10 to 40 times more potent than losartan. Therefore, the effects of both losartan and its metabolite after the dose of losartan might be similar..

Basic pharmacokinetic parameters in children are unknown. Literature reports (FDA search revealed publications for the key words combination 'cozaar and pediatrics' -0, for 'cozaar and children'-2, for 'losartan and children'- 37. None of these publications reported the results of clinical study of losartan in children with hypertension. Dose recommendations in children has not been established.

Current Submission:

The primary objective of this Application was to obtain Pediatric Exclusivity for Cozaar, to evaluate the efficacy and safety of losartan in pediatric population, and to provide the labeling changes related to the losartan use in children. In this Application, NDA 20,386 SE5-029, the sponsor included 3 studies. These were

Study 216: "An open-labeled, randomized, two-period, crossover study to determine the relative bioavailability of losartan 50-mg suspension and losartan 50-mg tablet administered orally as single doses,"

Study 225: "An open-label study to investigate the pharmacokinetics of losartan in hypertensive children and infants," and

Study 227: "A double-blind, randomized dose-response study of losartan in children with hypertension."

In addition to the clinical studies described above, this submission presents data from the sponsor's Database, a losartan chart review study in a pediatric nephrology practice, as well as a review of the clinical literature regarding the use of losartan in pediatric patients.

REVIEWER COMMENTS

GENERAL

1. The Agency considered that the information provided in the Supplement No. SE5 029 to NDA 20,386, for Cozaar tablets 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.

CLINICAL PHARMACOLOGY COMMENTS

2. Pharmacokinetics of losartan and its metabolite were properly characterized in Study 225. Pharmacokinetics of losartan and its metabolite in plasma in pediatric population of 6 to 16 years of age and in adults (Study 216) were similar.
3. Clinical study Protocol 227 included effectiveness and safety data of losartan administration to children (6 to 17 years old) in the dose range of 2.5 and 50 mg per day. The medical reviewer of DCRDP is evaluating this study.

Labeling Comments: (an annotated labeling is provided)

1. Special populations: Pediatrics: The sponsor proposed the starting dose of 0.75 mg/kg (up to 50 mg) once daily in children. This dose is similar to the dose recommended for adults (50 mg for 70 kg person is resulting in 0.7 mg/kg). Since the pharmacokinetics of losartan and its metabolite were similar in children and adults, no dose adjustment except for the body weight is required. However, since the effectiveness and safety of losartan were evaluated only in children older than 6 years of age, the drug should not be recommended for use in r patients less than 6 years of age. The reviewer agrees with the starting dose of 25 mg in children with possible titration up to 100 mg. The suggested labeling is as follows:

"Special Populations

Pediatric: [

2. Dosing Recommendations:

Although, normally, patients older than 6 years of age can swallow tablets, there could be some children and elderly patients who might benefit from a suspension preparation. It was found that the metabolite kinetics of the suspension and tablet were bioequivalent, but the parent kinetics were not bioequivalent. The reviewer agrees with the sponsor's proposal to include the suspension preparation in the labeling, provided that the medical reviewer feels that there would be no additional safety concern with the 20% increase in the parent C_{max} when compared to the tablets. Conditional upon the medical reviewer's assessment, the preparation of the suspension should be included in the labeling. Also, additional changes in this section are recommended, as shown below:

"Pediatric Hypertensive Patients

3. Pharmacokinetics: General: The label currently included one single value for clearance and volume of distribution at steady-state (V_{ss}) of losartan and its active metabolite calculated from the IV data. The current labeling language does not clearly specify that these parameters are for the IV data of losartan and metabolite administered separately. A review of the original NDA indicates that a wide range of pharmacokinetic parameters determined in several studies using oral dosing. Hence it might be informative to update the labeling with the range of the pharmacokinetic parameters, determined after oral dosing. Also, AUC and C_{max} ranges need to be included and not just clearance and volume. The suggested labeling is as follows:

[

]

**APPEARS THIS WAY
ON ORIGINAL**

QUESTION BASED REVIEW

1. Were Cozaar administered as suspension and as tablet bioequivalent?

No. The results of Study 216 showed that the AUCs of the losartan suspension and losartan tablets in healthy volunteers were similar but Cmaxs were not. Losartan metabolite after the dose of losartan tablet was bioequivalent to the same dose administered as a suspension both by AUC and Cmax.

The sponsor has developed a liquid formulation of losartan in order to administer losartan to children, who are not able to swallow the tablet. Additionally, this formulation may afford dosing flexibility (administration of the dose based on body weight) and may support a starting dose of 25 mg for children with respect to pharmacokinetics. This study compared the relative bioavailability of losartan 50-mg suspension and losartan 50-mg tablet following single-dose oral administration of the losartan 50-mg suspension and the losartan 50-mg tablet.

For this study, the losartan suspension was prepared from the clinical image 50 mg tablet (differing only from the market image — by suspending in Ora-Sweet SFT™ and OraPlus™. The 50-mg dose of the suspension (20 mL of 2.5 mg/mL losartan suspension) was selected for this study given that 50 mg once daily is the usual starting dose of COZAAR™ when treating patients with hypertension.

This was an open-labeled, randomized, 2-period, crossover study in 12 healthy adult volunteers.

Losartan and its metabolite plasma profiles for both formulations are shown in Figure 1.

Mean (SD) Plasma Concentrations of Losartan and L-158641 (EXP-3174) Following Administration of Single Oral Doses of Losartan 50-mg Tablet and 20 mL of 2.5 mg/mL Losartan Suspension

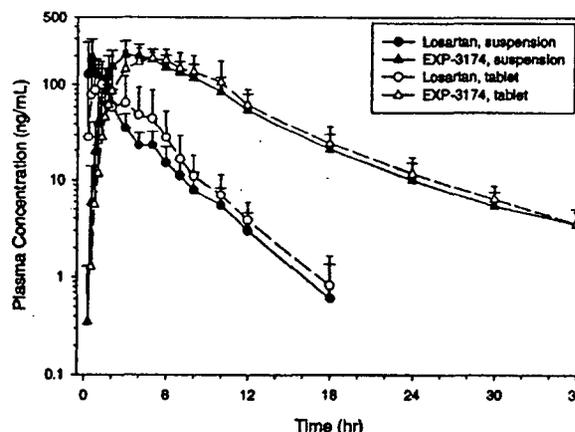


Figure 1. Mean plasma losartan (circles) and its metabolite (triangles) concentrations. Open symbols are for the tablet, and closed symbols are for the suspension formulation.

The 90% confidence intervals (CI) were constructed on the log-transformed parameters ($AUC_{0-\infty}$, AUC_T and plasma C_{max}) for both losartan and its metabolite. The geometric mean ratio and 90% CI are shown in Table 1 (losartan) and Table 2 (metabolite).

Table 1.

Summary of Statistical Analyses—
 Losartan AUC and C_{max} Potency Normalized to the 50-mg Dose

| Variable | Geometric Mean | | Geometric Mean Ratio [†] | p-Value | Within-Subject MSE | df |
|-------------------------------------|-------------------------|-------------------------|-----------------------------------|---------|--------------------|----|
| | Suspension | Tablet | | | | |
| $AUC_{0-\infty}$ ng·hr/mL 90% CI | 366.3 (309.1, 434.1) | 395.0 (333.3, 468.1) | 0.927 (0.834, 1.031) | 0.229 | 0.0288 | 14 |
| AUC_T ng·hr/mL 90% CI | 358.4 (301.4, 426.1) | 387.7 (326.1, 461.0) | 0.924 (0.830, 1.029) | 0.219 | 0.0299 | 14 |
| C_{max} ng/mL 90% CI | 208.1 (167.2, 259.1) | 174.2 (140.0, 216.9) | 1.195 (0.984, 1.450) | 0.128 | 0.0968 | 14 |

Table 2.

Summary of Statistical Analyses—
 L-158641 [E-3174] AUC and C_{max} Potency Normalized to the 50-mg Dose

| Variable | Geometric Mean | | Geometric Mean Ratio [†] | p-Value | Within-Subject MSE | df |
|-------------------------------------|----------------------------|----------------------------|-----------------------------------|---------|--------------------|----|
| | Suspension | Tablet | | | | |
| $AUC_{0-\infty}$ ng·hr/mL 90% CI | 1813.7 (1608.0, 2045.8) | 1787.1 (1584.4, 2015.7) | 1.015 (0.912, 1.129) | 0.811 | 0.0295 | 14 |
| AUC_T ng·hr/mL 90% CI | 1781.1 (1578.3, 2009.9) | 1755.8 (1555.9, 1981.4) | 1.014 (0.910, 1.131) | 0.820 | 0.0303 | 14 |
| C_{max} ng/mL 90% CI | 219.0 (193.3, 248.2) | 211.4 (186.2, 239.2) | 1.038 (0.910, 1.184) | 0.628 | 0.0448 | 14 |

Losartan tablet was bioequivalent to the suspension formulation by exposure (AUC) but not by C_{max} . C_{max} values obtained for the treatment with the losartan suspension were about 20% higher than the same values for losartan tablet, and the difference was statistically significant. Losartan tablet was bioequivalent to the suspension formulation with respect to its active metabolite both by AUC and C_{max} . Since the suspension formulation had higher C_{max} than tablet formulation, the effectiveness of losartan may not be compromised by the administration of the suspension. The safety of losartan suspension is to be evaluated by the medical officer, specifically to assess if this 20% increase in C_{max} of losartan is relevant.

2. Were the pharmacokinetics of Cozaar adequately characterized in the pediatric population?

Yes. Pharmacokinetics of Cozaar in pediatric population was characterized in study 225. Four groups of pediatric patients included infants and toddlers (1 to 24

months), preschool children (25 months to <6 years), school-age children (6 to <12 years), and adolescents (12 to <16 years). The study groups were well balanced by age and gender (Table 3).

Table 3.

| | Group I (Infants and Toddlers) | Group II (Preschool Children) | Group III (School-Age Children) | Group IV (Adolescents) |
|--------------------|--------------------------------------|-------------------------------------|---------------------------------------|---------------------------|
| ENTERED: Total | 11 | 13 | 12 | 14 |
| Male (age range) | 8 (3 to 23 mo) | 8 (2 to 5 yr) | 8 (6 to 11 yr) | 9 (12 to 15 yr) |
| Female (age range) | 3 (10 to 23 mo) | 5 (2 to 5 yr) | 4 (7 to 8 yr) | 5 (12 to 15 yr) |
| COMPLETED: | 11 | 13 | 12 | 14 |

Children younger than 6 years of age received once daily losartan dose in suspension formulation, all other patients received losartan tablets (12.5, 25, or 50 mg) as approximate dose of 0.7 mg/kg/day. Plasma (up to 36 hours, extensive sampling) and urine (over 24 hours) samples were collected after the dose on day 7. Urine samples were collected only from toilet trained patients. The sponsor estimated AUC₀₋₂₄ and C_{max} for losartan and its metabolite. The patients included in study 225 were heterogeneous. Several patients had chronic or acute renal insufficiency. However, there were only 2 patients with chronic renal insufficiency who were 6 years or older. Since the recruited population was obese, ideal body weight (IBW) was found to be a good predictor of the clearance and volume of distribution of both losartan and its metabolite. The unexplained variability, after adjusting for IBW, was moderately high.

3. Are the pharmacokinetics of Cozaar in pediatric population predictable from those in adults?

Comparison of plasma pharmacokinetic profiles and urinary recovery indicate that the pharmacokinetics of losartan as well as its metabolite were similar in all studied groups of children (given body size adjusted doses) and similar to the pharmacokinetics in adults from study 216.

Figures 2 and 3 show the mean losartan and its metabolite plasma concentrations for all groups. Plasma concentrations at early time points have a very high variability but the plasma concentration profiles of groups III and IV look similar to each other.

Figure 2. Losartan plasma concentrations vs time.

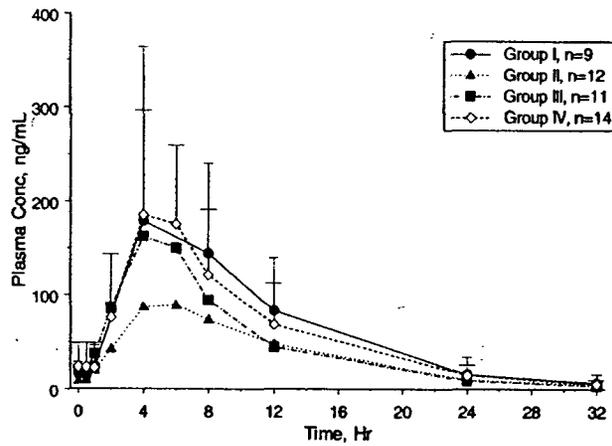
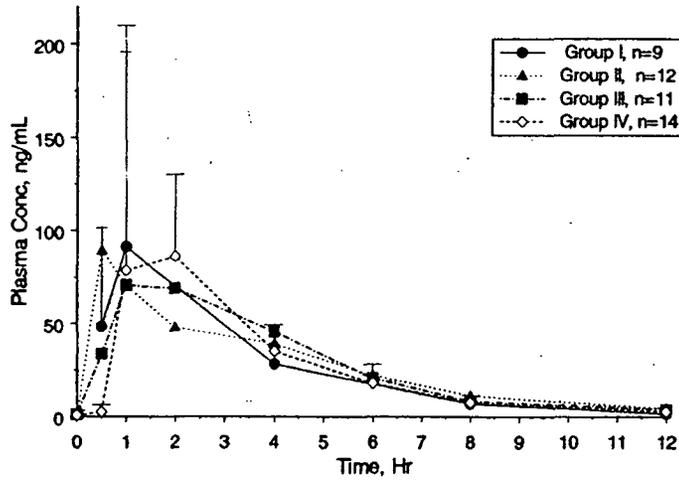


Figure 3. Losartan metabolite plasma concentrations vs time.



As shown in the Figure 4, the C_{max} and AUC values in all the pediatric patients (filled circles), receiving 1 mg dose, are similar to those in adults (solid reference line) for patients heavier than 40 kg. Hence, it can be concluded that the PK in pediatrics is predictable from that in adults by simply adjusting for body size.

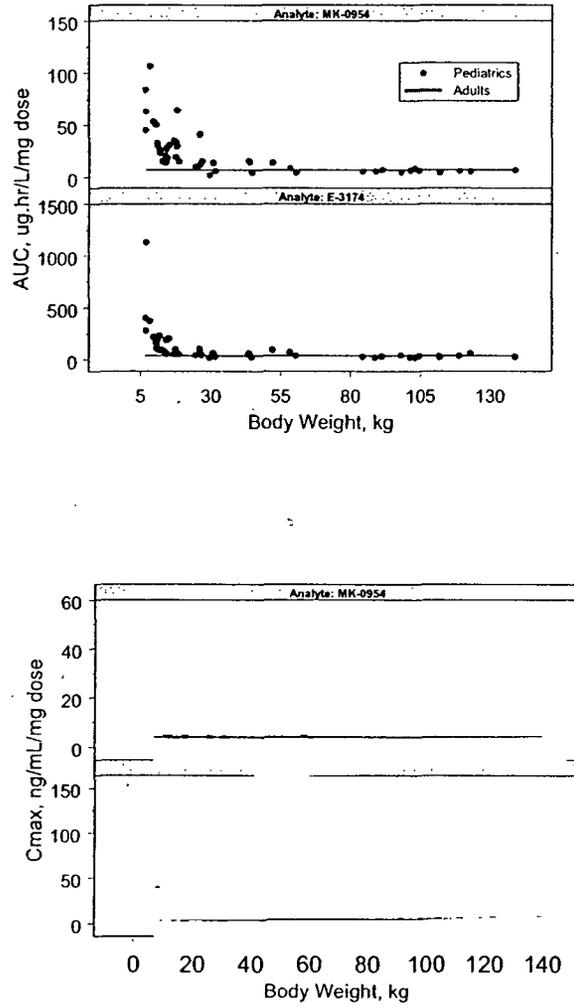


Figure 4. AUC (upper panel) and Cmax value in pediatric patients (symbols) normalized to 1 mg dose of losartan. The lines represent the reference values of AUC and Cmax estimated for adults.

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APPENDIX I
Proposed Package Insert

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

APPENDIX II

NDA 20,386

Individual Study Summaries

STUDY #216

PROTOCOL TITLE:

An Open-Labelled, Randomized, Two-Period, Crossover Study to Determine the Relative Bioavailability of Losartan 50-mg Suspension and Losartan 50-mg Tablet Administered Orally as Single Doses.

INVESTIGATOR/STUDY CENTER:

|

TREATMENT and DURATION:

Each subject received each of 2 treatments.

Treatment A: single-dose oral administration of a 50-mg losartan tablet
Treatment B: single-dose oral administration of losartan suspension (2.5 mg/mL x 20 mL = 50 mg of losartan)

Between each treatment period there was a washout of a minimum of 7 days.
The study duration was ~4 weeks.

OBJECTIVES:

1. To assess the relative bioavailability of losartan 50-mg suspension and losartan 50-mg tablet following single-dose oral administration of the losartan 50-mg suspension and the losartan 50-mg tablet.
2. To compare the plasma-concentration-time profile of losartan following single-dose oral administration of the losartan 50-mg suspension and the losartan 50-mg tablet.
3. To compare the plasma-concentration-time profile of the metabolite L-158641 [E-3174] following single-dose oral administration of the losartan 50-mg suspension and the losartan 50-mg tablet.

METHODS

Study Design:

Open-label, randomized, single oral dose administration, 2-period, crossover with a minimum 7-day washout between periods.

SUBJECTS:

Nonsmoking healthy male and nonpregnant female subjects between 18 and 45 years of age, which were within 20% of ideal body weight.

ENTERED: Total 16

COMPLETED: 16

DISCONTINUED: Total 0

Clinical adverse experience 0

| Gender | No | Age range |
|--------|----|---------------|
| Male | 14 | (21 to 42 yr) |
| Female | 2 | (28 to 31 yr) |

DOSAGE/FORMULATIONS.:

| Clinical Supplies | Potency | Clinical Lot No. | Formulation No. |
|---------------------------|----------------|------------------|-----------------|
| Losartan tablets | 50 mg | WP-G370 | 0954 FCT061C001 |
| Losartan tablets | 50 mg | WP-G370A | 0954 FCT061C001 |
| Losartan tablets | 50 mg | WP-G371 | 0954 FCT061C001 |
| Losartan tablets | 50 mg | WP-G371A | 0954 FCT061C001 |
| Ora-Sweet SF™ diluent | Not applicable | WP-G372 | 9C6533 |
| OraPlus™ diluent | Not applicable | WP-G373 | 9C6540 |
| PET (polyethylene) bottle | Not applicable | WP-G371 | 307/0581/070899 |

Bioanalytical Methods:

Concentrations of losartan and L-158641 in plasma were determined using _____ for sample preparation, HPLC for the chromatography, and MS/MS for detection. The limits of quantitation for both losartan and L-158641 are _____ ng/mL by using _____ mL of plasma, and the linear range for both analytes is _____ ng/mL.

The CV% ranged from 0.8 to 5.5% and the accuracy ranged from 90 to 105% for losartan at concentrations across the standard curve. For EXP-3174, the CV% ranged from 2.1 to 7.7% and accuracy ranged from 90 to 107.0%.

Pharmacokinetic Methods:

Plasma AUC up to the last measured time point (AUC_T) for losartan and L-158641 was calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. $AUC_{0-\infty}$ for losartan and L-158641 was obtained by summing AUC_T and $AUC_{t-\infty}$; the latter was obtained by dividing the last measured plasma concentration by λ . The terminal disposition rate constant λ was

estimated by regression of the terminal log-linear plasma concentration time points. Terminal disposition half-life was calculated as the quotient of the natural log of 2 and λ . The parameters C_{max} , AUC_T and $AUC_{T-\infty}$ were adjusted to 50 mg from actual assayed potencies of tablets and the suspensions.

Data Analysis:

Plasma AUC (defined as $AUC_{0-\infty}$ and AUC_T) and plasma C_{max} were log transformed prior to statistical analysis. Each was evaluated according to the same strategy, which without loss of generality is presented for log AUC. Summary statistics were provided for both plasma AUC and C_{max} .

RESULTS

The demographic characteristics and treatment sequence for the subjects participated in the study are shown in Table 1.

Table 1. Subject Characteristics by Treatment Sequence

| AN | Gender | Age (yrs) | Race | Weight (lbs) | Height (in) | Treatments Received (In Sequence) |
|---|--------|------------------------------------|-----------|--------------------------|----------------------|-----------------------------------|
| 0001 | F | 31 | Black | 176 | 65 | B → A |
| 0002 | F | 28 | Caucasian | 111 | 63 | A → B |
| 0003 | M | 36 | Black | 181 | 71 | B → A |
| 0004 | M | 40 | Spanish | 171 | 68 | A → B |
| 0005 | M | 22 | Caucasian | 142 | 67 | A → B |
| 0006 | M | 24 | Caucasian | 150 | 66 | B → A |
| 0007 | M | 31 | Black | 182 | 71 | A → B |
| 0008 | M | 28 | Black | 206 | 69 | B → A |
| 0009 | M | 42 | Caucasian | 164 | 68 | A → B |
| 0010 | M | 35 | Caucasian | 149 | 64 | B → A |
| 0011 | M | 21 | Caucasian | 130 | 69 | B → A |
| 0012 | M | 27 | Caucasian | 150 | 69 | A → B |
| 0013 | M | 31 | Black | 191 | 67 | B → A |
| 0014 | M | 24 | Caucasian | 169 | 71 | A → B |
| 0015 | M | 32 | Black | 208 | 72 | B → A |
| 0016 | M | 38 | Black | 165 | 64 | A → B |
| Mean: | | 30.6 | | 165.3 | 67.8 | |
| Range: | | Male: 21 to 42 Female: 28 to 31 | | 130 to 208 111 to 176 | 64 to 72 63 to 65 | |
| Treatments | | | | | | |
| A = U.S. clinical image losartan 50-mg tablet. | | | | | | |
| B = 20 mL of 2.5 mg/mL losartan suspension (50 mg). | | | | | | |

Mean plasma concentrations for losartan and its metabolite, E-3174 are shown in Figure 1.

Mean (SD) Plasma Concentrations of Losartan and L-158641 (EXP-3174) Following Administration of Single Oral Doses of Losartan 50-mg Tablet and 20 mL of 2.5 mg/mL Losartan Suspension

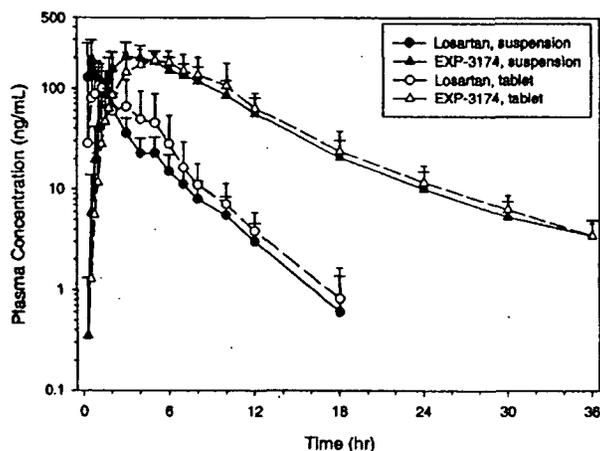


Figure 1.

Figure 2 shows individual plasma concentrations for losartan and its metabolite.

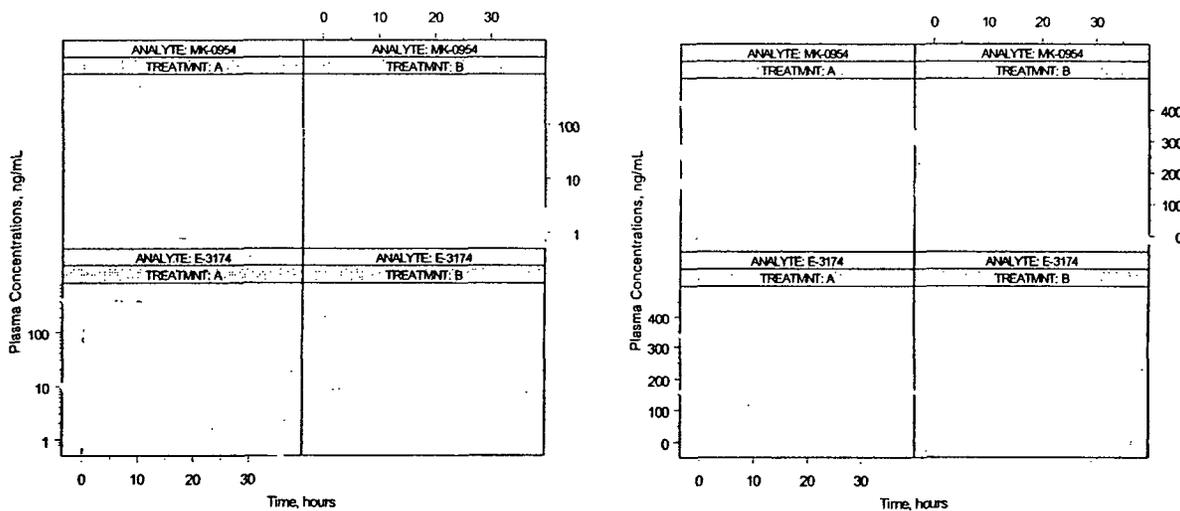


Figure 2. Individual plasma concentrations for losartan (triangles, MK-0954) and its metabolite (circles, E-3174). Treatment A: 50 mg losartan tablet, treatment B: 50 mg losartan suspension. The lines are the Loess smoothing lines. Plasma concentrations are on log scale in the left panel and in normal scale in right panel.

Table 3 summarizes the results of the statistical analysis for AUC and Cmax for losartan.

Table 3.

Summary of Statistical Analyses—
 Losartan AUC and C_{max} Potency Normalized to the 50-mg Dose

| Variable | Geometric Mean | | Geometric Mean Ratio [†] | p-Value | Within-Subject MSE | df |
|---------------------------------------|-------------------------|-------------------------|-----------------------------------|---------|--------------------|----|
| | Suspension | Tablet | | | | |
| AUC _{0-∞} ng•hr/mL 90% CI | 366.3 (309.1, 434.1) | 395.0 (333.3, 468.1) | 0.927 (0.834, 1.031) | 0.229 | 0.0288 | 14 |
| AUCT ng•hr/mL 90% CI | 358.4 (301.4, 426.1) | 387.7 (326.1, 461.0) | 0.924 (0.830, 1.029) | 0.219 | 0.0299 | 14 |
| C _{max} ng/mL 90% CI | 208.1 (167.2, 259.1) | 174.2 (140.0, 216.9) | 1.195 (0.984, 1.450) | 0.128 | 0.0968 | 14 |

Losartan tablet was bioequivalent to the suspension formulation by exposure (AUC) but not by C_{max}. C_{max} values obtained for the treatment with the losartan suspension were about 20% higher than the same values for losartan tablet, and the difference was statistically significant.

Table 4 summarizes the results of the statistical analysis for AUC and C_{max} for losartan metabolite, E-3174.

Table 4.

Summary of Statistical Analyses—
 L-158641 [E-3174] AUC and C_{max} Potency Normalized to the 50-mg Dose

| Variable | Geometric Mean | | Geometric Mean Ratio [†] | p-Value | Within-Subject MSE | df |
|---------------------------------------|----------------------------|----------------------------|-----------------------------------|---------|--------------------|----|
| | Suspension | Tablet | | | | |
| AUC _{0-∞} ng•hr/mL 90% CI | 1813.7 (1608.0, 2045.8) | 1787.1 (1584.4, 2015.7) | 1.015 (0.912, 1.129) | 0.811 | 0.0295 | 14 |
| AUCT ng•hr/mL 90% CI | 1781.1 (1578.3, 2009.9) | 1755.8 (1555.9, 1981.4) | 1.014 (0.910, 1.131) | 0.820 | 0.0303 | 14 |
| C _{max} ng/mL 90% CI | 219.0 (193.3, 248.2) | 211.4 (186.2, 239.2) | 1.038 (0.910, 1.184) | 0.628 | 0.0448 | 14 |

Losartan tablet was bioequivalent to the suspension formulation in respect to its active metabolite, E-3174 both by AUC and C_{max}.

COMMENT:

About 14% of an orally administered dose of losartan converts to the active metabolite. 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. 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. Therefore, relative exposure to losartan is approximately ten-fold larger than the exposure to its metabolite. The active metabolite is 10 to 40 times more potent by weight than losartan. Therefore, the effects of both losartan and its metabolite after the dose of losartan are comparable.

CONCLUSIONS:

1. Losartan tablet was bioequivalent to the suspension by exposure (AUC) but not by C_{max}. C_{max} values obtained for the treatment with the losartan suspension were about 20% higher than the same values for losartan tablet, and the difference was statistically significant. Losartan tablet was bioequivalent to the suspension formulation with respect to its active metabolite both by AUC and C_{max}.
2. Since the suspension formulation had higher C_{max} than tablet formulation, the effectiveness of losartan may not be compromised by the administration of the suspension. The safety concern from the slightly higher exposure of losartan when administered as a suspension is to be evaluated by the medical officer.

**APPEARS THIS WAY
ON ORIGINAL**

STUDY #: 225

PROTOCOL TITLE:

An Open-Label Study To Investigate The Pharmacokinetics Of Losartan In Hypertensive Children And Infants

INVESTIGATOR/STUDY CENTER:

| | |
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OBJECTIVE(S):

Primary:

To estimate the plasma pharmacokinetic parameters (AUC₀₋₂₄ hr, C_{max}, T_{max}, and half-life) of losartan and E-3174 in children aged 1 month to <16 years;

To evaluate the safety and tolerability of losartan in children aged 1 month to <16 years.

Secondary:

To estimate the urinary recovery and renal clearance of losartan and E-3174 in children who are toilet trained to <16 years of age.

STUDY DESIGN:

Open-label, multicenter investigation of pharmacokinetics after 7 days at a stable dose of losartan. Patients were grouped according to age:

- Group I: infants and toddlers (1 to 24 months);
- Group II: preschool children (25 months to <6 years);
- Group III: school-age children (6 to <12 years);
- Group IV: adolescents (12 to <16 years).

Blood samples for plasma losartan and E-3174 assay were collected prior to the first dose and predose and at 0.5, 1, 2, 4, 6, 8, 12, 24, and 32 to 36 hours following the Day 7 dose (except in children younger than 4 years, in whom the collections at Hours 2 and 6 were optional). Urine collections in the intervals of 0 to 8 hours, and 8 to 24 hours after the Day 7 dose (urine collections were optional in Group I patients and in older patients who were not toilet trained).

PATIENTS:

Male or female patients 1 month to <16 years of age. Patients were grouped by age:

| | Group I (Infants and Toddlers) | Group II (Preschool Children) | Group III (School-Age Children) | Group IV (Adolescents) |
|--------------------|--------------------------------------|-------------------------------------|---------------------------------------|---------------------------|
| ENTERED: Total | 11 | 13 | 12 | 14 |
| Male (age range) | 8 (3 to 23 mo) | 8 (2 to 5 yr) | 8 (6 to 11 yr) | 9 (12 to 15 yr) |
| Female (age range) | 3 (10 to 23 mo) | 5 (2 to 5 yr) | 4 (7 to 8 yr) | 5 (12 to 15 yr) |
| COMPLETED: | 11 | 13 | 12 | 14 |

Patients must have had a documented history of hypertension. Patients must have had a glomerular filtration rate >30 mL/min/1.73m².

DOSAGE/FORMULATION:

Losartan suspension was prepared from losartan 50-mg tablets suspended in sterile water, Ora-Plus TM, and Ora-Sweet SF TM. It was administered as 0.7 mg/kg/day dose in children <6 years and those who could not swallow tablets.

Losartan 12.5-mg tablets were administered once daily in children 6 years and older and weighing <25 kg.

Losartan 25-mg tablets were administered once daily in children 6 years and older and weighing ≥25 kg but <50 kg.

Losartan 50-mg tablets were administered once daily in children 6 years and older and weighing ≥50 kg.

Losartan formulations used in this study are listed in the Table 1.

Table 1.

| | Strength | Clinical Lot No. | Formulation No. |
|-----------------|----------|------------------|-----------------|
| Losartan tablet | 50 mg | WP-H253 | 0954 FCT061C001 |
| | 12.5 mg | WP-H254 | E-9284 |
| | 25 mg | WP-H255 | 0954 FCT013B001 |
| | 50 mg | WP-H256 | 0954 FCT061C001 |
| | 50 mg | WP-H288 | 0954 FCT061C001 |
| | 12.5 mg | WP-H289 | E-9284 |
| | 25 mg | WP-H290 | 0954 FCT013B001 |
| | 50 mg | WP-H291 | 0954 FCT061C001 |
| | 50 mg | WP-H294 | E-9671 |
| | 12.5 mg | WP-H295 | E-9284 |
| | 25 mg | WP-H296 | E-9287 |
| | 50 mg | WP-H297 | E-9671 |
| | 50 mg | WP-H300 | 0954 FCT061C001 |
| | 12.5 mg | WP-H301 | E-9284 |
| | 25 mg | WP-H302 | 0954 FCT013B001 |
| | 50 mg | WP-H303 | 0954 FCT061C001 |
| | 50 mg | WP-H332 | E-9671 |
| | 12.5 mg | WP-H333 | E-9284 |
| | 25 mg | WP-H334 | E-9287 |
| | 50 mg | WP-H335 | E-9671 |
| Ora-Plus™ | -- | WP-H257 | 0B6184 |
| | -- | WP-H292 | 0B6184 |
| | -- | WP-H298 | 0B6184 |
| | -- | WP-H304 | 0B6184 |
| | -- | WP-H336 | 0B6184 |
| Ora-Sweet SF™ | -- | WP-H258 | 9D6621 |
| | -- | WP-H293 | 9F6726 |
| | -- | WP-H299 | 9F6726 |
| | -- | WP-H305 | 9F6726 |
| | -- | WP-H337 | 9D6621 |

Bioanalytical Methods

Concentrations of losartan and E-3174 in plasma and urine were determined using C_{18} for sample preparation, HPLC for the chromatography, and MS/MS for detection. The limits of quantitation for both losartan and E-3174 were 1 ng/mL by using 0.1 mL of plasma, and the linear ranges for both analytes were 1 to 500 ng/mL . The limits of quantitation for both losartan and E-3174 were 2 ng/mL by using 0.5 mL of urine, and the linear ranges for both analytes were 2 to 1000 ng/mL .

Pharmacokinetic Methods

Plasma and urine samples collection is shown in Table 2.

The sponsor performed a non-compartmental data analysis. Plasma $\text{AUC}_{0-24 \text{ hr}}$ for losartan and E-3174 during the PK sampling interval following multiple daily dosing (6 to 15 continuous daily doses) was calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations WinNonlin. The terminal disposition rate constant λ was estimated by regression of the terminal log-linear plasma concentration time points. Terminal disposition half-life was calculated as the quotient of the natural log of 2 and λ . Renal clearance of losartan and E-3174 was calculated by the quotient: amount excreted in urine from 0- to 24-hour/ $\text{AUC}_{0-24 \text{ hr}}$.

24 hr. Glomerular filtrate rate (GFR) was measured by urinary creatinine and serum creatinine and normalized to 1.73 m^2 . When GFR could not be measured (in Group I and in some patients in Group II), the Schwartz formula was used to calculate GFR in $\text{mL}/\text{min}/1.73 \text{ m}^2$. The value of k is 0.45 for infants up to 18 months, and 0.55 otherwise.

Table 2.

Clinical and Laboratory Measurements Following the Day 7 Dose

| | Predose | Hour Postdose | | | | | | | | | |
|-------------------------------------|---------|---------------|-------|----------------|---|----------------|---|----|-------|----------------|---|
| | | 0.5 | 1 | 2 | 4 | 6 | 8 | 12 | 24 | 36 | |
| Blood collections [†] | X | X | X | X [†] | X | X [†] | X | X | X | X [†] | |
| Sitting BP [‡] /Heart rate | X | X | X | X | X | X | X | X | X | X | |
| Urine collections [§] | | X | ----- | | | | | X | ----- | | X |

[†] Blood collections: The collections at Hours 2 and 6 were optional in children <4 years of age. The Hour 36 collection could have been made at any time point between Hour 32 and Hour 36 postdose.
[‡] Supine blood pressure (BP) and heart rate in children who could not sit up.
[§] Urine was collected from the time of dosing, in the time periods shown. Urine collections were optional for children in Group I, and for older patients who were not toilet trained.

Statistical Analysis:

AUC_{0-24hr} and Cmax of losartan and E-3174 were estimated for each age group. Individual values were also dose-adjusted to 0.7 mg/kg to permit direct comparison across age groups. Geometric means and 95% confidence intervals were calculated for both adjusted and observed AUC_{0-24hr} and Cmax of losartan and E-3174 for each age group. The individual data were first natural log-transformed. In order to provide a better estimate of the between-subject standard deviation, the log-transformed data were evaluated in an ANOVA model having a factor for age group. The Shapiro-Wilk statistic was calculated from the residuals to test the normality assumption. Hartley's Fmax was applied to the ANOVA residuals to test for homogeneity of variances. If the variances were deemed similar, the mean square error from the ANOVA was used to obtain the 95% confidence interval for the arithmetic mean of the log-parameter in each age group, referencing a t-distribution. These limits were then exponentiated to obtain the 95% confidence interval for the geometric mean for each parameter.

Due to large dissimilarity of the variances across the 4 age groups the sponsor calculated the 95% confidence intervals for observed and adjusted AUC_{0-24hr} of losartan in each age group using the standard deviation for each age group, referencing a t-distribution.

Additionally, harmonic means and 95% confidence intervals for half-life were calculated for each age group for losartan and E-3174. Individual values of the elimination rate constant lambda were evaluated in an ANOVA model having a factor for age group. The variances in each age group were similar. The arithmetic mean rate constant for each group was back-transformed to obtain the estimated harmonic mean half-life. A 95% confidence interval for lambda for each age group was calculated using the mean square

error from the ANOVA, referencing a t-distribution. The limits were back-transformed to obtain corresponding 95% confidence intervals for half-life.

Urinary recovery and renal clearance of losartan and E-3174 were evaluated using the ANOVA methodology described above, but the data were not log-transformed. The normality and homogeneity assumptions were met for urinary recovery of losartan and urinary recovery and renal clearance of E-3174. Therefore, arithmetic means and 95% confidence intervals for these parameters for each age group were calculated from the ANOVA model. Renal clearance data for losartan exhibited nonnormality and heterogeneity of variances. Therefore, medians and distribution-free confidence intervals were calculated using Hodges-Lehmann estimation for each age group.

Exploratory Analyses

As an exploratory analysis, pairwise differences between age groups for pharmacokinetic parameters of losartan and E-3174 were examined.

RESULTS

Demographic Characteristics:

Patient's demographic characteristics are shown in Table 3.

Table 3.

Patient Demographics

| | Group I Infants and Toddlers (1 to 24 Mos) | Group II Preschool Children (25 Mos to <6 Yrs) | Group III School-Age Children (6 to <12 Yrs) | Group IV Adolescents (12 to <16 Yrs) |
|---|---|--|---|--|
| Total No. of Patients | 11 | 13 | 12 | 14 |
| Males (n) | 8 | 8 | 8 | 9 |
| Actual age range | 3 to 23 Mo | 2 to 5 Yr | 6 to 11 Yr | 12 to 15 Yr |
| Females (n) | 3 | 5 | 4 | 5 |
| Actual age range | 10 to 23 Mo | 2 to 5 Yr | 7 to 8 Yr | 12 to 15 Yr |
| Caucasian (n) | 8 | 7 | 4 | 8 |
| Black (n) | 1 | 2 | 5 | 5 |
| Hispanic (n) | 2 | 4 | 3 | 1 |
| Weight range (kg) | 7 to 14 kg | 10 to 19 kg | 24 to 59 kg | 52 to 139 kg |
| Patients Included in PK Analysis (n) | 9 | 13 | 11 | 14 |
| Males (n) | 8 | 8 | 7 | 9 |
| Actual age range | 3 to 23 Mo | 2 to 5 Yr | 6 to 11 Yr | 12 to 15 Yr |
| Females (n) | 1 | 5 | 4 | 5 |
| Actual age range | 23 to 23 Mo | 2 to 5 Yr | 7 to 8 Yr | 12 to 15 Yr |
| Caucasian (n) | 7 | 7 | 4 | 8 |
| Black (n) | 1 | 2 | 5 | 5 |
| Hispanic (n) | 1 | 4 | 2 | 1 |
| Weight range (kg) | 7 to 14 kg | 10 to 19 kg | 24 to 59 kg | 52 to 139 kg |

All 50 patients had a history of hypertension; 6 patients had a diagnosis of obesity; 6 patients had a history of hemolytic-uremic syndrome; 5 patients had a history of asthma;

3 patients had a history of seizure disorder; 1 patient had lupus. A number of patients had a history of one or more renal disorders: renal insufficiency-14; polycystic kidney-9; urinary tract infection-9; vesicoureteral reflux-5; nephrectomy-4; nephrotic syndrome-3; hydronephrosis-3; peritoneal dialysis-3; pyelonephritis-2; obstructive uropathy-2; glomerulonephritis-1; uremia-1; renal artery thrombosis-1; and miscellaneous urogenital anomalies-6.

Forty-seven of 50 patients had pharmacokinetic data. All subjects for whom pharmacokinetic parameters were calculated were included in the statistical analysis of pharmacokinetics. The following patients had plasma pharmacokinetic parameters, but not urinary recovery or renal clearance: all patients in Group I (due to unreliable urine collection from this age group); AN 4005, AN 4008, AN 4092, AN 4131, AN 4132, AN 5003, AN 6017, and AN 6046 in Groups II and III (incomplete 0- to 24-hour urine collection or no urine collection).

Representative patients plasma losartan and E-3174 concentrations are shown in Figure 1.

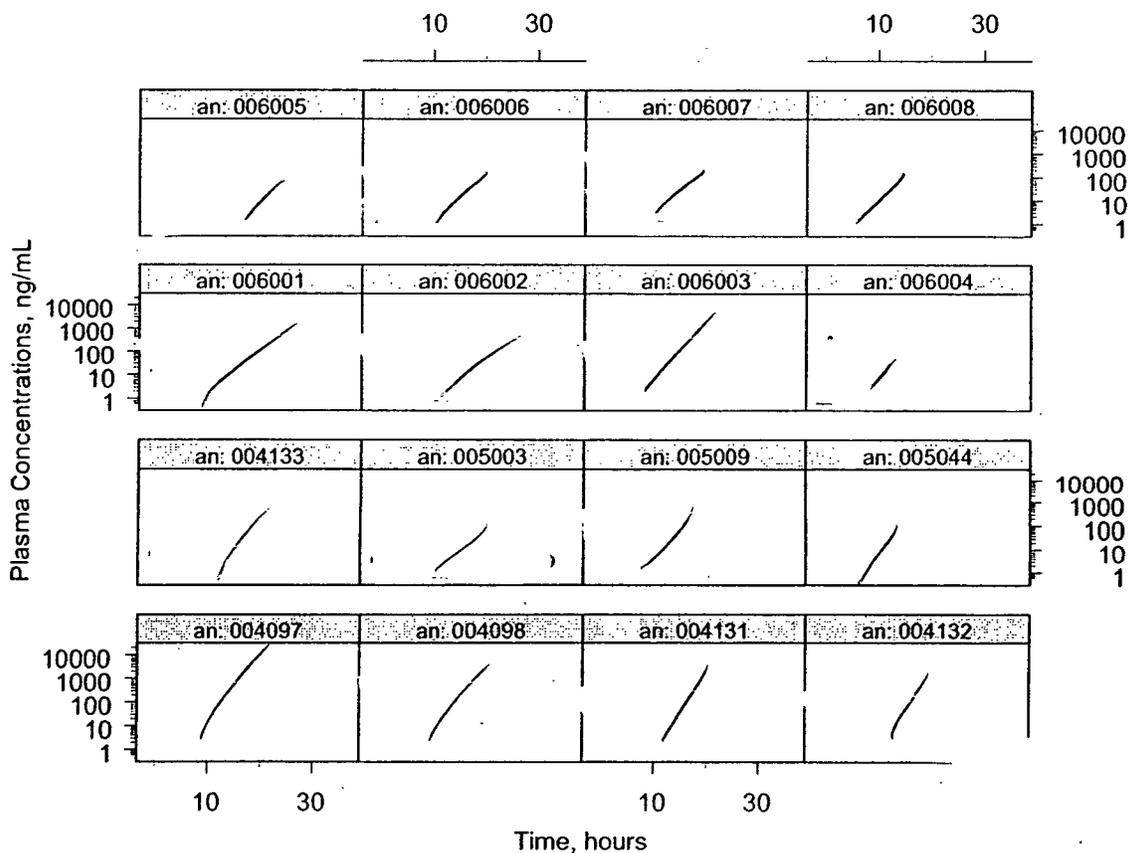


Figure 1. Individual patients plasma losartan (triangles) and E-3174 (circles).

Figure 2 shows the losartan and its metabolite plasma concentrations for each group of patients.

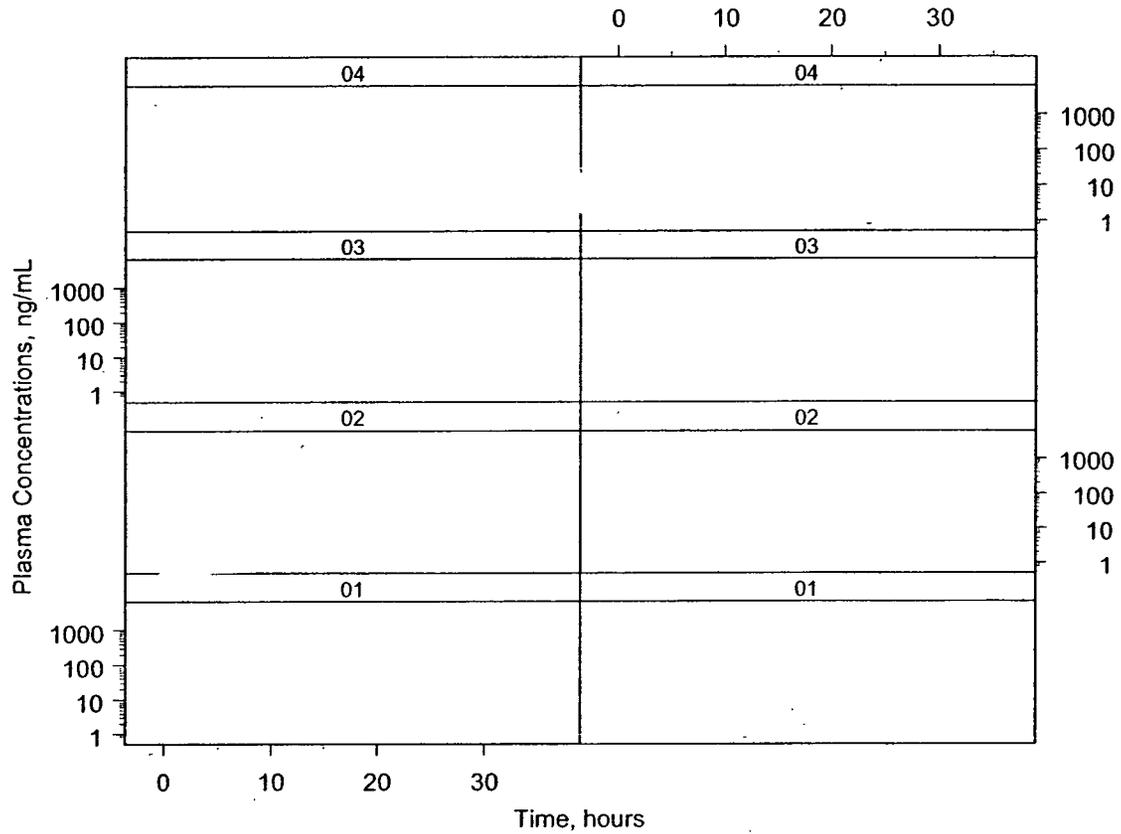


Figure 2. Losartan (right panel) and its metabolite (left panel) plasma concentrations for each group (1-4) of patients.

Tables 4 and 6 list the summary statistics of pharmacokinetic parameters estimated for losartan and its metabolite in plasma. The observed values for AUC and C_{max} were additionally normalized to 0.7 mg/kg dose of losartan to illustrate the comparison. Tables 5 and 7 demonstrate summary statistics for urinary recover and renal clearance of losartan and its metabolite.

Table 4

Summary Statistics for Plasma Pharmacokinetic Parameters
of Losartan in Hypertensive Infants and Toddlers,
Preschool Children, School-Age Children, and Adolescents

| | Group I (n=9) | Group II (n=13) | Group III (n=11) | Group IV (n=14) |
|--|------------------|--------------------|---------------------|--------------------|
| AUC_{0-24 hr} observed (ng•hr/mL) | | | | |
| Geometric Mean | 244.5 | 314.5 [†] | 251.0 | 303.1 |
| 95% CI | (162.2, 368.4) | (238.8, 414.3) | (141.5, 445.5) | (253.4, 362.5) |
| AUC_{0-24 hr} per 0.7 mg/kg | | | | |
| Geometric Mean | 246.1 | 305.2 | 232.6 | 405.4 |
| 95% CI | (168.4, 359.6) | (237.7, 391.9) | (134.7, 401.5) | (337.4, 487.1) |
| C_{max} observed (ng/mL) | | | | |
| Geometric Mean | 66.6 | 89.8 [†] | 98.7 | 105.1 |
| 95% CI | (40.9, 108.4) | (58.9, 137.0) | (63.5, 153.4) | (71.1, 155.4) |
| C_{max} per 0.7 mg/kg | | | | |
| Geometric Mean | 67.0 | 89.5 | 91.4 | 140.6 |
| 95% CI | (43.0, 104.4) | (61.9, 129.4) | (61.3, 136.5) | (98.6, 200.6) |
| T_{max} (hr) | | | | |
| Median [‡] | 1.05 | 1.07 | 2.03 | 1.54 |
| 95% CI [§] | (0.78, 2.53) | (0.77, 2.53) | (1.00, 3.54) | (1.49, 2.03) |
| Half-Life (hr) | | | | |
| Harmonic Mean | 1.93 | 2.37 | 2.18 | 2.41 |
| 95% CI | (1.62, 2.38) | (1.99, 2.95) | (1.83, 2.70) | (2.02, 2.98) |

Geometric mean dose normalized losartan C_{max} values for pediatric patients ranged from 129 ng/mL (group 3) to 251 ng/mL (group 4). These values were similar to the C_{max} value of 218 ng/mL, reported for adults in study 216.

Table 5

Summary Statistics for Urinary Recovery and Renal Clearance of Losartan
in Hypertensive Infants and Toddlers, Preschool Children,
School-Age Children, and Adolescents

| | Group II (n=7) | Group III (n=9) | Group IV (n=14) |
|---|-------------------|--------------------|--------------------|
| Urinary Recovery (% Dose) | | | |
| Arithmetic Mean | 2.00 | 2.80 | 2.01 |
| 95% CI | (1.00, 3.00) | (1.92, 3.68) | (1.31, 2.72) |
| Renal Clearance (mL/min/1.73m²) | | | |
| Median [†] | 29.54 | 56.43 | 45.30 |
| 95% CI [‡] | (17.51, 48.59) | (36.39, 118.91) | (30.93, 66.57) |

Losartan renal clearance was estimated for groups 2, 3, and 4. The mean renal clearance value in group 2 (2 to 6 years of age) was 30 mL/min and in group 4 (12 to 16 years of age) was 45 mL/min. These values were smaller than historical data for adults presented in the Package Insert (75 mL/min). Urinary recovery in children (2-2.8%) was smaller than in adults (4%).

Geometric mean AUC_{0-24 hr} of metabolite adjusted to 0.7 mg/kg was 1466 ng•hr/mL for Group I, 933 ng•hr/mL for Group II, 1078 ng•hr/mL for Group III, and 2127 ng•hr/mL for Group IV. The adjusted AUC for Group IV was significantly greater than the adjusted AUC for Groups II and III, and the adjusted AUC in Group I was marginally greater than the adjusted AUC in Group II (p=0.062).

Table 6

Summary Statistics for Plasma Pharmacokinetic Parameters of E-3174
in Hypertensive Infants and Toddlers, Preschool Children,
School-Age Children, and Adolescents

| | Group I (n=9) | Group II (n=13) | Group III (n=11) | Group IV (n=14) |
|--|------------------|--------------------|---------------------|--------------------|
| AUC_{0-24 hr} Observed (ng•hr/mL) | | | | |
| Geometric Mean | 1456.5 | 950.9 [†] | 1163.6 | 1589.9 |
| 95% CI | (988.5, 2146.2) | (679.7, 1330.2) | (819.5, 1652.3) | (1165.2, 2169.5) |
| AUC_{0-24 hr} Per 0.7 mg/kg | | | | |
| Geometric Mean | 1466.3 | 933.2 | 1078.0 | 2126.8 |
| 95% CI | (1017.3, 2113.3) | (688.4, 1264.9) | (774.5, 1500.4) | (1586.5, 2851.0) |
| C_{max} Observed (ng/mL) | | | | |
| Geometric Mean | 146.9 | 91.5 [†] | 139.1 | 188.2 |
| 95% CI | (96.8, 223.0) | (63.8, 131.4) | (95.3, 202.9) | (134.7, 263.0) |
| C_{max} Per 0.7 mg/kg | | | | |
| Geometric Mean | 147.9 | 92.0 | 128.8 | 251.7 |
| 95% CI | (99.8, 219.3) | (66.3, 127.7) | (90.2, 183.9) | (183.6, 345.1) |
| T_{max} (hr) | | | | |
| Median [‡] | 5.53 | 6.01 | 4.46 | 5.00 |
| 95% CI [‡] | (3.68, 7.83) | (5.01, 7.00) | (3.01, 6.04) | (4.00, 5.13) |
| Half-Life (hr) | | | | |
| Harmonic Mean | 4.83 | 5.59 | 5.37 | 5.72 |
| 95% CI | (4.29, 5.53) | (4.98, 6.36) | (4.77, 6.15) | (5.11, 6.50) |

Geometric mean dose normalized losartan metabolite AUC values for pediatric patients older than 6 years of age ranged from 1078 ng•hr/mL (group 3) to 2127 ng•hr/mL (group 4). These values were similar to 1814 ng•hr/mL obtained in Study 216 for adults who received 50 mg/kg tablet of losartan.

Table 7

Summary Statistics for Urinary Recovery and Renal Clearance of E-3174 in Hypertensive Preschool Children, School-Age Children, and Adolescents

| | Group II (n=7) | Group III (n=9) | Group IV (n=14) |
|---|-------------------|--------------------|--------------------|
| Urinary Recovery (% Dose) | | | |
| Arithmetic Mean | 2.69 | 3.58 | 3.93 |
| 95% CI | (1.40, 3.98) | (2.44, 4.72) | (3.02, 4.84) |
| Renal Clearance (mL/min/1.73m²) | | | |
| Arithmetic Mean | 11.69 | 17.68 | 16.39 |
| 95% CI | (6.15, 17.23) | (12.80, 22.57) | (12.47, 20.31) |
| CI = Confidence interval. | | | |

Losartan metabolite renal clearance was estimated for groups 2, 3, and 4. The mean renal clearance values were from 11 mL/min (group 2, 2 to 6 years of age) to 18 mL/min (group 3, 12 to 16 years of age). These values were smaller than historical data for adults presented in the Package Insert (25 mL/min). Urinary recovery in children was smaller (2.7-3.9%) than in adults (6%).

In order to compare the clearance and volume of distribution values and to evaluate the influence of demographic covariates on these parameters, the reviewer performed a population pharmacokinetic analysis using NONMEM.

Reviewer's PK Data Analysis

Objective:

To evaluate the influence of the demographics on the pharmacokinetic parameters of losartan.

Data:

Although the sponsor collected PK data, patients who were less than 6 years of age did not contribute any effectiveness and safety data (long term). Hence the PK of patients less than 6 years of age were excluded from the analysis. Also, older patients were mostly obese. The individual values of clearance (CL) and volume of distribution (V_d) for the parent drug were calculated based on the following equations, for each patient:

$$CL = \frac{Dose}{AUC_{0-24,obs}}$$

$$V_d = \frac{Dose}{k * AUC_{0-24,obs}}$$

From Figure 1, the losartan concentrations seem to decrease mono-exponentially and hence the calculation of Vd and not Vss is reasonable.

Methods:

Population pharmacokinetic model was built for each parameter (CL, and V_d) using NONMEM (Version V, level 1.1) and NM-TRAN pre-processor. Models were run using the Digital Visual Fortran Compiler (Version 6.1A) on a personal computer with Microsoft Windows NT 4.0 operating system.

Initially, no demographic variables were included in models for clearance (CL/F), volume of distribution (V/F), as shown below:

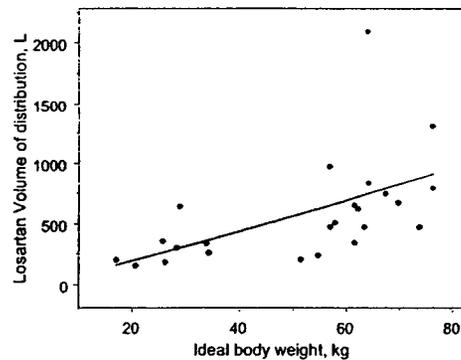
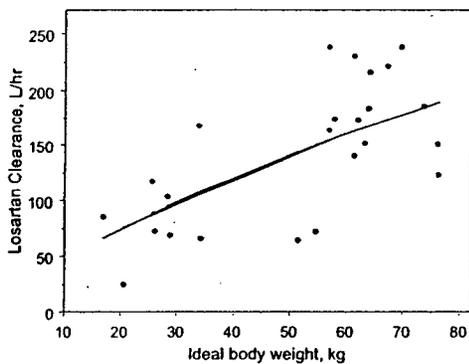
$$PARAMETER_j = TVPARAMETER \cdot \exp(\eta_{jPARAMETER})$$

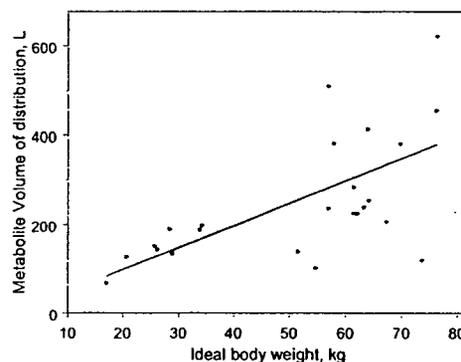
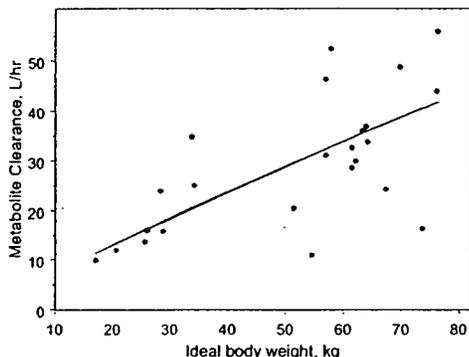
where $\eta_{jPARAMETER}$ denotes the proportional difference between the true parameter (PARAMETER_j) of individual j and the typical value TVPARAMETER.

Residual error was not estimated as each individual had one observation.

The relationship between the covariates and individual parameters for losartan (CL and V) were graphically explored. (Figure 3).

Figure 3. Relationship between ideal body weight, apparent clearance, and apparent volume of distribution for losartan and its metabolite. The symbols are calculated individual parameters and lines are the result of regression.





Body size parameters and demographic parameters (age, gender, and race) were tested as covariates. Gender and race (White, Black and Others) were expressed as the categorical covariates, the continuous covariates (BW and AGE) were centered. Important covariates were selected based on mechanistic understanding and the log likelihood ratio test, which uses the objective function value (OFV). For every additional parameter in the model, a decrease of 10.83 signifies a $p=0.001$.

The results of covariate model building are shown in Table 1 (losartan).

Table 1. Covariate model building for losartan's apparent clearance and volume.

| Parameter | Covariate | OFV |
|-----------|--------------|--------------|
| Clearance | No covariate | 221.9 |
| | WT | 215.4 |
| | IBW | 207.8 |
| Volume | No covariate | 314.0 |
| | WT | 302.6 |
| | IBW | 295.3 |

Inclusion of bodyweight, as expected decreased the OFV by about 6 points. Ideal body weight (IBW), on the other hand, decreased the OFV by 15 points. The choice of IBW is justified biologically, since the body weight of the patients ranges from 24 to 139 kg (6 to 16 years). The volume of distribution of losartan is 34 L (from IV study), which is 0.5 L/kg in a 70 kg adult and implies that the drug is not extensively distributed in the body tissues. The usage of IBW is thus justified.

The results from a similar analysis for losartan's metabolite are shown in Table 2.

Table 2. Covariate model building for metabolite's apparent clearance and volume.

| Parameter | Covariate | OFV |
|-----------|--------------|--------------|
| Clearance | No covariate | 148.2 |
| | WT | 141.0 |
| | IBW | 128.8 |
| Volume | No covariate | 260.7 |
| | WT | 253.5 |
| | IBW | 236.6 |

Again, IBW was found to be an important covariate and better predictor than total body weight.

The confidence intervals of the parameter estimates were determined using the bootstrap procedures (N=1000). For each of the parameters, the 95% confidence intervals were estimated using S-PLUS.

The parameter estimates and their 95% confidence intervals are shown in Table 2.

Table 2. Pharmacokinetic parameters for losartan.

| Parameter | Mean | 95% Confidence Interval |
|-----------------------------|------|-------------------------|
| CL ^a (L/hr/50kg) | 141 | (120, 159) |
| CLIBW | 0.7 | (0.48,1.1) |
| Between-subject variability | 33% | (24%,41%) |
| V ^b (L/50kg) | 554 | (436,705) |
| VIBW | 1.14 | (0.568,1.66) |
| Between-subject variability | 51% | (29%, 66%) |

^a Clearance in a subject = CL·IBW^{CLIBW}

^b Volume in a subject = V·IBW^{VIBW}

Table 3. Pharmacokinetic parameters for losartan's metabolite.

| Parameter | Mean | 95% Confidence Interval |
|-----------------------------|-------|-------------------------|
| CL ^a (L/hr/50kg) | 28.8 | (25, 32.8) |
| CLIBW | 0.869 | (0.5,1.08) |
| Between-subject variability | 31% | (21%, 40%) |
| V ^b (L/50kg) | 244 | (205, 288) |
| VIBW | 1.01 | (0.691, 1.22) |
| Between-subject variability | 34% | (0.24, 0.45) |

^a Clearance in a subject = CL·IBW^{CLIBW}

^b Volume in a subject = V·IBW^{VIBW}

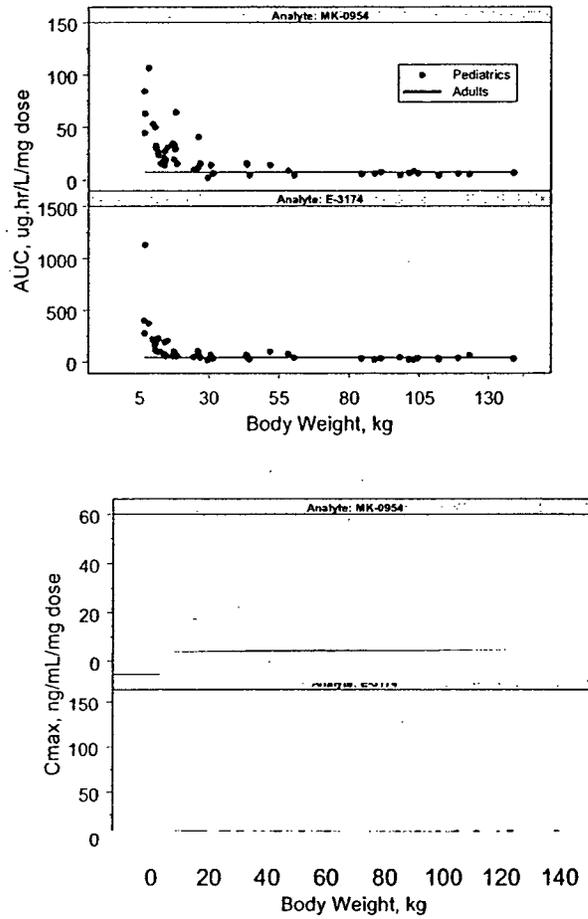


Figure 4. AUC (upper panel) and Cmax value in pediatric patients (symbols) normalized to 1 mg dose of losartan. The lines represent the reference values of AUC and Cmax estimated for adults.

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COMMENTS & CONCLUSIONS:

1. It is important to note that the patients included in this trial are highly heterogeneous. For example, in neonates the dose adjusted metabolite's AUC of patient#4133 is 5545 ng.hr/mL. The range of AUCs, for the metabolite, in other neonates is between 558 to 2169 ng.hr/mL. Patient#4133 happens to be the youngest (0.3 years) and lightest. This patient also has kidney cyst, hyperthyroidism and chronic renal insufficiency. The metabolite is primarily cleared via kidneys. But this patient's parent PK parameters are reasonably comparable to other patient's within the age group, probably because the parent is not cleared renally. Let us consider another patient, patient#6017 who is 8.5 years old and weighs about 30 kg. The parent and metabolite concentrations are very low compared to other patients with similar demographics. The AUC and Cmax of parent in this patient are 37.8 ng.hr/mL and — ng/mL. This patient has gastroesophageal reflux, nephrotic syndrome, pneumonia and lead poisoning. Given this heterogeneity and the small sample size, the effect of various manifestations on the PK parameters cannot be assessed accurately. Nevertheless, the range of PK parameters in pediatrics is in the range observed in adults (study 217).
2. The summary of PK parameters provided by the sponsor is not necessarily the best way to understand the variability in the PK parameters across the patients. The sponsor normalized the PK parameters (AUC and Cmax) for dose and body weight, and categorized them by age group. This classification is misleading because the relationship between bodyweight and the PK parameters is forced to be linear, when biology dictates that it is not, particularly when the patients range from neonates to adolescents. The following graph demonstrates the distribution of dose-normalized AUCs and Cmaxs, for a 1mg dose, across the weight range for the pediatric patients. The mean AUC and Cmax, for a 1mg dose, of the adults are also shown (solid line). Evidently, the Cmax is higher in lighter patients when compared to the heavier ones. This is because of smaller volumes of distribution in the lighter patients. Although, IBW was found to be a better predictor than total body weight, the graphs below use total body weight for easy comparison to adults. Clearly, this relationship is not linear implying an interplay between body weight and age, especially for the younger patients. Similar trend exists for AUC, smaller patients have slower clearances and hence higher AUCs. The PK in pediatric and adult patients are similar.
3. Final parameter estimates obtained with the population modeling for the study of losartan in pediatric patients were similar to the same parameters calculated for healthy adults (Study 216) but differ from the parameters listed in the current label. The request to the sponsor (8/15/2002) and the following telecon with the sponsor (8/19/2002) revealed that the parameters shown in the label correspond to the intravenous administration of losartan. The information in the label should be clarified.

STUDY #: 227

PROTOCOL TITLE:

A Double-Blind, Randomized Dose-Response Study Of Losartan In Children With Hypertension

INVESTIGATOR/STUDY CENTER: 42 investigators: 13 in U.S., 15 in Europe, 9 in South America, 2 in Canada, 2 in South Africa, and 1 in Mexico.

OBJECTIVES:

Primary:

To define a dose-response relationship for losartan in hypertensive children aged 6 to 16 years after a 21-day double-blind treatment period.

To investigate the safety and tolerability of losartan in the dose range 2.5 to 100 mg in hypertensive children aged 6 to 16 years.

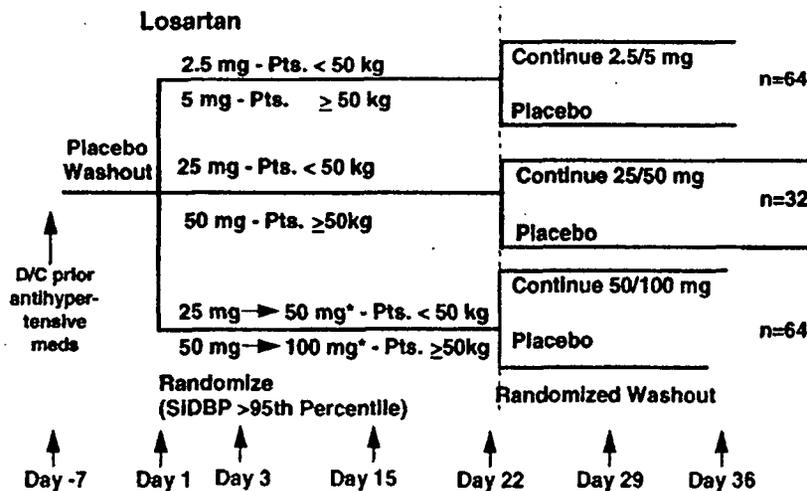
Secondary:

To determine whether discontinuation of active losartan treatment is associated with return of hypertension.

STUDY DESIGN:

This was a double-blind, randomized, multi-center study in at least 160 hypertensive, pediatric patients. The basic design is shown in Figure 1. A sufficient number of patients were entered to ensure that at least 150 patients entered the randomized washout period. The study began with a 2- to 7-day washout period in which patients discontinued their prior antihypertensive medication.

Figure 1. Study Design.



* All patients titrated at Day 3 unless limited by an adverse experience or excessive hypotension.

Losartan placebo suspension and losartan placebo tablets were administered once daily during this period. If patients became hypertensive (mean trough SiDBP >95th percentile for gender, height, and age) and met all other entry criteria and did not meet any of the exclusion criteria, they qualified to enter the double-blind treatment phase. Newly diagnosed hypertensive patients had their blood pressure measured on at least 2 separate occasions before randomization. Patients were then randomized to 1 of 3 treatment arms (Low Dose 2.5/5.0 mg, Middle Dose 25/50 mg, High Dose 50/100 mg). In the 2.5-/5.0-mg treatment group, the study drug was administered in a suspension formulation, prepared at the study site. In the other treatment groups, dosing was with tablets. The blind was maintained by double-dummy design of the tablets and suspension for all patients. Patients were assigned by allocation schedule to receive a starting dose of losartan 2.5 or 25 mg (patients <50 kg) and 5 or 50 mg (patients =50 kg) once daily.

Dose Escalation:

On Day 3, all patients were reevaluated. Patients in the 50/100-mg group, started on 25 mg, who weighed <50 kg had their dose increased to 50 mg unless limited by an adverse experience or excessive hypotension. Patients in the group started on 50 mg who weighed 50 kg had their dose increased to 100 mg unless limited by an adverse experience or excessive hypotension. The dosage adjustments were performed in a double-blind fashion. All patients were to remain on the randomly assigned dose of losartan from Day 3 through Day 22. Patients returned to the clinic for trough (i.e., 24 hours postdose) blood pressure measurements at Day 15. A trough blood pressure visit was optional at Day 7.

Randomized Washout:

Following the 21-day double-blind treatment period, patients underwent a randomized washout to placebo or continued active treatment (1:1) for up to 14 days. Patients had blood pressure monitored at home or school and rescue medication was available. Patients returned to the clinic for trough blood pressure measurements at Day 22 and again at Day 29. The patient completed the randomized washout period at any point his/her blood pressure returned to or exceeded the baseline level.

All clinical observations and laboratory measurements are listed in Table 1.

Table 1. Schedule of clinical observations and laboratory measurements.

| Visit Number Visit (Study Day) | Placebo Washout ¹ | | Double-Blind Treatment | | | | Randomized Washout | |
|--|------------------------------|------------------|------------------------|----------------|----|----|--------------------|-----------------|
| | 1 | 2 | 3 | 4 ¹ | 5 | 6 | 7 | 8 |
| | -7 | 1 | 3 | 7 | 15 | 22 | 29 | 36 ¹ |
| Informed consent | X | | | | | | | |
| Discontinued antihypertensives | X | | | | | | | |
| Medical history | X | | | | | | | |
| Physical exam | X | | | | | | | X |
| Blood pressure/heart rate | X ¹ | X ^{1,2} | X ¹ | X | X | X | X | X |
| Electrocardiogram | X | | | | | | | |
| Laboratory evaluation ³ | X | X | | | | | | X |
| Pregnancy test ^{1,4} | X | | | | | | | X |
| Prepared/dispensed study drug ⁵ | X | X | | | | X | | X |
| Titrated study drug dose ⁶ | | | X | | | | | |
| Measured returned study drug | | X | X | | | X | | X |
| Adverse experience assessment | | X | X | X | X | X | X | X |

The primary measurement from this study was the change in trough SiDBP from baseline to Day 22, the end of the double-blind treatment period. A secondary measurement was the change in trough SiDBP from Day 22 to the end of the randomized washout period.

FORMULATION:

Losartan suspension was prepared with losartan 50-mg tablets, sterile water, Ora-Plus™ and Ora-Sweet SF™ for the 2.5-/5.0-mg dosages. Losartan 25-, 50- or 100-mg tablets were used in this study. Study formulations are listed in Table 2.

Table 2. Study drug formulations.

| Dosage | Control Number | Formulation Number |
|-----------------------|---|--------------------|
| Losartan 25 mg | WP-H272, WP-H275, WP-H306, WP-H698, WP-H697 | 0954 FCT 013B 001 |
| Losartan 25 mg | WP-H340, WP-H278, WP-H343, WP-H352, WP-H352D | E-9287 |
| Placebo (25-mg image) | WP-H272, WP-H275, WP-H306, WP-H698, WP-H697 | P0954 FCT 014B 001 |
| Placebo (25-mg image) | WP-H340, WP-H278, WP-H343, WP-H352, WP-H352C | E-9578 |
| Losartan 50 mg | WP-H272, WP-H275, WP-H306, WP-H698, WP-H697 | 0954 FCT 061C 001 |
| Losartan 50 mg | WP-H340, WP-H278, WP-H343, WP-H352, WP-H352B, WP-H352G | E-9671 |
| Placebo (50-mg image) | WP-H272, WP-H275, WP-H306, WP-H698, WP-H697 | P0954 FCT 062C 001 |
| Placebo (50-mg image) | WP-H272, WP-H275, WP-H306, WP-H698, WP-H697 | P0954 FCT 005T 001 |
| Placebo (50-mg image) | WP-H340, WP-H343, WP-H278, WP-H352, WP-H352E | E-9706 |
| Placebo (50-mg image) | WP-H340, WP-H278, WP-H343, WP-H352, WP-H352A | P0954 FCT 006T 001 |
| Ora-Sweet SF™ | WP-H273, WP-H276, WP-H353, WP-H353A | 0B6182 |
| Ora-Sweet SF™ | WP-H341, WP-H344, WP-H279 | 0A6108 |
| Ora-Sweet SF™ | WP-H307 | 9F6726 |
| Ora-Plus™ | WP-H342, WP-H277, WP-H345, WP-H280, WP-H308, WP-H274, WP-H354, WP-H354A | 0B6184 |

Pharmacodynamic Methods:

Blood samples for plasma losartan and E-3174 assay were not collected during the study. Therefore, only dose-response relationship was assessed in this study.

The primary efficacy endpoint was the slope of change in sitting diastolic blood pressure at the end of the 21-day, double-blind treatment period (Period I) as compared to baseline as a function of dose.

The secondary efficacy endpoint was the average difference in trough sitting diastolic blood pressure (SiDBP) between the losartan and placebo groups with regard to mean changes observed at the end of Period II compared to Day 22.

As supportive analyses, the following variables were explored:

differences of mean change in trough SiDBP between losartan and placebo at each dose level;

other variables including sitting systolic, standing diastolic and systolic blood pressure measurements.

Statistical Analysis:

The primary analysis of the slope was based on the stratified simple linear regression model on change in trough SiDBP (Day 22 versus Day 1) with weight group as the stratified intercept and dose ratio as the continuous covariate. The last-measurement-carried-forward approach was used for patients who did not have measurements on Day 22. However, baseline measurements were not carried forward.

ANOVA Model:

The dose-response relationship may not be linear as a function of dose, or may be different between the 2 weight groups. An ANOVA model for change in SiDBP was performed with terms including dose (low/middle/high), weight (light/heavy), and interaction between dose and weight. The linearity of the dose response and dependency of the dose response on the weight strata was investigated.

Subgroup Analysis:

The effect of losartan was examined for selected patient characteristics and baseline covariates. The patient characteristics and baseline variables of interest were pre-selected as follows:

| | |
|--------------|------------------------|
| Age | (...12, >12 years old) |
| Tanner Stage | (...3, >3) |
| Gender | (male, female) |
| Race | (White, Black, Others) |
| Country | (U.S., Non-U.S.) |

For each subgroup variable listed above, the stratified (weight) regression model, as described in the primary analysis for the primary hypothesis, was performed separately within each subgroup. The slope estimates along with 95% confidence intervals were provided.

RESULTS

Patient' demographics and baseline characteristics are shown in Tables 4.

Table 5 demonstrates the summary of trough sitting diastolic blood pressure changes during the study.

Table 4.

Baseline Patient Characteristics by Treatment Group

| | Low Dose 2.5/5 mg (N=70) | Middle Dose 25/50 mg (N=41) | High Dose 50/100 mg (N=66) | Total (N=177) |
|---|--------------------------------|-----------------------------------|----------------------------------|------------------|
| | n (%) | n (%) | n (%) | n (%) |
| Gender | | | | |
| Male | 38 (54) | 24 (59) | 37 (56) | 99 (56) |
| Female | 32 (46) | 17 (41) | 29 (44) | 78 (44) |
| Race | | | | |
| White | 34 (49) | 22 (54) | 42 (64) | 98 (55) |
| Hispanic | 13 (19) | 9 (22) | 16 (24) | 38 (21) |
| Black | 12 (17) | 3 (7) | 5 (8) | 20 (11) |
| Other [†] | 11 (16) | 7 (17) | 3 (5) | 21 (12) |
| Age (Years) | | | | |
| <6 [†] | 0 (0) | 3 (7) | 1 (2) | 4 (2) |
| 6 to 12.9 [†] | 30 (43) | 14 (34) | 35 (53) | 79 (45) |
| 13 to 16.9 | 40 (57) | 24 (59) | 30 (45) | 94 (53) |
| Mean | 12.3 | 12.1 | 11.6 | 12.0 |
| SD | 3.2 | 3.2 | 2.9 | 3.1 |
| Median | 13.5 | 13.0 | 12.0 | 13.0 |
| Range | 6 to 16 | 5 to 16 | 5 to 16 | 5 to 16 |
| Duration of Hypertension (Years) | | | | |
| ≤1.01 | 31 (44) | 21 (51) | 27 (41) | 79 (45) |
| 1.02 to 2 | 18 (26) | 5 (12) | 7 (11) | 30 (17) |
| 2.01 to 4 | 11 (16) | 6 (15) | 17 (26) | 34 (19) |
| 4.01 to 8 | 7 (10) | 6 (15) | 10 (15) | 23 (13) |
| 8.01 to 12 | 2 (3) | 1 (2) | 5 (8) | 8 (5) |
| 12.01 to 16.9 | 1 (1) | 2 (5) | 0 (0) | 3 (2) |
| Mean | 2.1 | 2.6 | 2.6 | 2.4 |
| SD | 2.6 | 3.6 | 2.8 | 2.9 |
| Median | 1.2 | 1.0 | 1.9 | 1.4 |
| Range | 0.08 to 13.8 | 0.08 to 16.8 | 0.08 to 11.1 | 0.08 to 16.8 |

Table 5.

Summary of Trough SiDBP (mm Hg) in Period I (Day 1 to Day 22)
(Intention-to-Treat Approach)

| | N [†] | Day 1 | Day 15 | Day 22 | Mean Change (Day 15-Day 1) (SD) | Mean Change (Day 22-Day 1) (SD) | 95% CI For Mean Change (Day 22-Day 1) |
|----------------------|----------------|-------|--------|--------|---------------------------------------|---------------------------------------|---|
| Low (2.5/5 mg) | 70 | 87.92 | 80.80 | 81.91 | -7.12 (6.47) | -6.01 (7.61) | -7.82, 4.19 |
| Middle (25/50 mg) | 40 | 89.38 | 78.40 | 77.73 | -10.98 (8.66) | -11.65 (9.08) | -14.55, -8.75 |
| High (50/100 mg) | 64 | 88.80 | 78.56 | 76.59 | -10.24 (9.14) | -12.21 (8.86) | -14.42, -10.00 |

[†] AN 1205, AN 1215, and AN 1317 are excluded from efficacy analyses. (See Section II.C.2.)
N = Patients with both baseline (on Day 1) and postdose measurements.
SD = Standard deviation.
Mean Change = Measurement on Day 15 (or 22) minus measurement on Day 1.
CI = Confidence Interval

The increase of the losartan doses from low to middle and high were associated with larger reductions in SiDBP. Results for middle and high doses were similar (Figure 2).

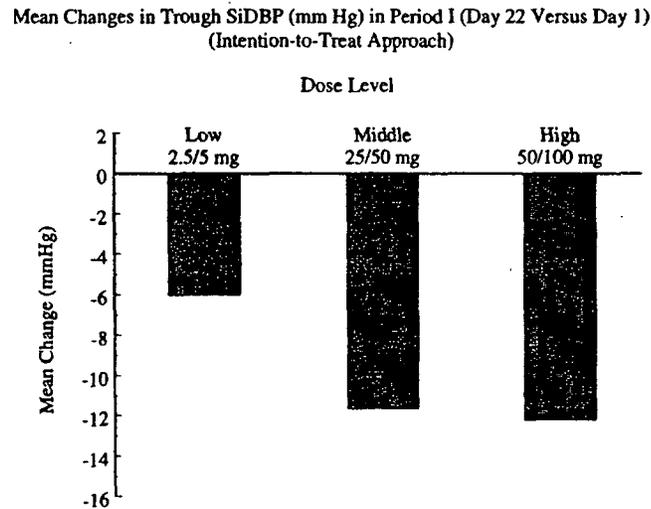
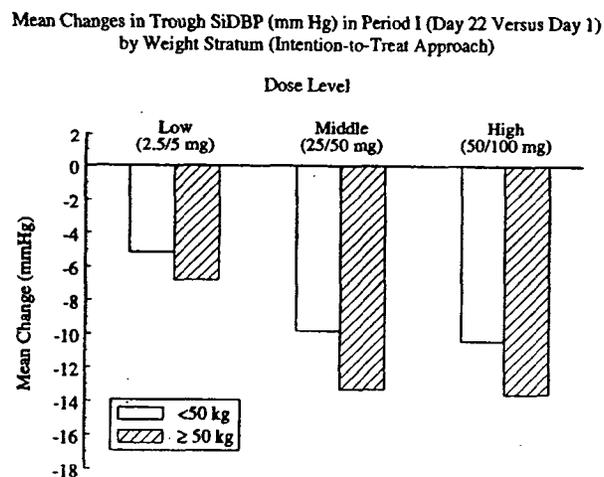


Figure 2.

Since patients were stratified by weight at randomization, patients of lighter weight received smaller doses. Heavier patients had a numerically greater reduction in trough SiDBP than lighter patients at the low- middle- and high-dose levels. Increasing doses of losartan were associated with greater reductions for both weight groups (Figure 3).

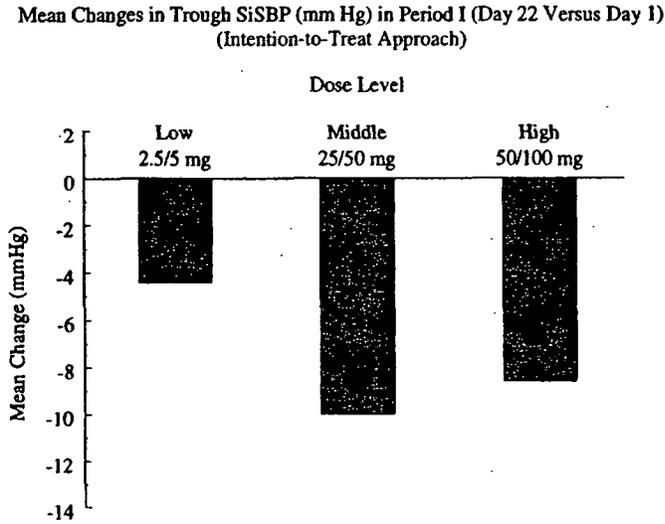
Figure 3.



The antihypertensive effect of losartan was also estimated using sitting systolic blood pressure (SiSBP), and standing diastolic and systolic blood pressures.

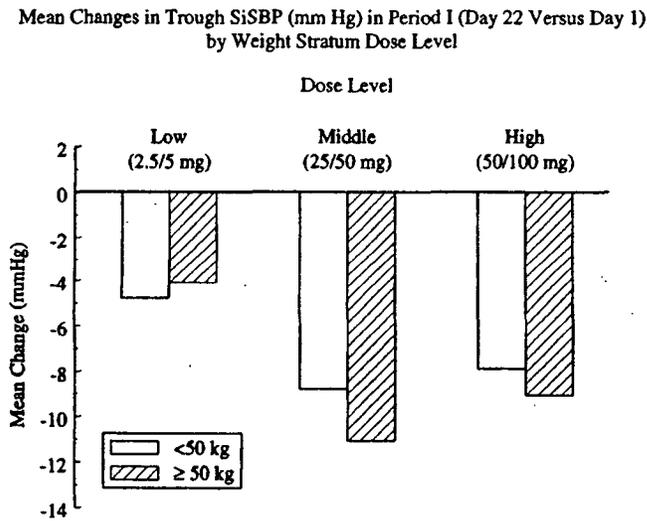
Similar results were shown for the changes in sitting systolic blood pressure, Figure 4.

Figure 4.



The changes in SiSBP stratified by weight are shown in Figure 5.

Figure 5.



COMMENT:

Statistical data analysis of this study was performed satisfactorily, and no additional PK/PD modeling was conducted by the reviewer. The review of statistical data analysis performed by the sponsor is provided by the medical officer.

CONCLUSION:

Losartan appears to be effective in lowering blood pressure when administered to children 6 to 16 years of age at starting doses of 2.5, 25 and 50 mg/day with following titration to 5, 50, and 100 mg/day. SiDPB decreased for 12 mmHg after 22 days of repeated administration at middle and high doses. Similar results were observed for SiSBP: it decreased for 9-10 mmHg after 22 days of repeated administration at middle and high doses.

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