ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

for

Cozaar Tablets

(50 mg losartan potassium)

NDA 20-386 / SE5-029

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products
(HFD-110)

May 20, 2002

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-386 / SE5-029

Cozaar Tablets

(50 mg losartan potassium)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

In support of their supplemental new drug application for Cozaar Tablets, Merck & Co., Inc. has prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal from use of the product.

Losartan potassium is a chemically synthesized drug, which is currently approved to treat hypertension. This supplemental application describes a pediatric formulation using 50 mg Cozaar Tablets to be administered to pediatric hypertensive patients.

Losartan potassium may enter the environment from patient use and disposal. It is expected to enter predominately into the aquatic environment. As the drug is expected to persist in the environment for some time, the toxicity of losartan potassium to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at expected environmental concentrations.

In U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of the unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY
Florian Zielinski
Chemist, Center for Drug Evaluation and Research

CONCURRED BY
Nancy B. Sager
Environmental Officer, Center for Drug Evaluation and Research

CONCURRED BY
Yuan-yuan Chiu, Ph.D.
Director, Office of New Drug Chemistry, Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Appended Electronic Signature Page

NDA 20-386 COZAAR® (Losartan Potassium)
Losartan Pediatric Use
Environmental Assessment

1. **Date:** 20 September 2001

2. **Name of Applicant/Petitioner:** Merck & Co., Inc.

3. **Address:** Sumneytown Pike, West Point, PA 19486

4. ***Description of Proposed Action:***

   a. **Requested Approval**

   The Merck Research Laboratories, a division of Merck & Co., Inc., is filing a Supplemental New Drug Application to NDA 20-386 COZAAR® (losartan potassium) to request approval for a pediatric formulation using 50 mg COZAAR® tablets. An environmental assessment (EA) has been submitted pursuant to 21 CFR part 25. NDA 20-386 also includes 25 mg and 100 mg tablets. These are not included in this request. COZAAR® 50 mg tablets are packaged in high density polyethylene bottles (HDPE).

   b. **Need for Action**

   A pediatric formulation has been developed for COZAAR® to support the use of losartan in pediatric hypertensive patients who may be unable to swallow COZAAR® tablets.

   c. **Locations of Use**

   The product will be used in hospitals, clinics, and/or in homes throughout the United States.

   d. **Disposal Sites**

   At U.S. hospitals, pharmacies, or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy, or clinic procedures. In the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system, which may include landfills, incineration, and recycling, although minimal quantities of unused drug could be disposed of in the sewer system.

NDA 20-386 COZAAR® (Losartan Potassium)
Losartan Pediatric Use
Environmental Assessment

5. ***Identification of Substances that are Subject of the Proposed Action:***

   a. **Nomenclature**

      i. **Established Name (U.S. Adopted Name – USAN):** Losartan potassium

      ii. **Brand/Proprietary Name/Trade Name:** COZAAR®

      iii. **Chemical Names:**

      - **Chemical Abstracts (CA) Index Name (inverted form):** 1*H*-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt

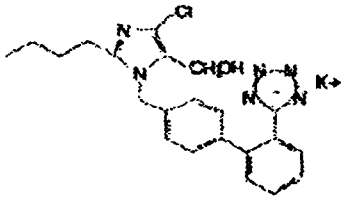
      - **Systematic Chemical Name (uninverted form):** 2-butyl-4-chloro-1-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1*H*-Imidazole-5-methanol monopotassium salt

   b. ***Chemical Abstracts Service (CAS) Registration Number:*** *124750-99-8*

   c. **Molecular Formula:** $C_{22}H_{22}ClN_6OK$

   d. **Molecular Weight:** 461.01

   e. **Structural (graphic) Formula:**



6. Environmental Issues:

Summary. The pharmacologic agent losartan potassium that is the active material in COZAAR® (NDA 20-386), is also an active in a related drug HYZAAR® (NDA 20-387, losartan potassium/hydrochlorothiazide). The Expected Introduction Concentration (EIC) for losartan for both products, based on the greatest of fifth year production estimates (Confidential/Appendix B) is — ppb, or — ppb applying metabolism as a depletion factor. Since the EIC is greater than 1 ppb, an Environmental Assessment (EA) was conducted as described by the Guidance for Industry (July, 1998). Data and testing procedures used for the assessment were

originally reported in the 1995 revised Environmental Assessment (Bacher, 1995) submitted with original NDA 20-386. Based on the very slight environmental toxicity of losartan, no environmental impact is expected from the use of this drug.

Physical/Chemical Characteristics. A Summary of Physical/Chemical data is given in Appendix A. Losartan is freely soluble in water (500 mg/mL). The Log K_{ow} is 1.19 (pH 7.0). The solubility and low octanol/water partitioning suggest little potential for binding to sludge or other organic material. As a result, losartan is not expected to bind to sludge that is applied to soil and, therefore, soil biodegradation data were not obtained. The vapor pressure of losartan ($<10^{-7}$ torr) also indicates that the compound will not volatilize to the air compartment. The aquatic environment was further evaluated since patient use of losartan will introduce it to the water compartment via POTW (Publicly Owned Treatment Works) effluents.

Depletion Mechanisms. Depletion mechanisms are summarized in Appendix A. While losartan is stable to hydrolysis and biodegradation, it photolyzes rapidly in the presence of light. This characteristic was not included in the assessment due to the unpredictable potential for exposure to light, but does play a role in reducing losartan in the aquatic environment. The absorbance of an oral dose of losartan is 33%. (Supporting data and test methodology were provided in original NDA 20-386, Part F (Bacher, 1995). This depletion mechanism is factored into the reported EIC. Absorbed losartan is extensively metabolized with 10% or less being excreted as a mix of metabolites and some residual losartan.

EIC Calculation. The EIC was calculated in accordance with the formula given in Guidance for Industry (July, 1998), and was determined to be —— ppb without consideration of metabolism, or — ppb (µg/L) if dose absorbance is factored in. The calculations are provided in Appendix B/Confidential. Since the EIC exceeded 1 ppb, a Tiered Assessment was performed in accordance with the Guidance.

Tier 1 Assessment. Losartan does not partition to the soil compartment. The high solubility and low K_{ow} preclude partitioning to sludge that may be applied to soil. Losartan also does not volatilize to air (vapor pressure $<10^{-7}$ torr). However, losartan may potentially enter the water compartment so that route was evaluated further. Losartan does not rapidly hydrolyze or biodegrade in water. Microbial Inhibition Tests were performed, and Appendix A provides these data. The MIC's for all organisms tested are > 1000 mg/L. The inhibition of activated sludge organisms is ≥ 1000 mg/L. Consequently the EIC for losartan will not impact aquatic or sewage plant microorganisms. Since the Log K_{ow} for losartan is less than 3.5, the assessment proceeded to Tier 1. Acute toxicity values for losartan are given in Appendix A (All test methods and results were reported in the Environmental Assessment submitted in 1995.) The most sensitive organism in acute toxicity testing was *Daphnia magna*

with a 48 hr. LC_{50} = 331 mg/L. The EIC (—— µg/L) was selected as the MEEC (Maximum Expected Environmental Concentration).

[331 x (1000, conversion factor mg to µg)] + —' = ——

Since the ratio is greater than 1000, and there are No Observed Effects for losartan at the MEEC, the assessment was considered complete with a conclusion of no environmental impact due to the use of losartan in both COZAAR® and HYZAAR®.

7. Mitigation Measures:

No adverse environmental effects have been identified. Therefore, no mitigation measures are needed.

8. Alternatives to the Proposed Action:

No potential adverse environmental effects have been identified for the proposed action so no alternatives are necessary.

9. List of Preparers:

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Safety & the Environment
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M. S., Microbiology, Indiana University, Bloomington, IN, 1970
Ph.D., Microbiology, Indiana University, Bloomington, IN, 1972

10. References:

a. Bacher, S. 1995. COZAAR and HYZAAR Environmental Assessments: Revision submitted to FDA (Chemical and Pharmaceutical Manufacturing and Control Documentation, Section F. Environmental Assessment).

b. U.S. Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). 1998. Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications. CMC 6, Revision 1.

11. Appendices:

(Attached)

NDA 20-386 COZAAR® (Losartan Potassium)
Losartan Pediatric Use
Environmental Assessment

APPENDIX A/Non-Confidential

NDA 20-386 COZAAR® (Losartan Potassium)
Losartan Pediatric Use
Environmental Assessment

APPENDIX A: DATA SUMMARY TABLE/NON-CONFIDENTIAL

PHYSICAL/CHEMICAL CHARACTERIZATION	
Water Solubility	>500 mg/mL
Dissociation Constant (pK_a)	4.1 (1% methanol) 4.9 (1:1 methanol:water)
Log Octanol/Water Partition Coefficient (Log K_{ow})	Log K_{ow} = 1.19 @ pH 7.0
Vapor Pressure	$<10^{-7}$ torr @ 59°C
DEPLETION MECHANISMS	
Hydrolysis	Stable at pHs 5, 7, and 9
Aerobic Biodegradation	28 day recovery = 93.1%
Soil Biodegradation	Not relevant
Photolysis	Half-life @ pH 5 = 10.9 hrs Half-life @ pH 7 = 11.8 hrs Half-life @ pH 9 = 17.6 hrs
Bioavailability	ca 33% orally (67% into waste stream)
Metabolism	90 % of absorbed dose is metabolized 10% excreted – 4% losartan 6% active carboxylic acid metabolite
ENVIRONMENTAL EFFECTS	
Microbial Inhibition	*Azotobacter paspali* MIC > 1000 mg/L *Scenedesmus quadricauda* MIC > 1000 mg/L *Fusarium acuminatum* MIC > 1000 mg/L *Aspergillus niger* MIC > 1000 mg/L *Pseudomonas putida* MIC > 1000 mg/L *Anabaena flos-aquae* MIC > 1000 mg/L *Paramecium caudatum* MIC > 1000 mg/L
Activated Sludge Inhibition	Maximum Non-Inhibitory Effect Concentration ≥ 1000 mg/L
Acute Toxicity	*Daphnia magna* 48 hr. LC_{50} = 331 mg/L *Pimephales promelas* 48 hr. LC_{50} = >1000 mg/L *Oncorhynchus mykiss* 96 hr. LC_{50} = >929 mg/L *O. mykiss* NOEC = >929 mg/L
Chronic Toxicity	*Selenastrum capricornutum* 10 days (Alga) Cell growth NOEC 143 mg/L, MIC = 245 mg/L Growth rate NOEC 245 mg/L, MIC = 381 mg/L *Microcystis aeruginosa* 10 days (Alga) Cell growth NOEC 556 mg/L, MIC = 949 mg/L Growth rate NOEC ≥949 mg/L, MIC ≥ 949 mg/L

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

/s/

Florian Zielinski
5/21/02 12:59:46 PM

Nancy Sager
5/21/02 01:40:26 PM

Yuan-Yuan Chiu
5/22/02 09:05:04 AM
Concurred without comments

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-386/S-019 and 029

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

NDA NUMBER/SUPPLEMENT:	20-386/SE5
SERIAL NUMBER:	S 029
DRUG NAME:	COZAAR (Losartan Potassium)
INDICATION:	Children with Hypertension
SPONSOR:	Merck Research Laboratories
DOCUMENTS REVIEWED:	Vols. 1 and 2

BIOMETRICS DIVISION:	**DIVISION OF BIOMETRIC I (HFD-710)**
REVIEWER:	Jasmine Choi, M.S.
TEAM LEADER:	HM James Hung, Ph.D.
DIVISION DIRECTOR:	George Chi, Ph.D.
MEDICAL DIVISION:	**CARDIO-RENAL DRUG PRODUCTS (HFD-110)**
PROJECT MANAGER:	Mr. Edward Fromm
MEDICAL OFFICER:	Abraham Karkowsky M.D.

Distribution: NDA 20-386/S029
HFD-110/Karkowsky
HFD-110/Stockbridge
HFD-110/Throckmorton
HFD-110/Fromm
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HFD-710/Hung
HFD-710/Mahjoob
HFD-710/Chi
HFD-710/Anello

File Directory: C:/nda/reviews/cozaar.doc

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Tables

Figures

1 Executive Summary and Statistical Findings

1.1 Overview of the Studies Reviewed

Losartan was approved for the treatment of hypertension in adults. This current NDA supplement was submitted for an approval of Losartan in hypertensive pediatric patient. This NDA supplement included the results of 2 studies recently conducted in pediatric patients: an open-label study to investigate the pharmacokinetics of losartan in hypertensive children and infants (P225); and a double-blind, randomized dose-response study of losartan in children with hypertension (P227). This NDA also provided 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 bioabailability of the losartan suspension and marketed 50mg tablets (P216). This reviewer evaluated the dose-response relationship study (P227)

Study P227 is a double-blind, randomized, multicenter study to assess the dose response of losartan and to determine whether losartan is well tolerated and safe in hypertensive pediatric patients.

The study begins with a 2 to 7-day washout period in which patients will discontinue their prior antihypertensive medication. Patients were then allocated, via a randomized allocation schedule, to receive 1 of 3 losartan treatments once daily for 21 days: low-dose regimen (2.5/5 mg), middle-dose regimen (25/50 mg), or high-dose regimen (50/100 mg). Patients who weighed <50 kg received the lower dose in the respective treatment group (2.5 mg, 25 mg, or 50 mg), and patients who weighed ≥ 50 kg received the higher dose (5 mg, 50 mg, or 100 mg). Patients in the high-dose group (5/50/100mg) received a half dose, respectively, for the first 2 days, and the full dose for the rest of the 21-day double-blind period (Period I), unless limited by an adverse experience or excessive hypotension. Following the 21-day treatment period, patients were randomly assigned to either continue the double-blind medication for an additional 14 days or placebo for 14 days (Period II). Following Period I and II, patients were able to enter an optional, open-label 6-month extension.

1.2 Principal Findings

The primary efficacy endpoint was the slope of change in trough SiDBP (sitting diastolic blood pressure) at the end of Period I, as compared to baseline, as a function of dose. A stratified simple linear regression model was applied for the evaluation of change in trough SiDBP (Day 22 vs. Day 1) with weight group as the stratified intercepts and dose ratio (1:10:20) as the continuous covariate. The slope analysis investigated whether increasing the dose of losartan was associated

with greater reduction of the trough SiDBP. The results showed a dose response for losartan with a slope of –0.32 mmHg per unit increase in dose ratio and p-value <0.0001 (Table 1).

Table 1: Primary Slope Analysis of Day 22 (ITT)

	Estimate	SE*	P-value
Slope (β) (mmHg per unit increase in dose ratio)	-0.32	0.08	<0.0001

*Standard error

Normality of the regression model was questionable after Shapiro-Wilk normality test. Therefore, Jonckheere-Terpstra nonparametric test for a positive dose response was conducted. The nonparametric analysis confirmed the significant dose response for losartan with p-value < 0.0001.

The secondary objective was to determine whether discontinuation of active losartan treatment was associated with return of hypertension. The increase for each dose level was measured by the difference of mean changes (placebo minus losartan) from the end of Period I (Day 22) to the end of Period II (or whenever the patient's BP returned to or exceeded baseline levels). For this analysis, an ANOVA model was performed. The difference between losartan and placebo was significant within each of the middle- (p=0.0351) and high- (p=0.0274) dose levels. The difference between losartan and placebo within low dose was 1.11 mmHg with insignificant p-value=0.628, but the trended in favored direction. The overall F-test for existence of an increase in trough SiDBP between placebo-treated patients as compared with losartan-treated patients was statistically significant (p=0.0240). The results indicate an increase in blood pressure among patients switched to placebo compared with patients who continued on losartan treatment. Table 2 summarizes the results from the analysis.

Table 2: ANOVA Model for Secondary Efficacy Analysis

	Estimate (mm Hg)	Standard Error	Numerator Degrees of Freedom	p-Value
Overall Treatment Effect			3	0.0240
Difference (Losartan vs. Placebo):				
— Low Dose	1.11	2.28	1	0.6280
— Middle Dose	6.70	3.15	1	0.0351
— High Dose	5.38	2.42	1	0.0274
Mean of Middle + High	6.04	1.99	1	0.0027
Mean of Low + Middle + High	4.40	1.53	1	0.0046
Weight Stratum	-1.05	1.48	1	0.4818
Note: Among the total of 174 patients, 164 patients entered Period II and had postrandomization blood pressure measurements in Period II.				

1.3 Conclusions

Both parametric (stratified simple regression) and nonparametric (Jonckheere-Terpstra) tests showed statistically significant positive dose-response relationship of losartan treatment in pediatric patients.

Statistically significant increase in blood pressure among patients switched to placebo compared with patients who continued on losartan treatment was observed in the middle and high dose levels.

All point estimates from results of the primary analyses with respect to slope (in Period I) and all the mean differences across the three dose levels in Period II trended in the favored direction in subgroup analysis by age, gender, race country and Tanner stage.

2 Statistical Review and Evaluation of Evidence

2.1 Introduction

Losartan was the first angiotension II antagonist approved for the treatment of hypertension in adults. Prior to the data reported here, there were no data from prospective, controlled, adequately sized studies with an angiotension II antagonist in pediatric patients. In addition, data have not been available regarding a suspension formulation of losartan for use by children who are unable to swallow tablets or who require a dose less than the lowest available tablet strength.

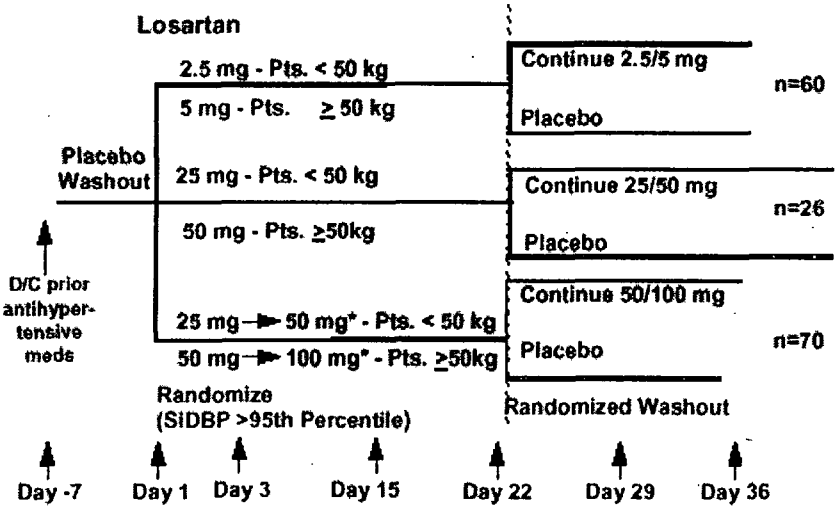
This NDA supplement includes the results of 2 studies recently conducted in pediatric patients: an open-label study to investigate the pharmacokinetics of losartan in hypertensive children and infants (P225); and a double-blind, randomized dose-response study of losartan in children with hypertension (P227). This document also provides information on the preparation of an extemporaneous suspension formulation of losartan potassium for use in patients that cannot swallow tablets, and data from an open-label, two-period crossover study to determine the relative bioavailability of the losartan potassium suspension formulation and the marketed tablets in healthy adults (P216). This reviewer evaluated the dose-response relationship study (P227)

2.2 Background and Study Design

Study P227 is a double-blind, randomized, multicenter study to assess the dose response of losartan and to determine whether losartan is well tolerated and safe in hypertensive pediatric patients. The basic design is shown in Figure 1.

The study begins with a 2 to 7-day washout period in which patients will discontinue their prior antihypertensive medication. Patients were then allocated, via a randomized allocation schedule, to receive 1 of 3 losartan treatments once daily for 21 days: low-dose regimen (2.5/5 mg), middle-dose regimen (25/50 mg), or high-dose regimen (50/100 mg). Patients who weighed <50 kg received the lower dose in the respective treatment group (2.5 mg, 25 mg, or 50 mg), and patients who weighed ≥ 50 kg received the higher dose (5 mg, 50 mg, or 100 mg). Patients in the high-dose group (5/50/100mg) received a half dose, respectively, for the first 2 days, and the full dose for the rest of the 21-day double-blind period (Period I), unless limited by an adverse experience or excessive hypotension. Following the 21-day treatment period, patients were randomly assigned to either continue the double-blind medication for an additional 14 days or placebo for 14 days (Period II). Following Period I and II, patients were able to enter an optional, open-label 6-month extension.

Figure 1 : Study Design



2.3 Data Analyzed and Sources

Data used for review is from the electronic submission received on 12/21/01. The network path is " \\CDSESUB1\N20386\S_029\2001-12-21A\crt\ DATASETS\ 227" in the EDR. The following volumes were reviewed: 1 and 2.

2.4 Study Objectives

The primary objective of this study was to define a dose-response relationship for losartan in hypertensive children aged 6 to 16 years after a 21-day double-blind treatment period, and to investigate the safety and tolerability of losartan in the dose rage 2.5 to 100 mg in hypertensive children aged 6 to 16 years. The secondary objective of this study was to determine whether discontinuation of active losartan treatment is associated with return of hypertension.

2.5 Efficacy Endpoints

The primary efficacy endpoint was the slope of change in sitting diastolic blood pressure (SiDBP) at the end of the 22-day, double-blind treatment period as compared to baseline as a function of dose.

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

2.6 Sample Size Considerations

For the dose-response analysis at the end of the initial 21-day treatment period, with a total of at least 156 children, the power to detect a significant common trend (with 3 losartan dose levels) at a significance level of alpha=0.05 is approximately 80% for a 4-mm Hg difference in SiDBP between the extreme doses (assumes a standard deviation of 8 mmHg in SiDBP for change from baseline at Day 22). The power calculation is based on the simple regression model on dose ratio (1, 10, and 20).

2.7 Stratification

The study was stratified by weight: < 50 kg and ≥ 50 kg.

2.8 Interim Analysis

No interim analysis for efficacy was planned for this study.

2.9 Efficacy Analysis Methods

Intent-to-treat (ITT) using the last-measurement-carried-forward approach was used as the primary approach to address the primary hypothesis in the initial 21-day treatment period. In addition, supportive, per-protocol (PP) analyses and subgroup analyses were also carried out to assess the robustness of the overall findings. All tests of significance were 2-sided and performed at the 5% level of significance.

For the primary hypothesis, 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. In addition, a distribution-free test procedure for ordered alternatives, called the Jonckheere-Terpstra test was also conducted in the case when the assumptions for this regression model failed.

The objective for the secondary hypothesis was to determine whether discontinuation of active losartan treatment by switching to placebo was associated with an increased in blood pressure. The corresponding efficacy endpoint was the group difference (treatment – placebo) of mean change (end of Period II – end of Period I) in trough SiDBP for each assigned dose level in Period II; i.e., mean change in placebo group – mean change in treatment group. A statistically significantly positive group difference would provide strong evidence that discontinuation of losartan treatment by switching to placebo was

associated with an increase in SiDBP in the associated dose level. The analysis was to estimate the average group difference across the three dose levels using the statistical model of one-way ANOVA with a factor of 6 treatments (low/low, low/placebo, middle/middle, middle/placebo, high/high, high/placebo) on change in trough SiDBP.

2.10 Sponsor's Results and Statistical Reviewer's Findings/Comments

2.10.1 Baseline Characteristics

The baseline demographic characteristics including age, gender, race, and duration of hypertension were balanced between the three treatment groups (2.5/5mg, 25/50 mg, and 50/100 mg). The following table shows the baseline demographics of the patient population by treatment groups.

Table 3: Baseline 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)	3 (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
Media	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

[#]"Other" includes mixed race, Asian and American Indian patients.

• With permission from the Merck Clinical Monitor and the investigator, 3 otherwise healthy 5-year-old children (i.e., AN 1030 - 5 years, 10 months; AN 1207 - 5 years, 9 months; and AN1377 - 5 years, 7 months) entered the study; all 3 patients were Tanner Stage =3. One of these patients (AN 1205) discontinued early due to a drug-dispensing error at the study site, and was subsequently re-randomized into the study as AN 1207. This patient is counted twice in the number of patients <6 years of age.
s AN 1215 (age 8 years, 7 months) discontinued early due to a study site error and was re-randomized as AN 1220 (age 8 years, 8 months). This patient is counted twice in the number of patients in the 6- to 12.9-year age group.
SD = Standard deviation.

The following table summarizes patient baseline blood pressure, weight, and Tanner Stage by dose. There were 3 patients (An 1205/1207, An 1316, and AN 1442) who weighed slightly < 20 kg while inclusion criteria stated that patients' body weight should be ≥20 kg. Because these patients met all other study criteria, they were approved to enter the study by the Merck Clinical Monitor and the Investigator.

Table 4: Baseline Patient Blood Pressure, Weight, and Tanner Stage

	Low Dose 2.5/5 mg (N=70)	Middle Dose 25/50 mg (N=40)	High Dose 50/100 mg (N=64)	Total (N=174)
	N (%)	N (%)	N (%)	N (%)
Sitting Diastolic Blood Pressure (mmHg)				
Mean	87.9	89.4	88.8	88.6
SD	6.2	7.6	7.3	6.9
Median	88.3	87.3	87.5	87.5
Range	74.5 -107.5	79.0 - 109.0	76.0 – 110.0	74.5 - 110.0
Sitting Systolic Blood Pressure (mmHg)				
Mean	129.8	132.2	128.0	129.7
SD	12.0	16.1	12.1	13.1
Median	130.8	127.8	127.3	129.0
Range	107.0 -156.5	110.0 - 178.5	102.5 – 153.0	102.5 -178.5
Weight (kg)				
Mean	58.5	57.2	59.8	58.7
SD	24.3	29.6	27.1	26.5
Median	54.0	51.0	57.6	54.7
Range	17.0 – 117.9	19.2 – 152.0	18.0 – 131.0	17.0 – 152.0
Tanner Stage				
≤3: number(%)	38 (54.3)	24 (60.0)	41 (64.1)	103 (59.2)
>3:number (%)	32 (45.7)	16 (40.0)	23 (35.9)	0.8)

2.10.2 Primary Efficacy Analyses

The objective of the analysis for the primary hypothesis in Period I was to assess the existence of a positive dose response (i.e. a negative slope for change in

trough SiDBP from Day 1 to 22) with increasing doses of the losartan treatment in hypertensive children.

Among 177 allocation numbers assigned, 2 patients each received 2 allocation numbers, and 1 patient had no postdrug blood pressure measurement. Therefore, the effective sample size in Period I was 174 patients for efficacy analyses.

Table5 shows a summary of trough SiDBP, including changes and standard deviation in trough SiDBP at baseline (Day 1), on Day 15, and Day 22 as well as the difference (mean change) between the 2 measurements at each of the 3 dose levels.

Table 5: Summary of Trough SiDBP in Period I

	N	Day 1	Day 15	Day 22	Mean Change (Day 15 - 1) (SD)	Mean Change (Day 22 - 1) (SD)
Low (2.5/5)	70	87.92	80.80	81.91	-7.12 (6.47)	-6.01 (7.61)
Middle (25/50)	40	89.38	78.40	77.73	-10.98 (8.66)	-11.65 (9.08)
High (50/100)	64	88.80	78.56	76.59	-10.24 (9.14)	-12.21 (8.86)

The mean changes were all negative indicating that the trough SiDBP measurements were reduced following treatment with losartan. Increasing doses were associated with greater reductions from the low-dose to the middle- and high-dose groups. The difference of the mean changes between the extreme doses (High vs. Low) was –6.2 mmHg on Day 22.

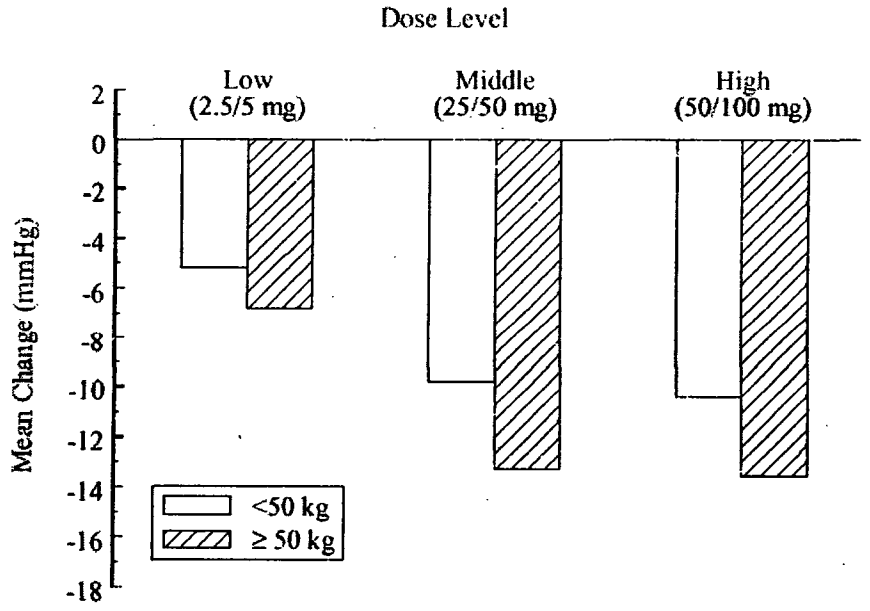
The protocol specified stratification by weight at randomization. Lighter patients were defined as weight <50 kg, and heavier patients were defined as weight ≥50kg. Lighter patients received 2.5, 25, and 50 mg for the low-, middle-, and high-dose groups, respectively, while heavier patients received 5, 50, and 100 mg for the low-, middle-, and high-dose groups, respectively. Table 6 presents the mean changes (Day 22 vs. Day 1) and standard deviations stratified by weight at randomization.

Table 6: Mean Changes from Day 1 to Day 22 in Trough SiDBP in Period I by Weight Stratum (ITT)

	< 50 kg			≥ 50 kg		
	Low (2.5 mg)	Middle (25 mg)	High (50 mg)	Low (5 mg)	Middle (50 mg)	High (100 mg)
N	34	19	28	36	21	36
Mean Changes	-5.16	-9.84	-10.43	-6.81	-13.29	-13.60
SD	8.71	11.16	8.38	6.43	6.55	9.09

The mean changes were all negative, indicating that the trough SiDBP measurements were reduced in both weight groups. 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, although in both groups the middle- and high-dose groups had similar results. The following Figure is the corresponding graphic representation.

Figure 2: Mean Changes in Trough SiDBP in Period I by Weight Stratum



A stratified simple linear regression model was applied for the evaluation of change in trough SiDBP (Day 22 vs. Day 1) with weight group as the stratified intercepts and dose ratio (1:10:20) as the continuous covariate. The slope analysis

investigated whether increasing the dose of losartan was associated with greater reduction of the trough SiDBP. The results showed a dose response for losartan with a slope of –0.32 mmHg per unit increase in dose ratio and p-value <0.0001. The pediatric patients with weight ≥50 kg had a greater mean change (2.59mmHg; p=0.0444) in trough SiDBP from baseline than those patients with weight <50 kg. The table below summarizes the results from the primary analysis.

Table 7: Primary Slope Analysis of Day 22 (ITT)

	Estimate	SE*	P-value
Slope (β) (mmHg per unit increase in dose ratio)	-0.32	0.08	<0.0001

*Standard error

The consistency of slope within each weight stratum was also investigated using the regression model with terms including weight strata, dose ratio, and interaction between weight strata and dose ratio. The test for interaction between dose ratio and weight was not significant; p=0.6327.

A Shapiro-Wilk test for normality of the regression model indicated non-normality (p=0.0025). Since the normality assumption associated with the regression model is questionable, the Jonckheere-Terpstra nonparametric test for a positive dose response was conducted with and without weight strata and for each weight stratum. The nonparametric analysis confirmed the significant dose response for losartan. The following table shows the results of nonparametric analysis.

Table 8:Jonckheere-Terpstra Nonparametric Test

	By Weight Stratum		Without Stratum
	< 50kg	≤ 50kg	
p-value	0.0156	0.0004	< 0.0001

Reviewer's Comments:

1. Statistically strong evidence for a positive dose-response relationship was observed by both parametric (stratified simple regression) and nonparametric (Jonckheere-Terpstra test) tests.

In order to evaluate the robustness of the significant dose response found in the slope analysis of trough SiDBP, 2 supportive analyses were performed.

Per-Protocol Analysis

Among 174 patients who entered Period I, 10 patients were excluded from PP analysis, so 164 patients were included in the analysis. The following table summarizes the results from the per-protocol analysis in Period I.

Table 9: Supportive Analysis: Slope Analysis of PP Population.

	Estimate	SE*	P-value
Slope (β) (mmHg per unit increase in dose ratio)	-0.34	0.08	<0.0001

*Standard error

The results are similar to those obtained from the primary ITT analysis.

ANOVA Model

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. Table10 summarizes the results from the ANOVA model.

Table 10: Supportive Analysis : ANOVA Model (ITT)

	Estimate (SD)	d.f.	p-value
Dose		2	<0.0001
High vs. Low	-6.03 (1.46)	1	<0.0001
Middle vs. Low	-5.58 (1.67)	1	0.0010
High vs. Middle	-0.45 (1.70)	1	0.7918
Weight Stratum		1	0.0379
Dose*Weight		2	0.8190

In this ANOVA model the nominal dose levels and weight strata were used, while in the regression model in the primary analysis the dose ratio (1:10:20) was treated as a continuous covariate. Based on the ANOVA model, the comparisons between high and low doses, and between the middle and low doses were both significantly different from zero (p-value <0.0001), while the comparison between high and middle doses was in the same direction but not significant (p-vlue=0.7918). Therefore, the analysis suggests that the dose-response relationship might not be linear over the ratio of 1:10:20.

Reviewer's Comments:

1. The stratified simple regression for PP population confirms the positive dose-response of losartan.

2. ANOVA model also showed statistically significant positive dose-response relationship of losartan treatment.

2.10.3 Secondary Efficacy Analyses

The secondary objective was to determine whether discontinuation of active losartan treatment was associated with return of hypertension. The secondary hypothesis was that at the end of the subsequent 14-day, double-blind, randomized, placebo-controlled washout period (Period II) following Period I, an increase in trough SiDBP between placebo-treated patients as compared with losartan-treated patients would be observed. The increase for each dose level was measured by the difference of mean changes (placebo minus losartan) from the end of Period I (Day 22) to the end of Period II (or whenever the patient's BP returned to or exceeded baseline levels). Among 174 patients included in the Period I analysis, 10 patients were discontinued in Period I and had no Period II blood pressure measurements. The 10 patients were excluded in the Period II analysis. Therefore, the effective sample size in Period II was 164 patients for the efficacy analyses.

The mean changes and standard deviations of trough SiDBP for the 6 treatment groups are shown in the table below.

Table 11: Mean Changes in Trough SiDBP in Period II (ITT)

	N	Mean Change	Group Difference	95% CI
Low/Low	33	2.4	0.9	-3.3, 5.1
Low/Placebo	35	3.3		
Middle/Middle	15	2.7	6.7	0.8, 12.6
Middle/Placebo	21	9.4		
High/High	29	2.6	5.3	0.1, 10.4
High/Placebo	31	7.9		

For treatment groups that continued losartan therapy (Low/Low, Middle/Middle, and High/High), the mean increases were relatively small (2.4, 2.7, and 2.6 mm Hg, respectively) suggesting that the antihypertensive effect of losartan had essentially stabilized by the end of the 3-week losartan treatment (Period I). The mean increases were larger in the treatment groups that switched to placebo, in particular in the middle- and high-dose levels (3.3, 9.4, and 7.9 mm Hg, for Low/Placebo, Middle/Placebo, and High/Placebo, respectively). The difference between the treatment group means for each dose

level (0.9, 6.7, and 5.3 mm Hg, respectively) indicated a loss of antihypertensive effect when switching to placebo. These data are graphically represented in the following Figure.

Figure 3: Mean Changes in Trough SiDBP in Period II

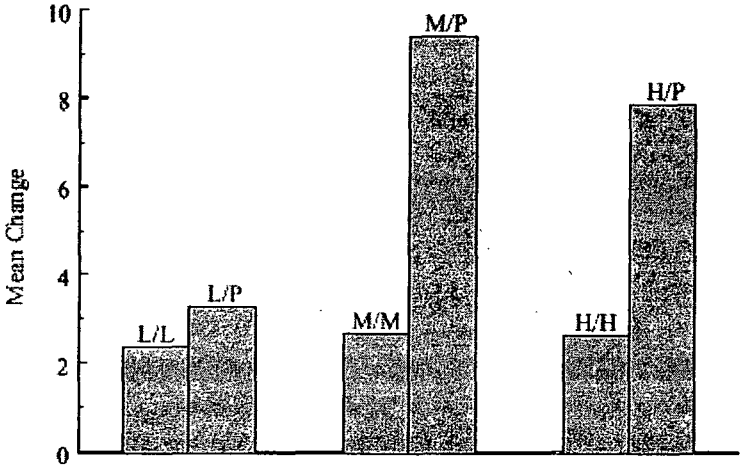


Figure 3 shows that the losartan groups (Low/Low, Middle/Middle, and High/High) had small changes relative to Day 22 measurements and the placebo groups (Low/Placebo, Middle/Placebo, and High/Placebo) revealed increased changes relative to Day 22 (particularly middle- and high-dose groups).

An ANOVA model was performed to test: 1) the overall dose response in Period II; 2) the difference between losartan and placebo for each assigned dose level; 3) the difference between losartan and placebo in the pooled middle- and high-dose levels; 4) the difference between losartan and placebo for all 3 assigned dose levels pooled. Table 12 summarizes the results from the analysis.

Table 12: ANOVA Model for Secondary Efficacy Analysis

	Estimate (mm Hg)	Standard Error	Numerator Degrees of Freedom	p-Value
Overall Treatment Effect			3	0.0240
Difference (Losartan vs. Placebo):				
— Low Dose	1.11	2.28	1	0.6280
— Middle Dose	6.70	3.15	1	0.0351
— High Dose	5.38	2.42	1	0.0274
Mean of Middle + High	6.04	1.99	1	0.0027
Mean of Low + Middle + High	4.40	1.53	1	0.0046
Weight Stratum	-1.05	1.48	1	0.4818
Note: Among the total of 174 patients, 164 patients entered Period II and had postrandomization blood pressure measurements in Period II.				

The model-adjusted estimate of the difference between losartan and placebo pooled over dose levels was 4.40 mm Hg (p-value = 0.0046); the result pooling over just the middle- and high-dose levels was 6.04 mm Hg (p-value = 0.0027). The difference between losartan and placebo was significant within each of the middle- (p=0.0351) and high- (p=0.0274) dose levels. The overall F-test for existence of an increase in trough SiDBP between placebo-treated patients as compared with losartan-treated patients was statistically significant (p=0.0240).

Reviewer's Comments:

1. The results indicate an increase in blood pressure among patients switched to placebo compared with patients who continued on losartan treatment.

2. The difference treatment and placebo within low dose group was 1.11 mmHg with insignificant p-value = 0.628, but trended in favored direction.

2.10.4 Efficacy Findings in Special/Subgroup Populations

A subgroup analysis of primary analysis was conducted to explore whether or not the effect of losartan was consistent in pre-specified subgroups of patients. 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, Hispanic, 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. Table 13 shows the results obtained from the subgroup analysis.

Table 13: Supportive Analysis: Subgroup Analysis for Slopes in Period I

		N[†]	Slope[‡]	Standard Error	95% CI
Age	≤12 yrs	80	-0.33	0.13	-0.59, -0.07
	>12 yrs	94	-0.30	0.09	-0.48, -0.11
Tanner	≤3	103	-0.29	0.10	-0.50, -0.09
	>3	71	-0.35	0.11	-0.58, -0.13
Gender	Male	97	-0.34	0.10	-0.54, -0.14
	Female	77	-0.31	0.12	-0.55, -0.07
Race	White	96	-0.49	0.12	-0.73, -0.25
	Black	20	-0.13	0.17	-0.48, 0.22
	Hispanic	37	-0.22	0.11	-0.44, -0.00
	Others[§]	21	-0.04	0.24	-0.54, 0.46
Country	U.S.	34	-0.25	0.16	-0.57, 0.07
	Non-U.S.	140	-0.32	0.09	-0.49, -0.15

During the 3 weeks of Period I, all the slopes for the blood pressure response for each of the subgroups were negative. The slopes of each category suggest the consistency of the slopes across the categories for every subgroup variable.

The same set of subgroup variables as those specified for the primary efficacy analysis were used for the secondary efficacy endpoint of the mean difference of changes in trough SiDBP between low/low versus low/placebo, middle/middle versus middle/placebo, and high/high versus high/placebo treatments. For each subgroup listed above, an ANOVA model with a factor of 6 treatment groups on change in trough SiDBP was run separately within each subgroup with 95% confidence intervals provided for differences between losartan and placebo within each dose level. Due to small sample size in each treatment group, the weight stratum was excluded from the ANOVA model. Table 14 shows the results obtained from the subgroup analysis.

Table 14: Subgroup Analysis for Mean Difference in Period II

		N[†]	Mean Difference[‡]	Standard Error	95% CI
Age	≤12 yrs	77	3.75	2.58	-1.39, 8.90
	>12 yrs	87	4.72	1.89	0.97, 8.47
Tanner	≤3	96	4.59	2.00	0.63, 8.56
	>3	68	3.68	2.51	-1.33, 8.70
Gender	Male	90	1.83	1.96	-2.06, 5.72
	Female	74	7.42	2.46	2.52, 12.32
Race	White	90	2.64	2.33	-1.99, 7.27
	Black	19	13.14	5.07	2.19, 24.09
	Hispanic	36	4.67	1.99	0.60, 8.74
	Others[§]	19	4.68	5.54	-7.19, 16.56
Country	U.S.	31	10.00	4.35	1.04, 18.96
	Non-U.S.	133	3.38	1.65	0.11, 6.65

[†] AN 1205, AN 1215, and AN 1317 plus 10 additional patients who had no Period II blood pressure measurements are excluded from Period II efficacy analyses. (See Section II.C.2.)

[‡] Mean Difference: mean difference of low-, middle-, and high-dose levels between placebo and losartan treatments.

[§] Others refers to Mixed race, Asian, and American Indian.

Reviewers' Comments:

1. During Period II, all the mean differences within subgroups were positive, indicating the increase in trough SiDBP for patients who switched to placebo.

2. A couple of subgroup stood out among others for a greater difference in mean change of SiDBP. The mean difference of black patients was 13.14 with 95% C.I., (2.19, 24.09), and the mean difference of patients in U.S. was 10.00 with 95% C.I., (1.04, 18.96) while the mean difference of other subgroups were about 3 to 4. Due to small sample size in these subgroups, no statistical conclusion can be drawn from this analysis.

3. Conclusions

Both parametric (stratified simple regression) and nonparametric (Jonckheere-Terpstra) tests showed statistically significant positive dose-response relationship of losartan treatment in pediatric patients.

Statistically significant increase in blood pressure among patients switched to placebo compared with patients who continued on losartan treatment was observed in the middle and high dose levels.

All point estimates from results of the primary analyses with respect to slope (in Period I) and all the mean differences across the three dose levels in Period II trended in the favored direction in subgroup analysis by age, gender, race country and Tanner stage.

/S/

Jasmine Choi M.S.
Mathematical Statistician
Date:

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