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APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
18-998/S-059**

**Clinical Pharmacology and Biopharmaceutics
Review**

JUN 27 2000

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation I

NDA 18-998
Supplement Serial No. 059

SUBMISSION DATE: January 14, 2000

Vasotec™ (Enalapril Maleate)
Merck Research laboratories
West Point, PA

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Pediatric Exclusivity Labeling Supplement

SUBMISSION:

Vasotec™ (enalapril maleate) is a long-acting angiotensin converting enzyme inhibitor, currently approved under NDA 18-998 for the treatment of hypertension.

Reference is made to the FDA's Written Request for pediatric studies on enalapril maleate dated September 8, 1999 and to the Written Agreement between FDA and Merck, dated September 8, 1999. This Supplement (SLR-059) to NDA 18-998 dated January 14, 2000, provides information to support the pediatric exclusivity requirements described in the FDA's Written Request and Written Agreement letters.

The provided pediatric information is as follows:

- Revised Labeling for Vasotec™, incorporating the pediatric information.
- Results of two studies recently conducted in pediatric patients: an open-label PK study in hypertensive infants and children 1 month up to 16 years, and a double-blind, dose-response study in children with hypertension aged 6 to 16 years.
- Information on the preparation of an extemporaneous suspension formulation of enalapril for use in patients that cannot swallow tablets, and data from an open, two period, crossover study to determine the relative bioavailability of the enalapril suspension formulation and the marketed Vasotec™ 10 mg tablets in healthy adults.
- Additional supportive information on the safety of enalapril (including Vasotec™ and Vasotec™ IV Injection) use in pediatric patients.

REVIEWER COMMENTS:

1. It should be noted that the Agency considered that the information provided in Supplement No. 059 to NDA 18-998 was appropriate to fulfill the pediatric exclusivity requirements described in the FDA's Written Request and Written Agreement letters. Therefore, on February 2, 2000, an additional six months of marketing exclusivity to the patent protection for Vasotec™ Tablets, Vasotec™ IV, and Vaseretic™ Tablets was granted by the Agency's "Pediatric Exclusivity Board," chaired by Dr. Mac Lumpkin (see Attachment I).
2. The following studies were provided in this submission.
 - Study No. 168 & 172: An Open-Label Study to Investigate the Pharmacokinetics of Enalapril in Hypertensive Children and Infants.
 - Study No. 170: An Open, Two-Period, Crossover Study to Determine the Relative Bioavailability of the Enalapril Suspension 10 mg and Marketed VASOTEC™ 10-mg Tablets.
 - Study No. 167 & 169: "A Double-Blind Randomized Dose Response Study of Enalapril in Children with Hypertension.
3. Studies No. 168 & 172 and No. 170 are clinical pharmacology and biopharmaceutic studies that have been reviewed by OCPB/DPE1 (see Attachment II and III). However, study No. 167 & 169 is a clinical study that needs to be evaluated by the medical reviewer of DCRDP.
4. Based on the review of studies No. 168 & 172 and 170, OCPB/DPE1 considers that the clinical pharmacology and biopharmaceutic data provided in these studies are appropriate to support the pediatric information included in the proposed labeling.
5. A copy of the revised pediatric-labeling for VASOTEC® Tablets showing the proposed changes is included in Attachment IV. OCPB/DPE1 recommends that the following two subsections of the proposed labeling be modified as follows:

- In the "*Clinical Pharmacology in Pediatric Patients*" subsection of the "CLINICAL PHARMACOLOGY" section of the labeling, it is recommended that the following paragraph:

DRAFT LABELING

be changed to:

A multiple dose pharmacokinetic study was conducted in 40 hypertensive male and female pediatric patients following daily oral administration of 0.07 to 0.14 mg/kg enalapril maleate. At steady state, the mean effective half-life for accumulation of enalaprilat was 14 hours. In children aged 2 to <16 years, the mean urinary recovery of total enalaprilat in 24 hrs was 67%, which reflects the extent of absorption of enalapril. Conversion of enalapril to enalaprilat was in the range of 64-76%.

The overall results of this study indicate that the pharmacokinetics of enalapril in hypertensive children aged 2 month to ≤16 years are consistent across the studied age groups and consistent with pharmacokinetic historic data in healthy adults.

Enalapril maleate given as VASOTEC tablets or suspension formulation, was generally well tolerated in these children.

- In the "Preparation of Suspension (for 200 mL of a 1.0 mg/mL suspension)" subsection of the "DOSAGE AND ADMINISTRATION" section of the labeling, it is recommended that the word VASOTEC™ be incorporated as follows:
 Add 50 mL of Bicitra®** to a polyethylene terephthalate (PET) bottle containing ten VASOTEC™ 20-mg tablets...etc.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPEI) has reviewed the pediatric information included in the Supplement SLR-059 to NDA 18-998 dated January 14, 2000 for Vasotec™ (enalapril Maleate). Based on the review of this information, OCPB is of the opinion that i) appropriate clinical pharmacological and biopharmaceutic information has been submitted to support the pediatric labeling and ii) the "CLINICAL PHARMACOLOGY AND DOSAGE AND ADMINISTRATION" sections of the labeling should incorporate the changes recommended in Reviewer Comment No. 5.

Please convey the above Recommendation and Reviewer Comment No. 5 as appropriate to the sponsor.

IS/

6/26/2000

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

IS/

RD/FT Initialed by Patrick J. Marroum, Ph.D.

6/24/2000

cc: NDA 18-998, HFD-110, HFD-860 (Dorantes, Metha), and CDR (Biopharm); HED 870 (Lara)

ATTACHMENT I

Includes;

NDA 18-998

Pediatric Exclusivity Form (MAPP 6020.6)

Attachment F

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION. UPON COMPLETION FORWARD TO THE PEDIATRIC EXCLUSIVITY BOARD, HFD-002.

Date of Written Request from FDA 9/18/99 Application Written Request was made to: NDA/IND# 18-998
Timeframe Noted in Written Request for Submission of Studies 9/18/01
NDA# 18-998 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR
Sponsor Merck & Co., Inc.
Generic Name Enalapril maleate Trade Name VASOTEC
Strength 2.5 mg Dosage Form/Route Tablet/Oral
Date of Submission of Reports of Studies 1/18/00
Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 3/18/00

Table with 2 columns: Question and Answer (Y/N with checkmarks). Questions include: Was a formal Written Request made for the pediatric studies submitted? Were the studies submitted after the Written Request? Were the reports submitted as a supplement, amendment to an NDA, or NDA? Was the timeframe noted in the Written Request for submission of studies met? If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles? Were the studies responsive to the terms of the Written Request?

FORWARD TO THE PEDIATRIC EXCLUSIVITY BOARD, HFD-002.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity [X] Granted [] Denied
Existing Patent or Exclusivity Protection:
NDA/Product # Eligible Patents/Exclusivity Current Expiration Date
18-998/001 4374829 22 FEB 2000
19-221/001 4374829 22 FEB 2000
19-309 4374829 22 FEB 2000
SIGNED [Signature] DATE 02/15/00
cc: Archival NDA/IND # 18-998
HFD-110
HFD-600

Originator: Deputy Center Director (Review Management)
October 6, 1998
HFD-110/CRX/4121

ATTACHMENT II

Includes;

NDA 18-998

Summary for Study No. 170

**"An Open, Two-Period, Crossover Study to Determine the Relative Bioavailability of the Enalapril Suspension 10 mg and
Marketed VASOTEC™ 10-mg Tablets"**

STUDY SUMMARY

Study No.: 170

Study Title:

An Open, Two-Period, Crossover Study to Determine the Relative Bioavailability of the Enalapril Suspension 10 mg and Marketed VASOTEC™ 10 mg Tablets.

Medical Monitor/Study Center: Kenneth C. Lasseter, M.D./Clinical Pharmacology Associates, Miami, FL.

Background:

Enalapril is an inactive ester prodrug which converts rapidly and completely to the active free acid, enalaprilat which is the active angiotensin converting enzyme inhibitor. Enalaprilat does not undergo further metabolism. In this study, "total enalaprilat" or "total drug" refers to enalapril + enalaprilat and "free enalaprilat" and "enalaprilat" refer to enalaprilat alone.

Rational for the Study and Dose:

It was necessary to develop a liquid formulation of enalapril to allow studies in younger pediatric patients. This suspension is fruit-flavored and is expected to be palatable to pediatric patients.

The selected 10 mg dose of the suspension is within the usual dosage range of 10-40 mg for hypertensive patients. The dose selected for children is 0.15 mg/kg (equal to a 10 mg dose in a 70 kg adult).

Objectives:

- To assess the relative bioavailability of the enalapril suspension 10 mg and the VASOTEC™ 10 mg tablet
- To compare the serum concentration profile of enalaprilat following administration of enalapril suspension 10 mg and the VASOTEC™ 10 mg tablet.
- To characterize the concentration-time profile of enalapril following administration of the enalapril suspension 10 mg and the VASOTEC™ 10 mg tablet.

Patient Population:

Sixteen volunteers [10 male (age: 18-44 years) and 6 female (age: 31-38 years)] meeting the inclusion/exclusion criteria were enrolled in the study.

Study Design:

This was an open, randomized, 2-period, crossover study in healthy subjects. Subjects were randomly assigned to one of two treatment sequence groups in which they received one

VASOTEC™ 10 mg tablet and one 10 mg dose of enalapril oral suspension. Following an overnight fast, subjects received the designated treatment at approximately 8 AM. Treatment A was administered with 240 mL of water. Treatment B was administered into the subject's mouth directly from a syringe, swallowed within 45 seconds, and immediately followed by 240 mL of water. To maintain urine output, approximately 1 cup of water was given to each subject every 2 hours for 12 hours after dosing. Subjects remained fasted until 4 hours postdose, when a light meal was provided. Each treatment period was separated by at least 7 days, making total study duration approximately 4 weeks.

Study Regimens:

- **Treatment A:** VASOTEC™ 10 mg tablets; Lot No. H8153
- **Treatment B:** Enalapril oral suspension (10 mL of 1 mg/mL suspension).

The following instructions were followed to prepare the 1 mg/mL enalapril suspension: Remove desiccant from bottle. Add 10 mL of sodium citrate (BICITRA™) to the bottle containing 2 tablets of enalapril 20 mg and disperse by shaking for at least 5 minutes. Allow to stand at room temperature for about 20 minutes. Add 30 mL of syrup vehicle (ORA-SWEET SF™) and shake to mix for about 2 minutes.

Blood Sampling Collection:

Blood samples for serum enalaprilat assay were collected during treatment A and B at pre-dose and at 15, 30, 45, minutes 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60, and 72 hours after drug administration. Urine samples were collected predose and at 0-2, 2-4, 4-8, 8-12, 12-24, 24-36, 36-48, and 48-72 hours postdose for assay of free and total enalaprilat concentrations.

Analytical Method:

Enalaprilat: ..

Enalapril:

Analytical Quality Control: Quality control was

TABLE 1

Summary of quality control data for the determination of free and total enalaprilat in serum

Nominal Concentrations (ng/mL)	Free Enalaprilat Mean Found (ng/mL)	N	
	1.93	10	
	9.83	10	
	102.60	10	

Nominal Concentrations (ng/mL)	Total Enalaprilat Mean Found (ng/mL)	N	
	1.92	8	
	8.97	8	
	88.79	7	

Summary of quality control data for the determination of free and total enalaprilat in urine

Nominal Concentrations (µg/mL)	Free Enalaprilat Mean Found (µg/mL)	N	
	0.184	4	
	0.990	4	
	10.25	4	

Nominal Concentrations (µg/mL)	Total Enalaprilat Mean Found (µg/mL)	N	
	0.208	3	
	0.960	3	
	10.05	3	

EVALUATION CRITERIA:

Pharmacokinetics: Serum AUC₀₋₇₂, serum C_{max}, and serum T_{max} were calculated from free enalaprilat and enalapril plasma-concentration-vs-time curves for each formulation. Urine free enalaprilat (% dose) and total enalaprilat (% dose) were calculated cumulatively from urine collections.

Statistics: Serum AUC₀₋₇₂ and C_{max} for enalaprilat, urine free and total enalaprilat were log transformed prior to statistical analysis. An ANOVA model with factors subject, period, and treatment was applied to AUC₀₋₇₂ and C_{max} of enalaprilat. 90% confidence intervals for the ratio of AUC₀₋₇₂ and C_{max} of the Treatment A to Treatment B were calculated.

Safety: Adverse events were collected and evaluated by the investigator; clinical evaluations included prestudy and poststudy PE, ECG, and laboratory safety tests.

RESULTS

Pharmacokinetics:

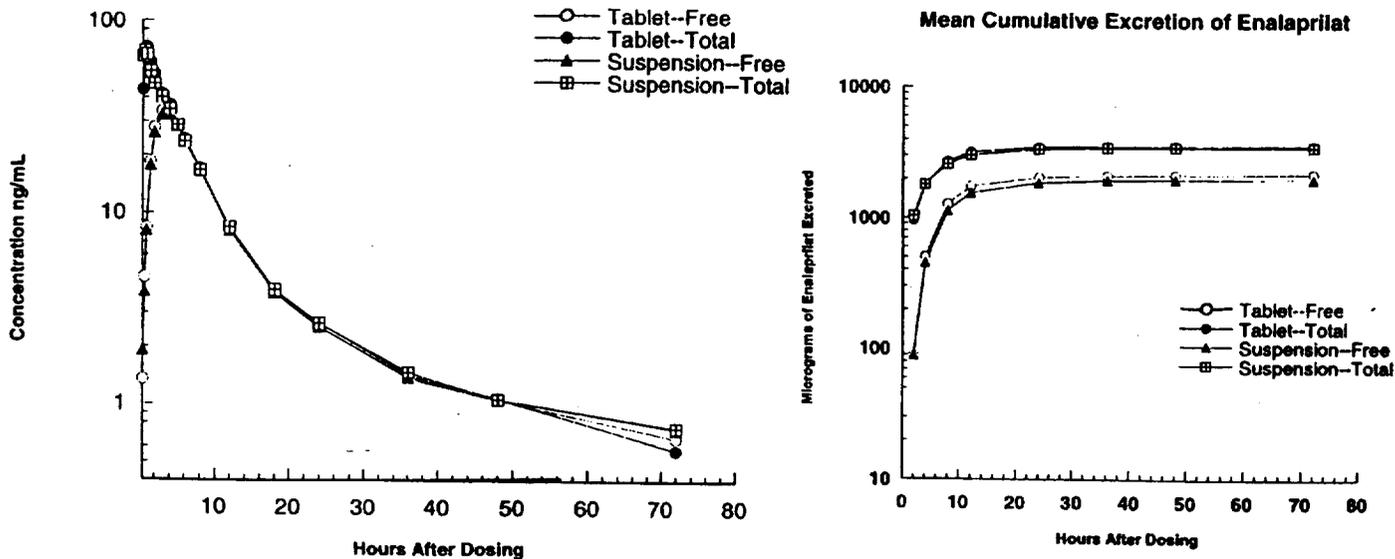
Concentrations of serum and urinary enalaprilat are expressed as the anhydrous acid. Table 2 shows the main pharmacokinetic parameters and descriptive statistics derived from enalaprilat in serum and urine following administration of 10 mg VASOTEC™ tablet and enalapril suspension 10 mg.

TABLE 2

	Serum Enalaprilat					
	TREATMENT A		TREATMENT B		Geo. Mean Ratio	90% CI
	Mean (CV)	Geo. Mean(CV)	Mean (CV)	Geo. Mean (CV)		
Cmax (ng/mL)	37.4 (23)	34.4	33.9 (12)	33.8	0.98	83-116
AUC0-72 (ng•h/mL)	337 (107)	328	333 (75)	331	1.01	90-113
Tmax (h)	3.9	---	3.4	---	---	---
	Urinary Recovery (0-72 hr)					
	TREATMENT A		TREATMENT B		Geo. Mean Ratio	90% CI
	Mean (CV)	Geo. Mean(CV)	Mean (CV)	Geo. Mean (CV)		
% Dose						
Free Enalaprilat	30.2 (9.4)	29.4	27.9 (7.7)	27.1	0.92	80-107
Total Enalaprilat	49.8 (12.3)	48.4	48.7 (9.2)	47.8	0.99	88-111

Figure 1 Shows the mean serum concentrations of free and total enalaprilat and the mean cumulative excretion of free and total enalaprilat following administration of a 10 mg VASOTEC™ tablet and a 10 mg suspension of enalapril.

FIGURE I



Mean (n=16) serum concentrations of free and total enalaprilat following a VASOTEC™ 10-mg tablet and a 10 mg Suspension of Enalapril

Mean (n=16) cumulative excretion of free and total enalaprilat following a VASOTEC™ 10-mg tablet and a 10 mg Suspension of Enalapril

The results indicate that the enalapril suspension formulation and VASOTEC™ tablets were similar in their bioavailability based on the geometric mean ratios and 90% confidence intervals (suspension/tablets) for the serum AUC and maximum concentration of free enalaprilat and the cumulative urinary excretion of free and total enalaprilat.

CONCLUSIONS

The enalapril suspension 10 mg and the VASOTEC™ 10 mg tablets were bioequivalent. Therefore, the inclusion in the labeling of a section indicating how the suspension should be prepared, is appropriate.

COMMENTS:

1. Complete analytical validation information for enalapril and enalaprilat was submitted under the original NDA. This study report only included Quality Control data for the determination of free and total enalapril in serum and urine. The provided Quality Control data showed that the
} is in the expected range for }
}
2. It should be noted that there was a statistically difference in the T_{max} of serum enalaprilat between formulations. However, the earlier T_{max} seen with the suspension would not be clinically significant since enalapril is dosed chronically and titrated according to blood pressure response.
3. The pharmacokinetic information and statistical analysis provided to support the sponsor's conclusion that the 10 mg enalapril oral suspension and the VASOTEC™ 10 mg tablets are similar in their bioavailability (bioequivalent), is appropriate and acceptable.

**APPEARS THIS WAY
ON ORIGINAL**

ATTACHMENT III

Includes;

NDA 18-998

Summary for Study No. 168 & 172

"An Open-Label Study to Investigate the Pharmacokinetics of Enalapril in Hypertensive Children and Infants"

STUDY SUMMARY

Study No.: 168/172

Study Title:

An Open-Label Study to Investigate the Pharmacokinetics of Enalapril in Hypertensive Children and Infants.

Investigators/Study Centers: D. Blowey, M.D./Kansas City, MO, J. Blumer, Ph.D./Cleveland, OH, R. Hogg, M.D./Dallas, TX, A. Sakarcan, M.D./Shreveport, LA, P. Walson, M.D./Columbus, OH, T. Wells, M.D./Little Rock, AR, A. Delucchi, M.D./Santiago, Chile.

Clinical Monitor: S. Shahinfar, M.D.

Pharmacokineticist: R. Rippley, Ph.D.

Background:

Studies in adults have described the pharmacokinetics of enalapril. Following absorption, enalapril is hydrolyzed to enalaprilat, which is a more potent ACE inhibitor than enalapril; in adults, conversion of enalapril to enalaprilat is approximately 68%. Peak serum concentrations of enalapril and enalaprilat occur approximately at 1 hr and 3-4 hrs, respectively, after an oral dose of enalapril. Based on urinary recovery, the extent of absorption of orally administered enalapril is approximately 60%. Excretion of enalapril is primarily renal. Approximately 94% of a dose is recovered in the urine and feces as total drug (enalapril + enalaprilat).

Rational for the Study and Dose:

Although enalapril is widely used to treat hypertension in children and adolescents, there have been no definitive studies to evaluate the pharmacokinetics of enalapril in the pediatric population. The study presented in this report was designed to estimate PK parameters of enalapril and enalaprilat in children aged 1 month to <16 years. The study was also designed to estimate the urinary recovery of total and free enalaprilat over a dosing interval following the first dose of study drug and at steady state.

The dose range in this study was designed to be approximately 0.10 to 0.17 mg/kg/day, which is consistent with the 0.15 mg/kg/day starting dose recommended by the National High Blood Pressure Working Group on Hypertension Control in Children and Adolescents. For children that are too small to swallow tablets or who are required doses less than the lowest available tablet dose (2.5 mg), enalapril tablets were reconstituted by dispersion in citrate buffer and a syrup base. The resulting suspension was orally administered to deliver an enalapril dosage of 0.15 mg/kg/day.

Objectives:

- To estimate the pharmacokinetic parameters (AUC_{0-24h} , C_{max} , and T_{max}) of enalapril and enalaprilat in children aged 1 month to <2 years, 2 to <6 years, 6 to <12 years, and 12 to <16 years

- To estimate the urinary recovery of total and free enalapril in children aged 1 month to <16 years
- To investigate the safety and tolerability of enalapril in children aged 1 month to <16 years.

Patient Population:

Forty male and female patients from 1 month to <16 years of age with documented history of hypertension; calculated glomerular filtration rate ≥ 30 mL/min/1.73 m²; patients in 1 month age range were to be at least 36 weeks gestational age were enrolled in the study. Patients were grouped according to age: Group I: 1 month to <2 years; Group II: 2 to <6 years; Group III: 6 to <12 years; Group IV: 12 to <16 years. The enrolled patients were as follows:

Children	Group I (n=9)	Group II (n=9)	Group III (n=10)	Group IV (n=12)
Male	6 (2-24 months)	5 (3-5 years)	6 (6 to 10 years)	7 (13 to 14 years)
Female	3 (3-24 months)	4 (3-4 years)	4 (6-10 years)	5 (12-15 years)

Study Design:

This was an open-label, multi-center study investigating the single (Day 1) and steady state (Day 7) pharmacokinetics of enalapril and enalaprilat in hypertensive patients aged 1 month to <16 years. Patients were grouped in above four groups according to age.

Dosage Regimens:

Enalapril oral suspension (prepared from VASOTEC 20 mg tablets suspended in sodium citrate buffer and syrup base) dosed at 0.15 mg/kg once daily in children <6 years and those who could not swallow tablets. Enalapril 2.5 mg tablets once daily in children 6 years and older, weighing <28 kg; enalapril 5 mg tablets once daily in children 6 years and older weighing > 28 kg. Patients over 12 years old received enalapril 5 mg once daily.

	Strength	Clinical Lot No.
Enalapril Maleate Tablet	20 mg	WP-E728
		WP-G197
	5 mg	WP-E731
		WP-E132
	2.5 mg	WP-G199
		WP-G200
		WP-E729
		WP-E730
		WP-G197
		WP-G198
Bicitra™	-	WP-E733
Ora-sweet SF™	-	WP-G201
		WP-E734
		WP-G202

Dose was administered daily between 7 and 11 AM. Patients remained in the clinic for 24 hours after the first dose of enalapril and collection of blood and urine samples. Patients were released following collection of the 24 hours samples and administration of the Day 2 dose. Doses 3

through 6 were given daily at home. On Day 7, patients reported to the clinic and received the final dose of enalapril in the clinic. Patients remained in the clinic for 24 hours after the final dose of enalapril, and timed blood and urine specimens were collected. Enalapril tablets were taken with approximately 250 mL of water, or as much water as the patient could comfortably drink if <250 mL. Patients who received enalapril suspension drank a comfortable quantity of water within about one minute after taking the suspension. To maintain the urine output, patients were encouraged to drink fluid during the urine collection period.

Blood/Urine Sampling Collection:

Blood (2 mL) samples for serum drug assay were collected at 1, 2, 4, 6, 8, 12, 16, and 24 hours following the Day 1 and Day 7 doses. For children younger than 4 years, blood collections were made only at 1, 4, 8, and 24 hours. Urine collections were made in the intervals of 0-4, 4-8, 8-12, and 12-24 hours after the Day 1 and Day 7 doses.

Analytical Methods:

Enalapril is an inactive ester prodrug which converts rapidly and completely to the active free acid, enalaprilat which is the active angiotensin converting enzyme inhibitor. Enalaprilat does not undergo further metabolism. In this study, "total enalaprilat" or "total drug" refers to enalapril + enalaprilat and "free enalaprilat" and "enalaprilat" refer to enalaprilat alone.

Enalaprilat:

Enalapril: Enalapril in human serum and urine was

Analytical Quality Control: Quality control was monitored using

controls, which are

Table 1 presents the summary of quality control data for the determination of free and total enalaprilat in serum and urine.

TABLE 1

Summary of Quality Control Data for the Determination of Free and Total Enalaprilat in Serum

Nominal Concentrations (ng/mL)	Free Enalaprilat Mean Found (ng/mL)	N	
	2.29	16	
	10.69	15	
	109.42	12	

Nominal Concentrations (ng/mL)	Total Enalaprilat Mean Found (ng/mL)	N	
	2.08	12	
	10.08	12	
	104.59	6	

Summary of Quality Control Data for the Determination of Free and Total Enalaprilat in Urine

Nominal Concentrations (µg/mL)	Free Enalaprilat Mean Found (µg/mL)	N	
	0.194	11	
	1.021	11	
	10.17	9	

Nominal Concentrations (µg/mL)	Total Enalaprilat Mean Found (µg/mL)	N	
	0.177	9	
	0.970	9	
	9.60	8	

EVALUATION CRITERIA:

Pharmacokinetics: Serum AUC₀₋₇₂, serum C_{max}, and serum T_{max} were calculated from free enalaprilat plasma-concentration-vs-time curves. Urine free enalaprilat (% dose) and total enalaprilat (% dose) were calculated cumulatively from urine collections.

Statistics: Geometric means and 95% confidence intervals were calculated for both adjusted and observed AUC₀₋₂₄ and C_{max} for serum enalaprilat at single dose and at steady state for each age group. The individual data for each parameter were log transformed and evaluated in an ANOVA

model having a factor for age group. Single dose and steady state parameters were evaluated separately. The mean square error from the ANOVA was used to obtain the 95% CI for the arithmetic mean of the log-parameter for each age group, referencing the t-distribution. These limits were then exponentiated to obtain the 95% CI for the geometric mean for each parameter. Distribution-free estimates of the median and exact 95% CI for T_{max} were calculated for each age group for serum enalaprilat at single dose and steady state using Hodges-Lehmann estimation. Summary statistics were provided for C_{max} and T_{max} of enalapril. Individual pharmacokinetic values were adjusted to 0.15 mg/kg and to 1.0 mg/m² body surface area.

Safety: Adverse events were collected and evaluated by the investigator; clinical evaluations included prestudy and poststudy physical examination, blood pressure, heart rate, Chest x-ray, ECG, laboratory evaluation and urinalysis.

RESULTS

Pharmacokinetics:

Figure 1 shows mean (SD) serum concentrations of enalaprilat for each group following single-dose and multiple-dose administration, respectively, of enalapril.

FIGURE 1

Mean (\pm SD) Serum Concentrations (ng/mL) of Free Enalaprilat Following Single Dose Administration of Enalapril Suspension 0.15 mg/kg (Groups I and II) or 2.5- or 5-mg Enalapril Tablets (Groups III and IV)

Mean (\pm SD) Serum Concentrations (ng/mL) of Free Enalaprilat Following Multiple Dose Administration of Enalapril Suspension 0.15 mg/kg (Groups I and II) or 2.5- or 5-mg Enalapril Tablets (Groups III and IV)

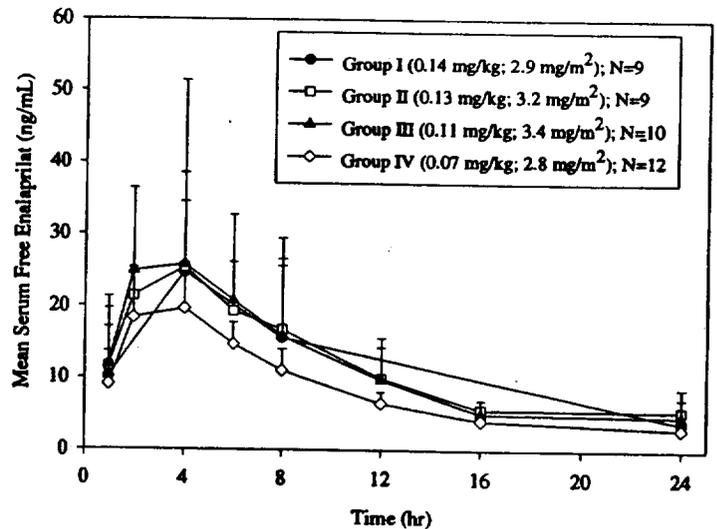
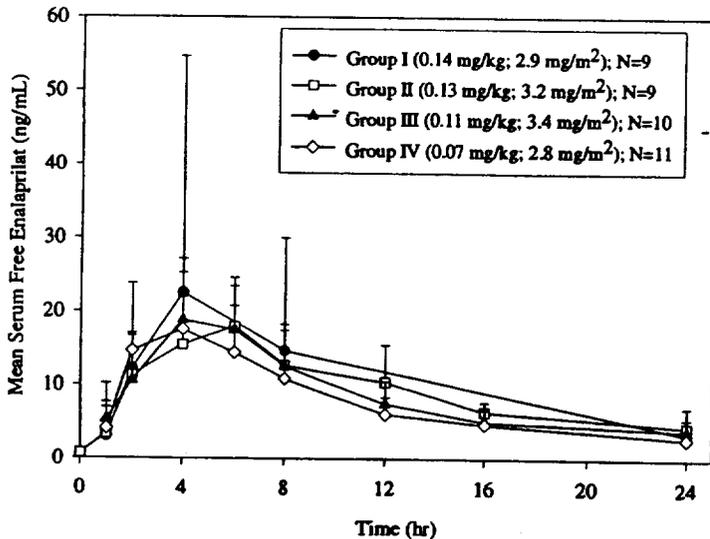


Table 2 shows the main pharmacokinetic parameters and descriptive statistics derived from enalaprilat in serum and urine following administration of enalapril.

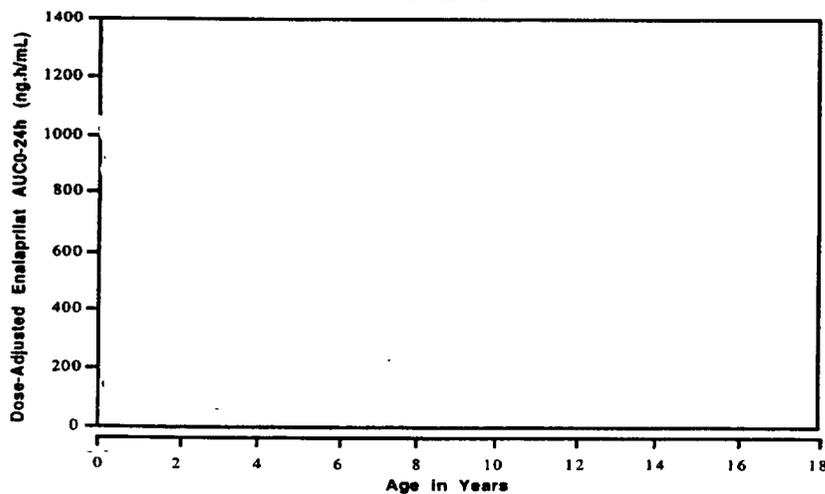
TABLE 2

Parameter	Group I (N=9)	Group II (N=9)	Group III (N=10)	Group IV (N=12)
AUC_{0-24h}, ng·hr/mL				
Observed, Mean ± SD	268.07 ± 215.42	305.34 ± 138.75	296.84 ± 165.78	204.15 ± 43.82
GM (95% CI) ^a	221.98 (163.23, 301.83)	277.58 (204.14, 377.43)	263.34 (196.76, 352.47)	199.87 (153.17, 260.81)
Per 0.15 mg/kg Dose ^b , Mean ± SD	289.74 ± 246.77	358.70 ± 188.14	383.39 ± 165.75	502.20 ± 247.46
GM (95% CI) ^a	235.56 (168.98, 328.37)	316.96 (227.37, 441.84)	352.02 (256.87, 482.42)	464.83 (348.62, 619.76)
Per 1.0 mg/m ² Dose ^c , Mean ± SD	99.03 ± 99.10	101.11 ± 58.24	86.05 ± 39.73	76.23 ± 22.21
GM (95% CI) ^a	77.23 (55.81, 106.87)	87.60 (63.30, 121.23)	78.74 (57.86, 107.17)	73.99 (55.85, 98.03)
C_{max}, ng/mL				
Observed, Mean ± SD	24.82 ± 26.59	25.67 ± 8.92	28.06 ± 12.79	21.18 ± 5.30
GM (95% CI) ^a	18.37 (13.31, 25.36)	24.17 (17.52, 33.36)	25.53 (18.80, 34.65)	20.52 (15.52, 27.12)
Per 0.15 mg/kg Dose ^b , Mean ± SD	26.92 ± 30.33	30.16 ± 13.37	36.75 ± 14.23	51.97 ± 25.16
GM (95% CI) ^a	19.50 (13.77, 27.61)	27.60 (19.50, 39.08)	34.12 (24.53, 47.46)	47.71 (35.31, 64.48)
Per 1.0 mg/m ² Dose ^c , Mean ± SD	9.37 ± 12.12	8.42 ± 3.96	8.16 ± 3.03	7.89 ± 2.40
GM (95% CI) ^a	6.39 (4.56, 8.96)	7.63 (5.44, 10.69)	7.63 (5.54, 10.51)	7.60 (5.67, 10.17)
T_{max}, hr				
Median (95% CI) ^a	4.17 (4.05, 6.01)	3.99 (3.02, 4.05)	3.05 (2.04, 4.05)	3.00 (2.00, 4.00)
Urinary Recovery (0-24 hr), % Dose^d				
Free Enalaprilat, Mean ± SD	-	46.32 ± 18.42	48.23 ± 21.94	48.94 ± 15.84
GM (95% CI) ^a	-	42.81 (31.27, 58.62)	43.92 (33.77, 57.13)	46.72 (36.36, 60.04)
Total Enalaprilat, Mean ± SD	-	68.81 ± 16.85	61.77 ± 21.27	73.87 ± 21.13
GM (95% CI) ^a	-	66.83 (52.54, 85.00)	58.29 (47.66, 71.28)	71.36 (58.91, 86.46)
% Conversion Enalapril to Enalaprilat	63.4 ± 16.5	70.8 ± 22.4	76.3 ± 13.5	65.9 ± 8.0
t_{1/2} for Accumulation, hr^e	-	14.59	13.75	13.69

^a Geometric Mean (GM) or Median and 95% Confidence Intervals supplied by BARDS.
^b Based on assayed potency of suspension (Table 5) or tablet (Table 4) and patient weight on appropriate study day.
^c Based on assayed potency of suspension or tablet and patient body surface area according to the Gehan-George method.
^d Based on assayed potency of suspension or tablet and the difference in molecular weight between anhydrous enalaprilat (348.4) and enalapril maleate (492.53).
^e Harmonic Mean.

Figure 2 illustrates the individual steady-state values of enalaprilat AUC_{0-24h}, adjusted per 0.15 mg/kg vs. the age of the 40 hypertensive children participating in the study. The plot shows that there is not a specific trend between the dose-adjusted AUC of enalaprilat and the children's age.

FIGURE 2



Safety: A total of 5 patients reported clinical adverse experiences and 2 patients had laboratory adverse experiences. Two patients reported serious adverse experiences (i.e., febrile convulsion and bronchitis). None of the adverse experiences in the study were considered drug related, and none cause discontinuation.

CONCLUSIONS

The results showed that AUC_{0-24h} and C_{max} across the entire range from 1 month to <16 years, were similar, therefore, the dosing regimens given in this study can be used in children. An alternative approach to dosing recommendations in children would be to adjust for body surface area (BSA) throughout the pediatric age range. This approach is supported by the similarity of AUC_{0-24h} and C_{max} values across the age range when dose-adjusted by BSA. This is not a surprising result since BSA is known to be an appropriate correction parameter for compounds excreted primarily by the kidney through filtration due to the relationship of glomerular filtration rate (GFR) to BSA.

Prior studies have described the PK of enalapril in adults. Following administration of enalapril 10 mg for 8 days to healthy young males, the mean enalaprilat AUC_{0-24h} , C_{max} , and T_{max} values of 316 ± 69 ng.h/mL, 30 ± 13 ng/mL, and 1 hour, respectively, appear consistent with the values seen in pediatric patients. Based on urinary recovery, the extent of absorption of orally administered enalapril is approximately 60% in adults. Comparable values ranging from 50-71%, were observed in children.

COMMENTS:

1. This study provides the first PK data from an adequate sized study with enalapril in hypertensive children.
2. The overall results of this study indicate that the PK of enalapril in hypertensive children aged 1 month to <16 years is consistent across age groups and consistent with PK historic data in healthy adults. Enalapril was generally well tolerated in hypertensive children and infants.
3. Analysis of the dose-adjusted parameters showed that dosing by weight may not be appropriate in children older than 12 years of age. However, adjusting the dose by body surface area seems appropriate across all age groups.
4. It should be noted that dose adjustment based on body surface area may be complicated by the need for accurate measurement of height or length which is difficult in young infants. The need for accurate lengths and use of nomograms for calculation of BSA may limit the clinic utility of BSA-adjusted dose recommendation and may increase the risk of errors in dose calculations.
5. This study showed that enalapril can be administered in a suspension formulation, with an acceptable PK profile to hypertensive children and infants who are unable to swallow tablets or who require a lower dose that is available in tablet form.
6. It should be noted that complete analytical validation information was submitted under the original NDA. This study report only included Quality Control data for the determination of free and total enalapril in serum and urine. The provided Quality Control data showed that the (is in the expected range for ()

ATTACHMENT IV

Includes;

NDA 18-998

Proposed Pediatric-Labeling Changes

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

MAR 30

MAR 30 1999

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation I

IND [redacted]
Amendment Serial No. 197

SUBMISSION DATE: March 18, 1999

VASOTEC™ (Enalapril Maleate)
Merck Research Laboratories
West Point, PA

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Revised Pharmacokinetic Pediatric Protocol submitted for Pediatric Exclusivity

BACKGROUND:

Vasotec™ is an ACE inhibitor, currently approved under NDA 18-998 for the treatment of hypertension, heart failure and asymptomatic left ventricular dysfunction. Reference is made to IND [redacted] for Vasotec™ (enalapril maleate) and to the Agency's written request for enalapril pediatric studies dated December 23, 1998.

Reference is made to the original protocol No. 168, entitled "An Open-Label Study to Investigate the Pharmacokinetics of Enalapril in Hypertensive Children and Infants", which was submitted on November 4, 1998 (Amendment Serial No. 184). Reference is also made to the Agency's letters dated November 4, 1998 and February 16, 1999 which included five reviewer comments for the above protocol and to the sponsor's responses included in Amendment Serial No. 186 dated December 28, 1998.

The present submission dated March 18, 1999 (Amendment Serial No. 197) is intended to fulfill the Agency's request for pediatric pharmacokinetic data for enalapril. It includes a revised protocol (No. 168-01) which incorporates the Agency's recommended changes. The protocol's synopsis and study flow chart are included in Attachment 1. It should be noted that this protocol replaces protocol No. 168-00 previously submitted on February 5, 1999 (Amendment Serial No. 191).

The major differences between this protocol and the previous version are as follows:

- **Protocol Title/Number:**
An Open-Label Study to Investigate the Pharmacokinetics of Enalapril in Hypertensive Children and Infants/Protocol No. 168-01.

- **Clinical Monitor:**
Shahinfar, M.D.

APPEARS THIS WAY
ON ORIGINAL

- **Objectives:**

1. To estimate the pharmacokinetic parameters (AUC₀₋₂₄ hr, C_{max}, and T_{max}) of enalapril and enalaprilat in children aged 1 month to <2 years, 2 to <6 years, 6 to 12 < years, and 12 to <16 years.
2. To estimate urinary recovery of total and free enalaprilat in children aged 1 month to <16 years.
3. To investigate the safety and tolerability of enalapril in children aged 1 month to <16 years.

REVIEWER COMMENTS:

1. The original Protocol No. 168-00 as well as the sponsor's responses to the FDA comments regarding the above protocol were reviewed by Dr. Nakissa Sadrieh on November 13, 1988 and January 22, 1999, respectively. The sponsor's responses to the FDA Comments No. 1, 2, and 5 were not accepted (see details in Dr. Sadrieh's reviews).
2. The amended protocol No. 168-01 incorporates the Agency's recommendation of determining the bioavailability of enalapril and enalaprilat based on the evaluation of pharmacokinetic parameters generated from plasma data (i.e., AUC, C_{max} and T_{max}). Also, the protocol includes the recommended additional drawing of a blood sample at 1 hour, in order to determine T_{max}. Therefore, the revised Protocol No. 168-01 incorporates the Agency's recommendations given in Comments No. 1 and 2.
3. For the collection of blood samples in the different age groups, the sponsor is proposing to use a classical sampling approach. Therefore, FDA's recommendation given in Comment No. 5, is not longer relevant.
4. It should be noted that in addition of plasma samples, the proposed protocol also includes the collection of urine samples for estimation of total amount of enalapril and enalaprilat excreted in urine.
5. Overall, the changes incorporated in the revised protocol are appropriate and OCPB considers that the sponsor has fulfilled the Agency's request for an adequate pediatric pharmacokinetic study to support the pediatric exclusivity for enalapril .

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPEI) has reviewed Protocol No. 168-01 included in Amendment Serial No. 197 to IND [redacted] dated March 18, 1999. Based on the review of this protocol, OCPB is of the opinion that the amended Protocol No. 168-01 has been properly design to collect pediatric pharmacokinetic information and is acceptable.

No further action is recommended at this time.

/s/ *3/29/99*

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

RD/FT Initialed by Patrick Marroum, Ph.D.

/s/ *3/30/1999*

cc: IND [redacted] HFD-110, HFD-860 (Dorantes), and CDR (Attention: B. Murphy).

ATTACHMENT I

IND 17,791

**Includes;
Protocol Synopsis and Study Flow Chart**

PROTOCOL SYNOPSIS

PRODUCT: MK-0421

PROTOCOL TITLE: An Open-Label Study to Investigate the Pharmacokinetics of Enalapril in Hypertensive Children and Infants

PROTOCOL/AMENDMENT NO.: 168-01 / Multicenter

U.S. IND NO.: CLINICAL PHASE: IV

HYPOTHESES/ESTIMATION: (1) Serum pharmacokinetic parameters ($AUC_{0-24 \text{ hr}}$, C_{max} , and T_{max}) of enalapril and enalaprilat will be estimated in children aged 1 month to <16 years of age, (2) urinary recovery of total and free enalaprilat will be estimated in children aged 1 month to <16 years of age, (3) enalapril will be safe and well tolerated by children aged 1 month to <16 years.

OBJECTIVES: Primary: (1) To estimate the pharmacokinetic parameters ($AUC_{0-24 \text{ hr}}$, C_{max} , and T_{max}) of enalapril and enalaprilat in children aged 1 month to <2 years, 2 to <6 years, 6 to <12 years, and 12 to <16 years, (2) to estimate the urinary recovery of total and free enalaprilat in children aged 1 month to <16 years, (3) to investigate the safety and tolerability of enalapril in children aged 1 month to <16 years.

STUDY DESIGN AND DURATION: Open-label, multicenter investigation of pharmacokinetics after the first dose and after 7 days at a stable dose of enalapril. Patients will be grouped according to age (Group I: 1 month to <2 years; Group II: 2 to <6 years; Group III: 6 to <12 years; Group IV: 12 to <16 years). Blood specimens for serum drug assay will be collected at Hours 1, 2, 4, 6, 8, 12, 16, and 24 following the Day 1 and Day 7 doses (except in children younger than 4 years, collections will only be made at Hours 1, 4, 8, and 24). Urine collections will be in the intervals of Hours 0 to 4, 4 to 8, 8 to 12, and 12 to 24 after the Day 1 and Day 7 doses.

PATIENT SAMPLE: A total of 32 hypertensive children, 8 patients in each age group (Group I: 1 month to <2 years; Group II: 2 to <6 years; Group III: 6 to <12 years; Group IV: 12 to <16 years).

DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN: Reconstituted enalapril (at a dose of 0.15 mg/kg) will be administered orally once daily for 7 days in patients in Groups I and II and patients in Group III who cannot swallow tablets; enalapril 2.5-mg tablets will be administered to patients in Group III who can swallow tablets and who weigh <28 kg; enalapril 5-mg tablets will be administered once daily to patients in Groups III (≥ 28 kg) and IV.

EFFICACY MEASUREMENTS: Blood pressure will be measured at Day 7 compared to baseline.

PHARMACOKINETIC MEASUREMENTS: Pharmacokinetic parameters will include timed blood collections after the first dose and at steady state (7 days of enalapril treatment) for measurement of serum enalapril and enalaprilat to assess $AUC_{(0-24 \text{ hr})}$, C_{max} , and T_{max} in children. Timed urine collections will also be performed to assess urinary recovery of enalapril and enalaprilat and to calculate half-life for accumulation.

DATA ANALYSIS: At steady state, 95% confidence intervals for the geometric mean of $AUC_{(0-24 \text{ hr})}$, C_{max} , and urinary recovery in children 1 month to <16 years of age will be

Product: MK-0421

Protocol/Amendment No.: 168-01

calculated using the between-subject standard error. Estimates may be obtained by age group, gender, and/or renal function. With 8 evaluable children in each age group after the first dose of enalapril and at steady state, the half-width of the 95% confidence interval for the arithmetic mean $AUC_{0-24 \text{ hr}}$ of enalaprilat on the log scale will be 0.175 log ng·hr/mL. If the observed geometric mean $AUC_{0-24 \text{ hr}}$ of enalaprilat is 700 ng·hr/mL, the 95% confidence interval will be 587 to 834 ng·hr/mL. The half-width of the 95% confidence interval for the arithmetic mean C_{max} of enalaprilat on the log scale will be 0.255 log ng/mL. If the observed geometric mean C_{max} of enalaprilat is 75 ng/mL, the 95% confidence interval will be 58.1 to 96.8 ng/mL. The half-width of the 95% confidence interval for the arithmetic mean urinary recovery of free enalaprilat on the log scale will be 0.265 log %. If the observed geometric mean urinary recovery of free enalaprilat is 30%, the 95% confidence interval will be 23.0 to 39.1%. The half-width of the 95% confidence interval for the arithmetic mean urinary recovery of total enalaprilat on the log scale will be 0.197 log %. If the observed geometric mean urinary recovery of total enalaprilat is 60%, the 95% confidence interval will be 49.3 to 73.1%.

ANY SERIOUS ADVERSE EXPERIENCE, INCLUDING DEATH DUE TO ANY CAUSE, WHICH OCCURS TO ANY PATIENT ENTERED INTO TREATMENT IN THIS STUDY OR WITHIN 14 DAYS FOLLOWING CESSATION OF TREATMENT, WHETHER OR NOT RELATED TO THE INVESTIGATIONAL PRODUCT, MUST BE REPORTED WITHIN 24 HOURS TO ONE OF THE INDIVIDUAL(S) LISTED ON THE CONTACT INFORMATION PAGE. ALL PATIENT WITH SERIOUS ADVERSE EXPERIENCES MUST BE FOLLOWED UP FOR OUTCOME.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Product: MK-0421

Protocol/Amendment No.: 168-01

Instructions for Reconstituting Enalapril and Weight-Adjusted Dosing

(Caution: Remove desiccants from bottle containing enalapril tablets before adding solutions)

Two 20-mg enalapril tablets will be placed in 10 mL of sodium citrate (Bicitra) and shaken for at least 5 minutes to disperse the tablet. Allow to stand at room temperature for about 20 minutes. After dispersion, add 30 mL of syrup vehicle (Orasweet SF) to the suspension and shake to mix for about 2 minutes.

The resulting 40 mL enalapril suspension will be at a concentration of 1 mg/mL. The suspension is stable for 4 weeks in the refrigerator (approximately 5°C), and should be shaken before use.

The suspension will be administered orally using a 3-mL or 5-mL syringe.

Administer 0.15 mL for each kilogram of body weight. For example, a 15 kg child will take 2.25 mL.

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APPEARS THIS WAY
ON ORIGINAL

Product: MK-0421

Protocol/Amendment No.: 168-01

STUDY FLOW CHART

Visit number	Baseline	Enalapril Treatment and Follow-up				Open-Label Extension (Enalapril)
	1	2	3	4	5	
Visit (study day)	-1	1	78	21	Month 6	
Informed consent	X					
Medical history	X					
Physical exam	X		X			
Blood pressure/heart rate ^a	X	X	X		X	
Chest X ray ^b	X				X	
Electrocardiogram	X					
Laboratory evaluation ^c	X		X			
Urinalysis ^d	X		X		X	
Blank blood and urine specimens ^e		X			X	
Timed blood and urine collections ^e		X	X			
24-hour in-patient stay ^e		X	X			
Dispense study drug ^f		X	X			
Timed blood pressure/heart rate		X	X			
Adverse experience assessment		X	X	X	X	

^a Instructions for measuring blood pressure are provided in Appendix 1.
^b Perform chest X ray only if patient has not had one in the past year.
^c All lab evaluations will include serum chemistry and hematology and will be performed by the investigator's local laboratory. Specific tests that will be analyzed are listed in Appendix 4.
^d A random urine sample will be collected for a urinalysis with microscopy, which will be performed at the investigator's local laboratory.
^e Timed blood and urine collections over 24 hours after the first dose and at steady-state (Day 7) will be obtained for pharmacokinetic determinations. A blank urine specimen (spot urine) and blank blood specimen will be collected pre-dose on Day 1.
^f The dose of reconstituted enalapril will be 0.15 mg/kg in patients in Groups I and II and in Group III patients who cannot swallow tablets. See Appendix 4 for preparation and dosing instructions for reconstituted enalapril. Patients in Group III who weigh <28 kg will receive enalapril 2.5-mg tablets, and patients who weigh ≥28 kg will receive enalapril 5-mg tablets. Patients in Group IV will receive enalapril 5 mg.
^g If patient is discontinued prior to Day 7, the measurements required at Visit 3 will be performed at discontinuation, and an adverse experience assessment performed 14 days later.

FEB 16 1999

IND

Merck Research Laboratories
Attention: Jeffery R. White, M.D.
Sumneytown Pike, P.O. Box 4
West Point, PA 19486

Dear Dr. White:

Please refer to your investigational new drug application (IND) for enalapril maleate.

In reviewing your submission of December 28, 1998, serial number 186, our Biopharmacist has raised a number of questions that require your attention. Our concerns with your submission are detailed as part of this correspondence (see enclosure).

Sincerely yours,

/S/

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

N Sadrieh 1-22-99 Biopharm Review
with R Lipicky 2-9-99 comments

cc:
Original
HFD-110
HFD-110/K Bongiovanni
~~sb/2/11/99~~
filename -

GENERAL CORRESPONDENCE

K.B

will be extended (as necessary, considering time limitations) to attempt to achieve a reasonable distribution of ages within each group. **The response is acceptable.**

- 4. In response to FDA comment #4, where the sponsor was asked to investigate the relationship between enalaprilat clearance and age, it is stated that since renal clearance depends on serum AUC, it may be confounded by the saturable binding of enalaprilat to ACE. Consequently, age will be correlated to the conversion of enalapril to enalaprilat, thus allowing inferences to be made about the activity of the hydrolyzing enzyme as a function of age. **The response is acceptable.**
- 5. In response to FDA comment #5, where the sponsor was asked to consider sparse sampling in the 1 month to 2 year age group, making sure to include 4 sampling time points for each subject, the reviewer is referred to response #2 above. **The response is not acceptable for the same reasons as those stated in the review of response #1.**

All in all, the sponsor has opted not to follow the Agency recommendations regarding the use of plasma data rather than urinary data in the establishment of bioequivalence for the proposed Vasotec formulation to be used in the pediatric PK studies. The sponsor is proposing to sample blood at various time points, for the sole purpose of establishing a Cmax and Tmax. No other plasma PK parameter will be evaluated. The main reason for the reluctance to carry out plasma PK determinations is that enalaprilat binds to ACE (a saturable binding site), thus extending the terminal elimination phase of the drug and consequently leading to erroneous values for renal CL, t_{1/2} and oral bioavailability. To circumvent this problem, the sponsor proposes to determine the bioavailability of enalapril as well as the conversion rate of enalapril to enalaprilat using urinary data. Therefore the sponsor's responses to comments #1, 2 and 5 are not acceptable. The determination of bioavailability of enalapril based on urinary recoveries is not acceptable and thus any study that does not include measurement of plasma levels of enalaprilat will be of little value for regulatory purposes.

Recommendation:

The following comment should be sent to the sponsor, in writing:

The responses to FDA comments 1, 2 and 5 are not adequate. The determination of the bioavailability of enalapril based on urinary recoveries is not acceptable and thus any study that does not include a measurement of plasma levels of enalaprilat will be of little value from the regulatory point of view.

Do not use urinary measures + bioavailability in the same sentence

/S/ 1/21/99

Nakissa Sadrieh, Ph.D.

RD/FT initialed by Patrick Marroum, Ph.D. */S/*

1/22/1999

cc: IND HFD-110 (Bongiovanni), HFD-860 (Sadrieh), CDER document room

you must supply plasma concentrations to us for analysis. RF 2/18/99

JAN 22 1999

Clinical Pharmacology/Biopharmaceutics Review

IND: [REDACTED]N(RD) 186
Letter Date: December 28th, 1998
Drug: Vasotec (enalapril maleate)
Sponsor: Merck

Reviewer: Nakissa Sadrieh Ph.D.

Re: Response to FDA comments regarding pediatric protocol submitted for pediatric exclusivity purposes.

Background:

Vasotec is an ACE inhibitor, currently approved for the treatment of hypertension, heart failure and asymptomatic left ventricular dysfunction. The sponsor, Merck, is seeking to extend the market exclusivity period of Vasotec by providing additional pediatric information, thus taking advantage of the section 111 of FDAMA, which was signed into law in November 1997.

The sponsor met with the division of cardio-renal drugs on November 13th, 1998 to present the pediatric program which includes the following features:

1. A randomized, double-blind, dose response study of 2 -weeks duration in 100 hypertensive children aged 6-16 years;
2. Development of a reconstituted enalapril suspension for use in younger children who cannot swallow tablets;
3. A bioavailability study in healthy adults to compare enalapril tablets with the reconstituted enalapril suspension;
4. Pharmacokinetic studies in children aged 1 month to 16 years;
5. An epidemiology study of a case series of pediatric patients treated with enalapril for hypertension over time in a representative clinical practice.

The protocol for the PK study in children ("A open-label study to investigate the PK of enalapril in hypertensive children and infants") was previously reviewed (November 13th, 1998).

Briefly, the PK of enalapril is as follows. T_{max} is at one hour after an oral dose. Based on urinary recovery, the extent of urinary absorption of orally administered enalapril is approximately 60%. Following absorption, enalapril is hydrolyzed to enalaprilat, which is a more potent ACE inhibitor. Peak levels of enalaprilat are reached after 3-4 hours after an oral dose. Excretion of enalapril is primarily renal, however, the disposition of enalapril in patients with renal insufficiency is similar to that in patients with normal renal function, until GFR is above 30 ml/min.

In the proposed pediatric study, urinary recovery of enalapril and enalaprilat will be estimated over a dosing range after the first dose and at steady state. C_{max} and T_{max} will also be estimated for enalapril and its active metabolite. The dose range that will be used will be 0.10-0.17 mg/kg/day. For children who cannot swallow tablets, enalapril tablets will be reconstituted by dispersion into citrate buffer, and the resulting suspension will be orally administered in the prescribed volume to deliver the desired dosage.

The primary estimation of the study is the urinary recovery of total and free enalaprilat in children aged 2 to <16 years of age.

The secondary estimation of the study is identical to the first one, with the exception that the estimation will be made in children aged from 1 month to less than 2 years. Additionally, serum PK parameters (C_{max} and T_{max}) will be estimated in children aged from 1 month to less than 16 years.

Patients in groups 1 and 2 (and those in group 3 who cannot swallow tablets) will receive reconstituted enalapril at a dose of 0.15 mg/kg once daily. Patients in group 3 who weigh more than 28 kg will receive 2.5 mg enalapril and those who weigh more than 28 kg, as well as patients in group 4 will receive 5 mg enalapril once daily. Enalapril will be administered for 7 consecutive days.

On day 1, blood will be collected for PK measurements at the following time points: predose, 2, 4, 6, 8, 12, 16 and 24 hours after dosing. Urine will be collected predose, from 1-4 hours, 4-8 hours, 8-12 hours and 12-24 hours. In the case of reliable patients, they will be allowed to go home after 12 hours, provided that the 12-24 hour urine is collected accurately. The patient will return for the 24 hour blood draw and the 16 hour blood draw will be omitted.

On day 7, patients will be assessed in an identical fashion to day 1. Blood and urine will be collected at the same time points.

Fourteen days after the last dose, the patients will be assessed for adverse events. Additionally, an optional 6-month open-label extension of the study will be carried out, and the end of the 6 month period, the patients will be assessed for adverse events and will undergo a physical examination.

Data analysis:

For the primary variable estimation, after the first dose and at steady state, 95% confidence intervals for the geometric mean of urinary recovery of free and total enalaprilat in children 2-16 years old will be calculated using the between-subject standard error. Estimates may be obtained by gender and/or renal function. The urinary recovery in children aged 1 month to 2 years will be measured in the same manner as for the older children, however, this will be considered a secondary estimation since the urine collections in younger children are reported to be inherently more variable than in older children.

For the secondary variable estimation, after the first dose of enalapril and at steady state, 95% confidence intervals for the geometric means of the dose-adjusted C_{max} and median T_{max} of free enalapril in children aged 1 month to 16 years will be calculated using the between-subject standard error. Estimates may be obtained by gender and/or renal function.

The comments sent to the sponsor were the following:

1. Determine the bioavailability of enalapril and enalaprilat based on plasma determinations of PK parameters rather than based on the amount of urinary excretion of enalaprilat;
2. Draw an additional blood sample at 1 hour, in order to cover the T_{max};
3. Recruit subjects in such a way that all ages are evenly distributed within each age group;
4. Investigate the relationship between enalaprilat clearance and age;
5. Consider sparse sampling in the event that the sampling schedule cannot be completed in the 1 month to 2 year age group, making sure to include at least 4 sampling time points drawn at various times, in order to cover the population profile.

With the present submission, the sponsor has responded to the FDA comments.

Sponsors' responses:

1. The sponsor summarizes the PK characteristics of enalapril and states that the prolonged terminal phase represents the fraction of the administered dose which is bound to ACE (a saturable binding site, since the amount bound does not increase with dose). Consequently, it is reported that the AUC is considered to be invalid in establishing bioequivalence, because it does not increase proportionally with dose (Ferguson protocol 006 referenced). *The conclusions reported in the pharmacokinetic study report to which the sponsor is referring to, do not correspond to the statements made by the sponsor. In fact, study 006 concludes*

that the serum profiles for enalaprilat after 3 different IV doses is polyexponential with a prolonged terminal phase similar to that for enalapril after oral dosing. All 3 doses converge to the same terminal serum concentration and the observed serum concentrations appear to reflect 2 separate linear processes (because the plot of AUC(0-inf) vs. dose is linear with a positive intercept). The 2 processes suggest that a fixed amount of drug, regardless of administered dose, is handled by one kinetic process (saturable binding to ACE), while the remainder of the dose is handled by another kinetic process. HOWEVER, the study concludes that the AUC(0-inf) is LINEARLY related to dose with a positive intercept and that the intercept can be eliminated by subtracting AUC(E) (area under the extrapolated terminal phase) from AUC(0-inf). In the referenced study, the AUC(0-inf) minus the area of the extrapolated terminal phase for the 3 doses used are: 274 ± 40 , 538 ± 80 and 1082 ± 181 for the 2.5, 5, and 10 mg IV doses of enalaprilat.

Additionally, the sponsor states that the PK characteristics of enalaprilat preclude accurate determinations of clearance, half-life, renal clearance and oral bioavailability from serum data alone. Since enalaprilat is quantitatively excreted in the urine unchanged (mean recovery ranging from 92% to 96%), urinary excretion is thought to directly reflect the bioavailability of the active entity. The sponsor also contends that since bioequivalence of enalaprilat has previously been established by comparing urinary recovery ratios of enalaprilat for various formulations (Vasotec vs. Vasoteric), then the bioavailability of enalapril suspension relative to the tablet formulation will be determined in adults using urinary data. C_{max} and T_{max} will only be used as surrogates for evaluating absorption rate but cumulative urinary recovery of free and total enalapril will be used to determine enalapril absorption and conversion to enalaprilat for the proposed pediatric PK study. In essence, the sponsor does not wish to comply with the Agency's recommendation, stating the above reasons. The urinary recovery of enalaprilat is not an acceptable measure of enalapril bioavailability. The sponsor should use the AUC(0-24h) which is an acceptable method for determining the bioavailability of enalapril. Binding to ACE should not interfere significantly with the determination of bioavailability based on AUC.

2. In response to FDA comment #2, where the sponsor was asked to include an additional blood sample at 1 hour in order to cover the T_{max}, the sponsor responds that AUC will not be used to assess the extent of absorption. Therefore there is no need to fully characterize the serum profile and the fixed sampling times (predose, 0.5, 2, 4, 6, 8, 12, 16 and 24 hours in children older than 4 years of age) will be enough to estimate the C_{max} and T_{max} of enalapril and enalaprilat. Again, this response is not acceptable since the Agency believes that AUCs should be used to determine the bioavailability of enalapril. In this case, it is advisable that a 1 hour time point be incorporated in the sampling scheme in order to cover the T_{max}. Additionally, in at least in one previous NDA (combination of enalapril and diltiazem), the sponsor used plasma levels of enalaprilat to obtain the bioavailability of enalapril from an oral dosage form of the drug.
3. In response to FDA comment #3, where the sponsor was asked to recruit subjects such that all ages are evenly distributed within each group, it is stated that recruitment

- will be extended (as necessary, considering time limitations) to attempt to achieve a reasonable distribution of ages within each group. **The response is acceptable.**
4. In response to FDA comment #4, where the sponsor was asked to investigate the relationship between enalaprilat clearance and age, it is stated that since renal clearance depends on serum AUC, it may be confounded by the saturable binding of enalaprilat to ACE. Consequently, age will be correlated to the conversion of enalapril to enalaprilat, thus allowing inferences to be made about the activity of the hydrolyzing enzyme as a function of age. **The response is acceptable.**
 5. In response to FDA comment #5, where the sponsor was asked to consider sparse sampling in the 1 month to 2 year age group, making sure to include 4 sampling time points for each subject, the reviewer is referred to response #2 above. **The response is not acceptable for the same reasons as those stated in the review of response #1.**

All in all, the sponsor has opted not to follow the Agency recommendations regarding the use of plasma data rather than urinary data in the establishment of bioequivalence for the proposed Vasotec formulation to be used in the pediatric PK studies. The sponsor is proposing to sample blood at various time points, for the sole purpose of establishing a Cmax and Tmax. No other plasma PK parameter will be evaluated. The main reason for the reluctance to carry out plasma PK determinations is that enalaprilat binds to ACE (a saturable binding site), thus extending the terminal elimination phase of the drug and consequently leading to erroneous values for renal CL, t 1/2 and oral bioavailability. To circumvent this problem, the sponsor proposes to determine the bioavailability of enalapril as well as the conversion rate of enalapril to enalaprilat using urinary data. Therefore the sponsor's responses to comments #1, 2 and 5 are not acceptable. The determination of bioavailability of enalapril based on urinary recoveries is not acceptable and thus any study that does not include measurement of plasma levels of enalaprilat will be of little value for regulatory purposes.

Recommendation:

The following comment should be sent to the sponsor, in writing:

The responses to FDA comments 1, 2 and 5 are not adequate. The determination of the bioavailability of enalapril based on urinary recoveries is not acceptable and thus any study that does not include a measurement of plasma levels of enalaprilat will be of little value from the regulatory point of view.

/S/ 1/21/99

Nakissa Sadrieh, Ph.D.

RD/FT initialed by Patrick Marroum, Ph.D. /S/

1/22/1999

cc: IND [redacted] HFD-110 (Bongiovanni), HFD-860 (Sadrieh), CDER document room