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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
18-998/S-059

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PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

View as Word Document

NDA Number:	018998	**Trade Name:**	VASOTEC (ENALAPRIL MALEATE) TABS
Supplement Number:	059	**Generic Name:**	ENALAPRIL MALEATE
Supplement Type:	SE8	**Dosage Form:**	
Regulatory Action:	AE	**COMIS Indication:**	TREATMENT OF HYPERTENSION (24-DEC-85) AND CONGESTIVE HEART FAILURE (24-JUN-88)
Action Date:	8/28/00		

Indication # 1 Hypertension

Label Adequacy: Adequate for SOME pediatric age groups

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any):

Ranges for This Indication

Lower Range	Upper Range	Status	Date
2 months	16 years	Completed	

This page was last edited on 5/3/01

/S/ U — 5/3/01

Signature Date

PEDIATRIC WRITTEN REQUEST CHECKLIST

NDA/IND# IND [redacted] Drug Product enalapril maleate

Have the following items been addressed in the Written Request? *Note:* [redacted]	YES	NO
Type of studies to be performed/submitted (check all that apply): ✓ [redacted]	✓	
Objective/rationale to reduce blood pressure in pediatric patients	✓	
Indication to be studied [redacted]	✓	
Study design Choice of 4	✓	
Age group(s) in which studies will be performed (if the age group(s) does not fall within the four defined age groups, check "Other" and specify the age range) [redacted]	✓	
Number of patients to be studied or power of study to be achieved	✓	
Entry criteria, i.e., inclusion/exclusion criteria	✓	
Clinical endpoints, including proposed primary efficacy endpoint	✓	
Study evaluations	✓	
Drug information (dosage form, regimen(s), route of administration, and formulation)	✓	
Safety concerns	✓	
Statistical information, including, power of the study and statistical analysis to be performed	✓	
Labeling that may result from the study(s)	✓	
Format of the report to be submitted to the agency	✓	
Timeframe for (note dates as mo/da/yr): **- Drafting the protocol** _____ **- Enrolling study participants** _____ **- Completing study(s)** _____ **- Drafting reports of the study(s)** **- Submitting the study reports** [redacted] – 2 years from date of letter	✓	

If "NO" is checked for any of the above, please attach an explanation.

PEDIATRIC WRITTEN REQUEST CHECKLIST

NDA 18-998 (and [redacted])

Drug Product Vasotec (enalapril maleate) Tablets

Have the following items been addressed in the Written Request? *Note: Highlighted areas must be completed*	YES	NO
Type of studies to be performed/submitted (check all that apply): ✓ Clinical efficacy; ✓ Safety; ✓ Pharmacokinetic; Other (describe):	✓	
Objective/rationale	✓	
Indication to be studied Hypertension	✓	
Study design	✓	
Age group(s) in which studies will be performed (if the age group(s) does not fall within the four defined age groups, check "Other" and specify the age range) ✓ Neonate (0-1mos) ✓ Infant (1 mos - 2 yrs) ✓ Children (2-12 yrs) ✓ Adolescents (12-16 yrs) Other (state the ages):	✓	
Number of patients to be studied or power of study to be achieved	✓	
Entry criteria, i.e., inclusion/exclusion criteria	✓	
Clinical endpoints, including proposed primary efficacy endpoint	✓	
Study evaluations		
Drug information (dosage form, regimen(s), route of administration, and formulation)	✓	
Safety concerns	✓	
Statistical information, including, power of the study and statistical analysis to be performed	✓	
Labeling that may result from the study(s)	✓	
Format of the report to be submitted to the agency	✓	
Timeframe for (note dates as mo/da/yr): - Drafting the protocol ____ - Enrolling study participants ____ - Completing study(s) ____ - Drafting reports of the study(s) ____ - Submitting the study reports 12 years from date of letter	✓	

If "NO" is checked for any of the above, please attach an explanation.

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 9/8/99 Application Written Request was made to: NDA/~~IND~~# 18-998
Timeframe Noted in Written Request for Submission of Studies 9/8/01
NDA# 18-998 Supplement #_____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR
Sponsor Merck & Co., Inc.
Generic Name enapramil 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

Was a formal Written Request made for the pediatric studies submitted?	Y ✓
Were the studies submitted after the Written Request?	Y ✓
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y ✓
Was the timeframe noted in the Written Request for submission of studies met?	Y ✓
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?	Y ✓
Were the studies responsive to the terms of the Written Request?	Y ✓

FORWARD TO THE PEDIATRIC EXCLUSIVITY BOARD, HFD-002.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity ___**Granted** ___ **Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date

SIGNED _____ DATE _____
cc:
Archival NDA/IND ##-###

Originator: Deputy Center Director (Review Management)
October 6, 1998

EXCLUSIVITY SUMMARY FOR NDA # 18-998 SUPPL #059

Trade Name: Vasotec Generic Name: enalapril maleate

Applicant Name: Merck Research Laboratories HFD # 110

Approval Date If Known: 24 December 1985

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /___/ NO /_X_/

b) Is it an effectiveness supplement?

YES /_X_/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE 8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

Yes: 13 February 2001

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X_/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 18-998 this NDA

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Clinical Study P 167 C

Pediatric Pharmakokinetic Study 168

Pediatric Bioavailability Study 170

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	IND [redacted]	YES /_X_/	NO /___/
Investigation #2	IND [redacted]	YES /_X_/	NO /___/
Investigation #3	IND [redacted]	YES /_X_/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Clinical Protocol P 167 C

Pediatric Pharmacokinetic Protocol 168-00

Pediatric Bioavailability Protocol 170-00

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # [redacted] YES /_X_/ NO /___/ Explain: _____

Investigation #2

IND # [redacted] YES /_X_/ NO /___/ Explain: _____

Investigation #3

IND # [redacted] YES /_X_/ NO /___/ Explain: _____

For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

Sandra Birdsong /S/ 19 March 2001
Signature Date
Title: Consumer Safety Officer

/S/

Raymond Lipicky, M.D. 20 March 2001
Signature of Date
Division Director
Cardio-Renal Drug Products
HFD-110

cc: Original NDA Division File HFD-93 Mary Ann Holovac

RHPM Review of Final Printed Labeling
NDA 18-998/SLR-059

Date Labeling Submitted: December 21, 2000

Date Reviewed: January 8, 2001

Product: Vasotec (enalapril maleate) Tablets

Sponsor: Merck and Company, Inc.

Background

This supplemental application provides for labeling revised to include information on pediatric use. An approvable letter (on draft labeling) issued on August 28, 2000.

Review

This final printed labeling was submitted on December 21, 2000. I found the labeling to be identical to the submitted draft labeling with the following minor exceptions:

1. Under **DOSAGE AND ADMINISTRATION**/Pediatric Hypertensive Patients, in the first paragraph of the text, in the third sentence, the number [redacted] is changed to "63-76%". This change was approved by Dr. Dorantes and communicated to the sponsor on September 25, 2000.

2. Under **DOSAGE AND ADMINISTRATION**/Pediatric Hypertensive Patients */Preparation of Suspension (for 200 mL of a 10 mg/mL suspension)* , the first sentence has been changed

From:

(DRAFT Labeling)

To:

Add 50 ml Bicitra*** to a polyethylene terephthalate (PET) bottle containing ten 20 mg tablets of VASOTEC and shake for at least 2 minutes.

3. Throughout the **HOW SUPPLIED** section, several packaging descriptions have been deleted.

Recommendation

An Approval Letter will be drafted for Dr. Lipicky's signature.

/S/ 2/14/01
Sandra Birdsong
Regulatory Health Project Manager

Slb/08 Jan 01

cc: NDA 18-998
HFD-110
HFD-110/S. Birdsong

110·1

AUG - 1 2000

RHPM Draft Labeling Review

17 P

Application:	NDA 18-998/S-059
Applicant Name:	Merck Research Laboratories
Product Name:	Vasotec (enalapril maleate) 2.5, 5, 10, and 20 mg
Date of Submission:	January 14, 2000
Date of Review:	June 28, 2000

Evaluation

This supplemental application provides for draft labeling revised to provide information relating to the use of Vasotec in the pediatric population. A *Clinical Pharmacology in Pediatric Patients* subsection of the **CLINICAL PHARMACOLOGY** section and a subsection for *Pediatric Use* under **the PRECAUTIONS** subsection were added. Under the **DOSAGE AND ADMINISTRATION** section, a subsection entitled *Pediatric Hypertensive Patients* was also added.

Dr. Steven Rodin performed the medical review of the application. Dr. Rodin's April 28, 2000 review stated, "The proposed label, on its face, is responsive to the Written Request. No new indication is sought."

Dr. Rodin's final comments in his June 26, 2000 review are as follows:

> "The findings obtained in response to the Written Request suggest that the Adverse Event (AE) profile in children was not different from that seen in adults, and these findings are adequately described in the proposed labeling."

The following was added to the draft labeling by the sponsor:

Under **CLINICAL PHARMACOLOGY**:

Clinical Pharmacology in Pediatric Patients

In a multiple dose pharmacokinetic study in 40 hypertensive pediatric patients, excluding neonates, VASOTEC was generally well tolerated. Pharmacokinetics following oral administration of enalapril are similar in these patients and comparable to historical values in adults.

In a clinical study involving 110 hypertensive pediatric patients 6 to 16 years of age, patients who weighed <50 kg received either 0.625, 2.5 or 20 mg of enalapril daily and patients who weighed ≥ 50 kg received either 1.25, 5, or 40 mg of enalapril daily. Enalapril administration once daily lowered trough blood pressure in a dose-dependent manner. The dose-dependent antihypertensive efficacy of enalapril was consistent across all subgroups (age, Tanner stage, gender, race). However, the lowest doses studied, 0.625 mg and 1.25 mg, corresponding to an average of 0.02 mg/kg once daily, did not appear to offer consistent antihypertensive efficacy. In this study, VASOTEC was generally well tolerated.

For hypertensive children and infants who are unable to swallow tablets or who require a lower dose than is available in tablet form, enalapril can be administered in a suspension formulation (see DOSAGE AND ADMINISTRATION, *Pediatric Hypertensive Patients).*

2. Under **PRECAUTIONS**/*General*:

Pediatric Use:

The safety and effectiveness of VASOTEC have been established in hypertensive pediatric patients age 1 month to 16 years. Use of VASOTEC in these age groups is supported by evidence from adequate and well-controlled studies of VASOTEC in pediatric and adult patients

as well as by published literature in pediatric patients. (See CLINICAL PHARMACOLOGY, *Clinical Pharmacology in Pediatric Patients* and DOSAGE AND ADMINISTRATION.)

VASOTEC is not recommended in neonates and in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m^2, as no data are available.

3. Under **ADVERSE REACTIONS**/*Pediatric Patients*:

The adverse experience profile for pediatric patients is not different from that seen in adult patients.

4. Under **DOSAGE AND ADMINISTRATION,** the subsection entitled "*Pediatric Hypertensive Patients*" has been added and the following paragraph added under this subsection:

The usual recommended starting dose is 0.08 mg/kg (up to 5 mg) once daily. Dosage should be adjusted according to blood pressure response. Doses above 0.58 mg/kg (or in excess of 40 mg) have not been studied in pediatric patients.

See CLINICAL PHARMACOLOGY, *Clinical Pharmacology in Pediatric Patients.*

VASOTEC is not recommended in neonates and in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m^2, as no data are available.

Preparation of Suspension (for 200 mL of a 1.0 mg/mL suspension)

Add 50 mL of Bicitra®** to a polyethylene terephthalate (PET) bottle containing ten 20-mg tablets and shake for at least 2 minutes. Let concentrate stand for 60 minutes. Following the 60-minute hold time, shake the concentrate for an additional minute. Add 150 mL of Ora-Sweet SF™*** to the concentrate in the PET bottle and shake the suspension to disperse the ingredients. The suspension should be refrigerated at 2-8°C (36-46°F) and can be stored for up to 30 days. Shake the suspension before each use.

The symbol "**" is footnoted by this statement:

Registered trademark of Alza Corporation

The symbol "***" is footnoted by this statement:

Trademark of Paddock Laboratories, Inc.

5. We also note that the following editorial change was made:

The address for Merck and Company, Inc. has been changed from,

To:

Whitehouse Station, NJ 08889, USA

This supplemental application was also reviewed by Dr. Angelica Dorantes for Clinical Pharmacology and Biopharmaceutics. In her review of June 26, 2000 she recommended that two subsections of the proposed labeling be modified.

1. In the **CLINICAL PHARMACOLOGY**/*Clinical Pharmacology in Pediatric Patients* subsection, Change from:

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.

2. In the **DOSAGE AND ADMINISTRATION**/*Preparation of Suspension (for 200 mL of a 1.0 mg/mL suspension)* subsection, it is recommended that the word "VASOTEC™" be incorporated into the first sentence as follows:

Add 50 mL of Bicitra®** to a polyethylene terephthalate (PET) bottle containing ten 20-mg tablets and shake for at least 2 minutes.

Dr. Lipicky reviewed the changes recommended by the reviewers. The following labeling changes are to be included in the Approvable letter to the sponsor, according to Dr. Lipicky's review comments dated August 1, 2000:

1. Under **CLINICAL PHARMACOLOGY**:

Clinical Pharmacology in Pediatric Patients

In a multiple dose pharmacokinetic study in 40 hypertensive pediatric patients, excluding neonates, the pharmacokinetics following oral administration of enalapril were comparable to historical values in adults and were consistent across age groups 2 months to 16 years.

In a clinical study involving 110 hypertensive pediatric patients 6 to 16 years of age, patients who weighed <50 kg received either 0.625, 2.5 or 20 mg of enalapril daily and patients who weighed ≥ 50 kg received either 1.25, 5, or 40 mg of enalapril daily. Enalapril administration once daily lowered trough blood pressure in a dose-dependent manner. The dose-dependent antihypertensive efficacy of enalapril was consistent across all subgroups (age, Tanner stage, gender, race). However, the lowest doses studied,
0.625 mg and 1.25 mg, corresponding to an average of 0.02 mg/kg once daily, did not appear to offer consistent antihypertensive efficacy. In this study, VASOTEC was generally well tolerated.

For hypertensive children and infants who are unable to swallow tablets or who require a lower dose than is available in tablet form, enalapril can be administered in a suspension

formulation (see DOSAGE AND ADMINISTRATION, *Pediatric Hypertensive Patients).*

2. Under **PRECAUTIONS**/*General*:

Pediatric Use:

The effectiveness of VASOTEC has been established in hypertensive pediatric patients age 1 month to 16 years. Use of VASOTEC in these age groups is supported by evidence from adequate and well-controlled studies of VASOTEC in pediatric and adult patients as well as by published

literature in pediatric patients. (See **CLINICAL PHARMACOLOGY**/*Clinical Pharmacology in Pediatric Patients* and **DOSAGE AND ADMINISTRATION.**)
VASOTEC is not recommended in neonates and in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m^2, as no data are available.

3. Under **ADVERSE REACTIONS**/*Pediatric Patients*:

   The adverse experience profile for pediatric patients appears to be similar to that seen in adult patients.

4. Under **DOSAGE AND ADMINISTRATION,** add the subsection entitled "*Pediatric Hypertensive Patients*" and the following paragraphs under this subsection:

   The usual recommended starting dose is 0.08 mg/kg (up to 5 mg) once daily. Dosage should be adjusted according to blood pressure response. Doses above 0.58 mg/kg (or in excess of 40 mg) have not been studied in pediatric patients.

   See **CLINICAL PHARMACOLOGY**, *Clinical Pharmacology in Pediatric Patients.*

   VASOTEC is not recommended in neonates and in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m^2, as no data are available.

   Preparation of Suspension (for 200 mL of a 1.0 mg/mL suspension)
   Add 50 mL of Bicitra®** to a polyethylene terephthalate (PET) bottle containing ten 20 mg tablets and shake for at least 2 minutes. Let concentrate stand for 60 minutes. Following the 60-minute hold time, shake the concentrate for an additional minute. Add 150 mL of Ora-Sweet SF™*** to the concentrate in the PET bottle and shake the suspension to disperse the ingredients. The suspension should be refrigerated at 2-8°C (36-46°F) and can be stored for up to 30 days. Shake the suspension before each use.

   The symbol "**" is footnoted by the following statement:

   Registered trademark of Alza Corporation

   The symbol "***" is footnoted by the following statement:

   Trademark of Paddock Laboratories, Inc.

5. We also note that the following editorial change was made:

   The address for Merck and Company, Inc. has been changed from,

   To:

   Whitehouse Station, NJ 08889, USA

Recommendation:

An approvable letter requesting final printed labeling in accordance with the revisions listed in the letter will be issued for this supplement as set forth under 21 CFR 314.70 (b) (3) [Any change in labeling.]

/S/

Sandra Birdsong
RHPM

cc: orig. NDA
HFD-110
HFD-110/Blount
HFD-110/Birdsong
HF-2/MedWatch

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(610) 397-2516
Attention:	Jeff White
Company Name:	MRL
Phone:	(610) 397-3180
Subject:	Minutes
Date:	12-10-98
Pages including this sheet:	5

From: **Kathleen Bongiovanni**
Phone: **301-594-5334**
Fax: **301-594-5494**

Please note: You are responsible for notifying us of any differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

K. Bongiovanni

DEC 10 1998

Minutes
November 13, 1998
NDA 18-998 Vasotec (enalapril maleate) Tablets
Merck Research Laboratories
Discussion of Pediatric Studies

Attending:

FDA:

Robert Temple, M.D.	HFD-101	Office Director
Rachel Behrman, M.D.	HFD-101	Deputy Office Director
Raymond Lipicky, M.D.	HFD-110	Division Director
Robert R. Fenichel, M.D., Ph.D.	HFD-110	Deputy Division Director
Charles Ganley, M.D.	HFD-110	Medical Team Leader
Khyati Roberts	HFD-006	Science Policy Analyst
Lu Cui, Ph.D.	HFD-710	Statistician
Patrick Marroum, Ph.D.	HFD-860	Biopharm. Team Leader
Nakissa Sadrieh, Ph.D.	HFD-860	Biopharmaceutist
Nancy Algranati, Pharm.D.	HFD-860	Biopharm. Fellow
Kathleen Bongiovanni	HFD-110	Project Manager/Minutes Recorder

Merck:

Dr. Jeffery Anderson	Clinical Research
Dr. Thiyagarajan Balasamy	Biostatistics
Dr. Larry Bell	Regulatory Affairs
Ms. Marie Dray	Regulatory Agency Relations
Dr. Gail Murphy	Clinical Pharmacology
Dr. Rhonda Rippley	Drug Metabolism
Dr. Shahnaz Shahinfar	Clinical Research
Dr. Karen Thompson	Pharmaceutical Research
Dr. Jeffery White	Regulatory Affairs
Dr. Zhongxin Zhang	Biostatistics

Consultants for Merck:

Cheston M. Berlin, Jr., M.D.	Prof. of Pediatrics and Pharmacology, Penn. State U. College of Medicine Chair, Committee on Drugs, American Academy of Pediatrics (AAP)
Thomas G. Wells, M.D.	Assoc. Prof. Pediatric Nephrology and Pharmacology U. of Arkansas for Medical Sciences Medical Director, Ped. Clinic Research Unit, Arkansas Children's Hospital Director, Pediatric Pharmacology Research Unit State Chair for Committee on Drugs, AAP

Related Submission: to IND [redacted] serial number 184, dated November 4, 1998
and to NDA 18-998, dated November 4, 1998

Background: On October 24, 1998, Dr. Temple signed a Pediatric Written Request Letter for Vasotec (enalapril maleate) Tablets. Merck asked for this meeting to discuss their proposed pediatric studies to qualify for pediatric exclusivity for enalapril maleate.

Meeting:

Acceptable Package

Dr. Temple told Merck that we recommend the following:

- 50% or more of the patients in the proposed efficacy trial should be Tanner Stage 3 or younger; this should be included in the protocol;
- Merck should take steps to obtain a reasonable distribution of age, race, and gender in the trials; this should be outlined in the protocol;
- For the efficacy trial, the primary analysis should be better defined; it could be blood pressures at day 14, using the last-value-carried-forward for patients who discontinued the study; the protocol should be clarified. All patients should be included in the analysis. If a patient drops out of the study, a blood pressure measurement should be made.
- It is acceptable to perform the efficacy trial without including hydrochlorothiazide;
- It is acceptable to omit studies to assess the effect of enalapril maleate on the growth and development of adolescents;
- Merck should include a summary of all available safety information in the final reports;
- It is acceptable to omit neonates in the pharmacokinetic studies.

With the above modifications, and assuming a positive slope of the dose-response curve if the firm chooses to perform the dose-response study without placebo, we agreed that the package would be sufficient for extended market exclusivity under the provisions of the FDA Modernization Act (FDAMA) We will send Merck a revised Written Request. Merck indicated that they would also like to develop a Written Agreement.

Positive Slope

Merck also asked whether the package, as defined, would be sufficient for extended market exclusivity under FDAMA if the dose-response slope is not positive. We told them it would not be acceptable without a positive slope, because without a slope the data are not interpretable. One would not know if all the doses cause the same effect or if none has any effect. There are alternatives: add a placebo group, or add a randomized withdrawal of therapy at the end of the proposed trial.

Dr. Cui noted that there may need to be a statistical adjustment for the multiplicity of endpoints, slope and randomized withdrawal. Drs. Temple and Lipicky agreed that Merck need not account for multiplicity in this case.

Dr. Ganley noted that the protocol encourages investigators to drop patients out of the study. If dropouts are numerous, this might cause the study to fail to provide any meaningful data.

Abbreviated Reports

Merck asked whether the Agency would accept a full analysis of the efficacy data and tabulations of safety data in an abbreviated study report format for purposes of extending market exclusivity, due to the extremely tight timeline. We agreed to accept an abbreviated report if the firm submits all data from the case report forms in electronic form. Merck said they will prepare the reports in the same way as they submitted the .

[Dr. Temple left the meeting at this point.]

Pharmacokinetic Studies

Dr. Lipicky suggested that the firm used mixed effects modeling for pharmacokinetic data. He suggested that they take one blood sample 30 minutes after dosing, and one just before the next dose, and 2 others at random, always recording the time the sample was taken and when the dose was administered. Dr. Marroum said that they could vary the timing for all four samples.

The study protocols mention primary and secondary endpoints of urine and plasma levels. Merck acknowledged that they are not testing a hypothesis, but are gathering data on both plasma and urine.

Randomized-Withdrawal Trial

After Dr. Temple left the meeting, Merck asked for clarification on whether there is an outcome requirement for the non-placebo-containing dose-response study with a randomized withdrawal portion at the end. Merck asked whether the trial would be acceptable if during the withdrawal period blood pressures did not rise, or if there was another unforeseen outcome that led to uninterpretable results. We said that the randomized-withdrawal portion would have to be powered to be able to show an effect. There was some disagreement about whether the trial would then be outcome independent. We told Merck we would get back to them after we confirm the answer with Dr. Temple. [Dr. Temple confirmed that so long as the randomized withdrawal phase was adequately powered, it would not need to show a statistically significant difference between drug and placebo.].

Merck asked whether they could in the withdrawal phase, randomize patients to placebo and continued therapy only, rather than to lower doses of enalapril. Dr. Lipicky thought that was acceptable [and Dr. Temple subsequently agreed].

Dr. Fenichel noted that the randomized withdrawal portion of the trial would yield information on the effect of missed doses on blood pressure, which may be important to the parents.

Merck asked whether they could do an interim analysis, so that they would go on to the randomized withdrawal portion of the trial only if there were not a positive slope in the dose-response portion of the trial. Dr. Fenichel said that all of the patients in the dose-response portion of the trial would have to finish at the same time to allow the analysis to occur with meaningful results. Dr. Lipicky said that with an interim look, they would need a very large number of patients, and we are not willing to concede the statistical penalty for an interim look.

Conclusion

Merck will submit revised protocols towards obtaining a Written Agreement. We will send them a revised Written Request letter.

Signature, minutes preparer: /S/

Kathleen F. Bongiovanni 12-8-98

Concurrence Chair: /S/

Robert Temple, M.D.

cc:

NDA 18-998
HFD-110
HFD-110/KBongiovanni
HFD-110/SBenton
HFD-101/RTemple/RBehrman
HFD-006/KRoberts
kb/11/16/98; 12/1/98; 12/8/98

R/D: RFenichel/11/17/98; CGanley/11/20/98; LCui/11/25/98; PMarroum/11/30/98; NSadrieh/12/1/98; NAlgranati/12/1/98; RBehrman; RTemple.