CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
18-998/S-059

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-998/S-059

FEB 13 2001

Merck and Company, Inc.
Attention: Michael C. Elia, Ph.D.
Director, Regulatory Affairs
P. O. Box 4
Sumneytown Pike, BLA-20
West Point, PA 19486

Dear Dr. Elia:

Please refer to your supplemental new drug application dated January 14, 2000, received January 14, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vasotec (enalapril maleate) 2.5, 5, 10, and 20 mg Tablets.

We acknowledge receipt of your submission dated December 21, 2000 that constitutes a complete response to our August 28, 2000 approvable letter.

This supplemental new drug application provides for final printed labeling revised to include information on pediatric use. In addition, minor editorial changes have been made under **CLINICAL PHARMACOLOGY**/*Pediatric Patients*, **DOSAGE AND ADMINISTRATION**/Pediatric Hypertensive Patients/*Preparation of Suspension (for 200 mL of a 10 mg/mL suspension)*, and throughout the **HOW SUPPLIED** section.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert included in your December 21, 2000 submission). Accordingly, the supplemental application is approved effective on the date of this letter.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Sandra L. Birdsong
Regulatory Health Project Manager
(301) 594-5334

Food and Drug Administration
Rockville MD 20857

Sincerely,

/S/

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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Food and Drug Administration
Rockville MD 20857

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AUG 2 8 2000

Merck and Company, Inc.
Attention: Michael C. Elia, Ph.D.
P.O. Box 4, BLA-20
Sumneytown, Pike
West Point, PA 19486

Dear Dr. Elia:

Please refer to your supplemental new drug application dated January 14, 2000, received January 14, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vasotec (enalapril maleate) Tablets 2.5, 5, 10, and 20 mg.

This supplemental new drug application provides for changes to the package insert to include pediatric information.

We have completed the review of this application, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

1. Under **CLINICAL PHARMACOLOGY**:

Clinical Pharmacology in Pediatric Patients

A multiple dose pharmacokinetic study was conducted in 40 hypertensive male and female pediatric patients aged 2 months to ≤16 years 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 and the mean urinary recovery of total enalapril + enalaprilat in 24 hours was 67% of the administered dose. 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 months to ≤16 years are consistent across the studied age groups and consistent with pharmacokinetic historic data in healthy 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.

In the above pediatric studies, enalapril maleate was given as VASOTEC tablets and for those children and infants who were unable to swallow tablets or who required a lower dose than is available in tablet form, enalapril was administered in a suspension formulation (see *Preparation of Suspension* under **DOSAGE and ADMINISTRATION**).

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

Pediatric Use:

Antihypertensive effects 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 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 VASOTEC® 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:

West Point, PA 19486, USA

to:

Whitehouse Station, NJ 08889, USA

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 paper copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, please call:

Ms. Sandra L. Birdsong
Regulatory Project Manager
(301) 594-5312

Sincerely,

/S/

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 18-998
HFD-110/Div. Files
HFD-110/S.Birdsong SLB 8/25/00
HFD-110/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: sb/July 13, 2000
Initialed by: Karkowsky/7/24/00, 8/25/00
Dorantes/7/13/00, 8/3/00, 8/24/00
Marroum/7/13/00, 8/4/00, 8/24/00
Rodin/7/31/00, 8/2/00
Zimmerman/7/25/00, 8/9/00
Srinivasachar/7/25/00, 8/9/00
Jagadeesh/7/26/00, 8/10/00
Resnick/7/26/00, 8/11/00
Revised: 8/1/00, 7/24/00, 8/23/00
Final: asb/8/2/00

APPROVABLE (AE)