DEPARTMENT OF HEALTH & OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-998/S-057
19-221/S-025
19-309/S-022
19-558/S-036
19 778/S 029
20-507/S-001

FEB 1 7 1999

Merck Research Laboratories
Attention: Jeffrey R. White, M.D.
Sumneytown Pike, P.O. Box 4
BLA-20
West Point, PA 19486

Dear Dr. White:

Please refer to your supplemental new drug applications dated December 10, 1997, received December 12, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vasotec (enalapril maleate) Tablets (NDA 1 8-998), Vaseretic (enalapril maleate/hydrochlorothiazide) Tablets (NDA 19-221), Vasotec (enalaprilat) I.V. (NDA 19-309), Prinivil (lisinopril) Tablets (NDA 19-558), Prinzide (lisinopril/hydrochlorothiazide) Tablets (NDA 19-778), and Teczem (enalapril maleate/diltiazem maleate) Tablets (NDA 20-507).

We acknowledge receipt of your submissions dated January 21, 1999.

These supplemental new drug applications provide for final printed labeling revised as follows:

NDA 18-998, 19-221, 19-309, and 20-507:
CONTRAINDICATIONS: The phrase "and in patients with hereditary or idiopathic angioedema" has been added to the first sentence.

WARNINGS, Neutropenia/Agranulocytosis: The word "several," referring to the number of cases of agranulocytosis reported, has been deleted from the third sentence.

PRECAUTIONS, General [, Enalapril Maleate]: A new subsection has been added: "Aortic Stenosis/Hypertrophic Cardiomyopathy: As with all vasodilators, enalapril should be given with caution to patients with obstruction in the outflow tract of the left ventricle."

PRECAUTIONS, Drug Interactions [, Enalapril Maleate]: A new subsection has been added: "Non-steroidal Anti-inflammatory Agents: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the coadministration of enalapril may result in a further deterioration of renal function. These effects are usually reversible."

ADVERSE REACTIONS, [Enalapril Maleate,] Respiratory: "eosinophilic pneumonitis" has been added.

OVERDOSAGE [, Enalapril Maleate]: A cross-reference, "(See WARNINGS, Anaphylactoid reactions during membrane exposure.)" has been added.

NDA 19-558 and 19-778:
CONTRAINDICATIONS: The phrase "and in patients with hereditary or idiopathic angioedema" has been added to the first sentence.

PRECAUTIONS, General [, Lisinopril]: A new subsection has been added: "Aortic Stenosis/Hypertrophic Cardiomyopathy: As with all vasodilators, lisinopril should be given with caution to patients with obstruction in the outflow tract of the left ventricle."

PRECAUTIONS, Drug Interactions [, Lisinopril]: A new subsection has been added: "Non-steroidal Anti-inflammatory Agents: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the coadministration of lisinopril may result in a further deterioration of renal function. These effects are usually reversible." The information formerly in the subsection "Indomethacin" now follows the above two sentences. The "Indomethacin" subheading has been deleted.

ADVERSE REACTIONS, [Lisinopril,] Special Senses: "taste disturbances" has been added.

OVERDOSAGE [, Lisinopril]: A cross-reference, "(See WARNINGS, Anaphylactoid reactions during membrane exposure.)" has been added.

NDA 18-998:
HOW SUPPLIED: Information on unit of use bottles of 180 2.5 mg tablets, 180 5 mg tablets, 180 10 mg tablets, and bottles of 4000 5 and 10 mg tablets has been deleted due to the discontinuation of production and sale of these items.

NDA 19-558
ADVERSE REACTIONS, Respiratory System: "eosinophilic pneumonitis" has been added.

NDA 19-778:
ADVERSE REACTIONS, Lisinopril, Respiratory: "eosinophilic pneumonitis" has been added.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstratethat the drug products are safe and effective for use as recommended in final printed labeling included in your January 21, 1999 submissions. Accordingly, the supplemental applications are approved effective on the date of this letter.

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:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
(301) 594-5334

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
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