CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S034

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
Approvable Letter	X
Final Printed Labeling	
Medical Review(s)	
Chemistry Review(s)	
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	
Administrative Document(s)	X
Correspondence	
Bioresearch Monitoring	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 18-998/S-34

Trade Name: Vasotec

Generic Name(s): (enalaprilat)

Sponsor: Merck Research Laboratories

Agent:

Approval Date: July 31, 1996

Indication: The treatment of hypertension.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 18-998/S-034

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA ~~18-998~~/S-034
19-309/S-012

JUL 31 1996

Merck Research Laboratories
Attention: Larry P. Bell, M.D.
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Bell:

Please refer to your November 20, 1992 supplemental new drug applications (NDAs) 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 (NDA 18-998) and Vasotec I.V. (enalprilat) Injection (NDA 19-309).

For both applications, we acknowledge receipt of your correspondence and amendments dated September 23, 1994, June 26, 1995 and June 27, 1996

The supplemental applications provide for final printed labeling revised as follows:

NDA 18-998/S-034 and NDA 19-309/S-012

WARNINGS, Fetal/Neonatal Morbidity and Mortality

Revision of the last statement to express the doses used in studies of enalapril in pregnant rats and rabbits in terms of the maximum recommended human daily dose (MRHDD) on a body surface area basis. As agreed between FDA and MRL, the conversion factor of — rather than — has been used.

PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility

Revision of the first and third paragraphs to express the doses used in studies of enalapril in male and female rats and mice in terms of the maximum recommended human daily dose (MRHDD) on a body surface area basis. As agreed between FDA and MRL, the conversion factor of — rather than — has been used.

PRECAUTIONS, Nursing Mothers

Revision of statements regarding the detection of enalapril and enalaprilat in human breast milk and the decision to discontinue nursing or discontinue Vasotec (or Vasotec I.V.) in nursing.

INDICATIONS AND USAGE

Revision of the last statement in this section to read: "In addition, it should be noted that black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks. (See WARNINGS, Angioedema)," as requested by FDA letter of September 28, 1995.

WARNINGS, Anaphylactoid and possibly Related Reactions, Anaphylactoid Reactions during Membrane Exposure

Deletion of [redacted] as requested by FDA letter of September 28, 1995.

PRECAUTIONS, Pediatric Use

Editorial revision to revise [redacted] to "pediatric patients" to comply with the FDA Final Rule regarding the Pediatric Use subsection in labeling (21 CFR 201.57).

NDA 18-998/S-034 only

DOSAGE AND ADMINISTRATION, Heart Failure

Editorial revision to correct the typographical error in the last statement of the second paragraph [redacted] to trials).

OVERDOSAGE

Deletion of [redacted]

NDA 19-309/S-012 only

HOW SUPPLIED

Update of the National Stock Number for the 1 ml vials

OVERDOSAGE

Deletion of the [redacted] and addition of statements regarding the lethality of enalaprilat in female mice.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drugs are safe and effective for use as recommended in the final printed labeling included in the June 27, 1996 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,

RL 7/31/96

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

cc:
Original NDA
HF-2/MedWatch (with draft/final labeling)
HFD-80 (with draft/final labeling)
HFD-110
HFD-110/Project Manager
HFD-40 (with draft/final labeling)
HFD-613 (with draft/final labeling)
HFD-735 (with draft/final labeling)
DISTRICT OFFICE
HFD-222/New Drug Chemistry Division Director
HFD-110/GBuehler/7/19/96;7/22/96
sb/7/22/96;7/31/96
R/D: JAdvani/7/23/96
RWolters/7/24/96
CGanley/7/25/96
CResnick/7/26/96
KBongiovanni/7/30/96
NMorgenstern/7/30/96 KB 7-31-96

Approval Date: 12/24/85 (NDA 18998)
2/9/88 (NDA 19309)

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 18-998/S-034

Approvable Letter (s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA ~~18-998/S-034~~
19-309/S-012

SEP 15 1994

Merck Research Laboratories
Attention: Patricia L. Kraft, Ph.D.
Sumneytown Pike
West Point, PA 19486

Dear Dr. Kraft:

Please refer to your November 20, 1992 supplemental new drug applications submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Vasotec (enalapril maleate) Tablets (NDA 18-998) and Vasotec (enalaprilat) I.V. (NDA 19-309).

The supplemental applications provide for draft labeling revised in response to our April 15, 1992 supplement request letter under **PRECAUTIONS, Carcinogenesis, Mutagenesis and Impairment of Fertility, PRECAUTIONS, Nursing Mothers** and **OVERDOSAGE**.

We have completed the review of these supplemental applications as submitted with draft labeling. Before these supplements may be approved, however, it will be necessary for you to submit final printed labeling. The labeling should be identical in content to the submitted draft labeling with the following exceptions:

NDA 18-998

The information in the **PRECAUTIONS** section, **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, should be corrected to read as follows:

1st Paragraph

There was no evidence of a tumorigenic effect when enalapril was administered [redacted]

3rd Paragraph, Last Sentence

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 [redacted]

NDA 19-309

The information in the **PRECAUTIONS** section, **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, should be corrected to read as follows:

2nd Paragraph

VASOTEC I.V. is the bioactive form of its ethyl ester, enalapril maleate. There was no evidence of a tumorigenic effect when enalapril was administered

3rd Paragraph; Last Sentence

There were no adverse effects on reproductive performance

The second sentence under **OVERDOSAGE** should be revised to read as follows:

In addition to the above labeling changes, all previous revisions as reflected in the most recently approved package inserts must be included. To facilitate review of your submissions, please provide highlighted or marked-up copies that show the changes that are being made.

If additional information relating to the safety or effectiveness of these drugs becomes available before we receive the final printed labeling, revision of that labeling may be required.

To each application, please submit fifteen copies of the printed labeling ten of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend these supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw these supplemental applications.

Should you have any questions, please contact:

Ms. Kathleen Bongiovanni
Consumer Safety Officer
Telephone: (301) 594-5300

Sincerely yours,

R L 9/15/94

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

cc:
Original NDA
HF-2 (with labeling)
HFC-130/JAllen
HFD-110
HFD-110/CSO
HFD-80
HFD-735/Baresh (with labeling)
HFD-110/KBongiovanni;12/20/93
sb/12/20/93;1/11/94;8/26/94
R/D: AProakis/12/20/93
CResnick/1/6/94
CGanley/1/7/94
SChen/1/7/94
GBuehler for NMorgenstern/1/7/94

Approval Date: NDA 18-998 - December 24, 1985
NDA 19-309 - February 9, 1988

APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 18-998/S-034

Administrative/Correspondence

JUL 30 1996

RHPM REVIEW OF LABELING

NDA 18-998/S-034 Vasotec (enalapril maleate) Tablets
NDA 19-309/S-012 Vasotec IV (enalaprilat) Injection

Merck Research Laboratories
PO Box 4, BLA-20
West Point, PA 19486

Date of Submission: November 20, 1992 (all)

Date of FPL Submission: June 27, 1996 (all)

The supplemental applications provide for final printed labeling revised as follows:

WARNINGS, Fetal/Neonatal Morbidity and Mortality

Revision of the last statement to express the doses used in studies of enalapril in pregnant rats and rabbits in terms of the maximum recommended human daily dose (MRHDD), based on a body surface area basis. As agreed between FDA and MRL, the conversion factor of — rather than — has been used.

PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility

Revision of the first and third paragraphs to express the doses used in studies of enalapril in male and female rats and mice in terms of the maximum recommended human daily dose (MRHDD), based on a body surface area basis. As agreed between FDA and MRL, the conversion factor of — rather than — has been used.

PRECAUTIONS, Nursing Mothers

Revision of statements regarding the detection of enalapril and enalaprilat in human breast milk and the decision to discontinue nursing or discontinue Vasotec (or Vasotec I.V.) in nursing.

INDICATIONS AND USAGE

Revision of the last statement in this section to read: "In addition, it should be noted that black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks. (See WARNINGS, Angioedema)", as requested by FDA letter of 9/28/95.

WARNINGS, Anaphylactoid and possibly Related Reactions, Anaphylactoid Reactions during Membrane Exposure

Deletion of the statement: ——————————————————
——————→ as requested by FDA letter of 9/28/95.

PRECAUTIONS, Pediatric Use

Editorial revision to revise ——— to "pediatric patients" to comply with the FDA Final Rule regarding the Pediatric Use subsection in labeling (21CFR 201.57).

NDA 18-998/S-034 only

DOSAGE AND ADMINISTRATION, Heart Failure

Editorial revision to correct the typographical error in the last statement of the second paragraph ——— to trials).

OVERDOSAGE

Deletion of ———

NDA 19-309/S-012 only

HOW SUPPLIED

Update of the National Stock Number for the 1 ml vials

OVERDOSAGE

Deletion of the statement regarding ——— and addition of statements regarding the lethality of enalaprilat in female mice.

The labeling was reviewed and found to be acceptable. An approval letter will be drafted for Dr. Lipicky's signature.

Gary Buehler 7/30/96

Gary Buehler, RHPM

Orig NDA
HFD-110
HFD-110 KBongiovanni
HFD-110 SBenton

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-998/S-034
19-309/S-012

MAY 30 1995

Merck Research Laboratories
Attention: Larry P. Bell, M.D.
Sumneytown Pike
West Point, PA 19486

Dear Dr. Bell:

Please refer to your November 20, 1992 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vasotec (enalapril maleate) Tablets (NDA 18-998) and Vasotec (enalaprilat) I.V. (NDA 19-309).

The supplemental applications provided for draft labeling revised under **PRECAUTIONS, Carcinogenesis, Mutagenesis and Impairment of Fertility, PRECAUTIONS, Nursing Mothers** and **OVERDOSAGE** sections in response to our April 15, 1992 supplement request letter.

We also refer to our letter of September 15, 1994 notifying you that your supplemental applications were approvable. Your September 23, 1994 correspondence informed us of your intent to file amendments to your supplemental applications. A notice of intent to file an amendment constitutes an agreement by you to extend the review period under 21 CFR 314.60.

We have no record that you have filed amendments fully responsive to our approvable letter. Since 8 months have passed we will consider these supplemental applications withdrawn under 21 CFR 314.110(a)(2) unless you file such amendments within thirty (30) days. Alternatively, you may wish to withdraw the supplemental NDAs under 21 CFR 314.65. Withdrawal would not prejudice any future resubmission of the supplemental applications. You may request that the information in the withdrawn supplemental applications be considered in conjunction with any resubmission.

We are concerned about improving our management of NDAs during the review process. Applications such as these, overburden our document rooms and distort our workload assignments. We, therefore, hope for your cooperation.

Sincerely yours,

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

cc:
Original NDA
HFC-130/JAllen
HFD-110
HFD-110/CSO
HFD-80/DDIR
HFD-110/SBenton/5/24/95

INFORMATION REQUEST

SEP 15 1994

CSO Review of Labeling

NDA: 18-998/S-034 Vasotec (enalapril maleate) Tablets
19-221/S-013 Vaseretic (enalapril maleate/HCTZ) Tablets
19-309/S-012 Vasotec (enalaprilat) I.V.

Date of submissions: November 20, 1992

Date of receipt: November 24, 1992

Applicant: Merck Research Laboratories

Background: Merck has submitted draft labeling in response to our supplement request letter of April 15, 1992, that requested that they revise their labeling as follows:

1) PRECAUTIONS, Carcinogenicity, Mutagenicity, Impairment of Fertility: Please express each animal/human dose comparison in both mg/kg and ——— terms;

2) PRECAUTIONS, Nursing Mothers: Please update this subsection if possible to include available information ———

3) OVERDOSAGE: Please replace the sentence on ——— with wording similar to the following: Single oral doses of X mg/kg were associated with significant lethality in rats and mice.

Review: The submitted labeling has been revised under PRECAUTIONS, Carcinogenicity, Mutagenicity, Impairment of Fertility, under PRECAUTIONS, Nursing Mothers, and under OVERDOSAGE.

The Pharmacologist, Anthony Proakis, Ph.D., has reviewed the labeling changes (see reviews dated March 3, 1993) and recommended alternative wording to the PRECAUTIONS, Carcinogenicity, Mutagenicity, Impairment of Fertility subsection. He agrees with the other changes.

We approved similar wording in the Nursing Mothers subsection of the Zestril and Zestoretic labeling (supplements 19-777/S-019 and 19-888/S-014, approved 9-23-93).

Recommendation: I will prepare an approvable letter for these supplements, including a request for the wording as revised by Dr. Proakis. These supplements fall under 21 CFR 314.70 (3), Supplements for changes requiring FDA approval before the change is made.

Kathleen F. Bongiovanni 12-15-93

cc: 18-998/S-034
19-221/S-013
19-309/S-012
HFD-110 (all)
HFD-111/KBongiovanni
HFD-111/SBenton
kb/12/15/93.