CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-309/S-019

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 19-309/S-019

Trade Name: Vasotec I.V. Injection

Generic Name(s): (enalaprilat)

Sponsor: Merck & Co. Inc

Agent:

Approval Date: September 28, 1998

Indication: The treatment of hypertension when oral therapy is not practical.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-309/S-019

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 19 1995

NDA 18-998/S-046
19-221/S-021
19-309/S-019
19-558/S-031
19-778/S-025

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

Dear Dr. Bell:

Please refer to your May 10, 1995 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vasotec (enalapril) Tablets (NDA 18-998), Vaseretic (enalapril/hydrochlorothiazide) Tablets (NDA 19-221), Vasotec (enalaprilat) Intravenous (NDA 19-309), Prinivil (lisinopril) Tablets (NDA 19-558) and Prinzide (lisinopril/hydrochlorothiazide) Tablets (NDA 19-778).

The supplemental applications, submitted in response to our January 27, 1995 letter, provide for draft labeling revised by adding information stating that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks, and that they cause a higher rate of angioedema in black than in non-black patients.

We have completed the review of these supplemental applications as submitted with draft labeling and they are approvable. Before these supplements may be approved, however, it will be necessary for you to submit revised final printed labeling (FPL) as follows:

Our January 27, 1995 letter asked you to add the following statement at the end of the **INDICATIONS AND USAGE** section:

> In considering use of [Tradename], it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. _____

[redacted] deleted from the first sentence of the **ADVERSE REACTIONS, Angioedema** subsection for Vasotec [redacted] Vaseretic [redacted] and Prinivil [redacted] It was not included in the other applications.

It is not clear why the sentences "In addition, it should be noted that black patients receiving ACE inhibitor monotherapy have been reported to have a higher incidence of angioedema compared to non-blacks." and [redacted] under **INDICATIONS AND USAGE** specify ACE inhibitor monotherapy, since angioedema was seen in patients on ACE inhibitor/HCTZ combination products. Therefore, please delete the word "monotherapy" from these sentences at the time of your next printing and add an "s" to "ACE inhibitor;" the sentences would then 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." and [redacted]

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 August 24, 1995 submission. Accordingly, the supplemental application 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,

RJL 9/28/95

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 labeling)
HFD-80 (with labeling)
HFD-110
HFD-110/CSO
HFD-240 (with labeling)
HFD-613 (with labeling)
HFD-735/DBarash (with labeling)
HFD-110/KBongiovanni
sb/9/14/95;9/27/95
R/D: SChen/9/15/95
GBuehler for NMorgenstern/9/21/95

Approval Dates:
18-998 - 12/24/85
19-221 - 10/31/86
19-309 - 2/9/88
19-558 - 12/29/87
19-778 - 2/16/89

APPROVAL

KBongiovanni 9-27-95

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-309/S-019

Approvable Letter (s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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19-221/S-021
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The supplemental applications, submitted in response to our January 27, 1995 letter, provide for draft labeling revised by adding information stating that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks, and that they cause a higher rate of angioedema in black than in non-black patients.

We have completed the review of these supplemental applications as submitted with draft labeling and they are approvable. Before these supplements may be approved, however, it will be necessary for you to submit revised final printed labeling (FPL) as follows:

Our January 27, 1995 letter asked you to add the following statement at the end of the **INDICATIONS AND USAGE** section:

> In considering use of [Tradename], it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. _____
> _____
> _____
> _____
> _____

You have responded to our letter, however, by proposing that instead of revising the **INDICATIONS AND USAGE** section as requested, you would revise the labeling under **WARNINGS** and **ADVERSE REACTIONS** as follows:

Under the single entity products (Vasotec, Vasotec I.V. and Prinivil), addition of the following paragraph to the **WARNINGS** section:

[redacted]

Addition of a heading for the next paragraph, "Patients with a history of angioedema," addition of a dependent clause in the angioedema section of the **ADVERSE REACTIONS** section stating that angioedema has a higher incidence in black than in non-black patients, and addition of the word [redacted]

Under the combination products (Vaseretic and Prinzide), you proposed adding the following paragraph to the **WARNINGS** section:

[redacted]

The additional revisions proposed above were also proposed for the combination labeling.

We have reviewed your proposal, and have decided that to maintain consistency in class labeling, the revisions should be made as we have originally requested. We have no objection to your reversing the order of the sentences in the statement used for the single entity products. The statements that you proposed for addition to the **WARNINGS** section may be used; they must, however, be placed in the **INDICATIONS AND USAGE** section.

The addition of the heading, [redacted] is acceptable. The addition of the clause in the **ADVERSE REACTIONS** section stating that angioedema has a higher incidence in black than in non-black patients is also acceptable, but because this is a restatement of what will be stated under **INDICATIONS AND USAGE**, is not needed.

The addition of the word ——— to describe the incidence of angioedema, under **WARNINGS** and **ADVERSE REACTIONS** in the Vasotec, Vaseretic, Vasotec I.V. and Prinivil labeling, however, is **NOT** acceptable. Also, please remove the word ——— from these sections in the Prinzide labeling. This was apparently a carry over from the original approval of this application and there are no data to indicate that the incidence of angioedema is ——— for Prinzide than it is for any other ACE inhibitor.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the FPL may be required. Please submit fifteen copies of the printed labeling to each application 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 an amendment, 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.

These changes may not be implemented until you have been notified in writing that these supplemental applications are approved.

Should you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
Telephone: (301) 594-5300

Sincerely yours,

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
HFC-130/JAllen
HFD-80
HFD-110
HFD-110/CSO
HFD-110/GBuehler;6/5/95
sb/6/5/95;6/8/95;6/8/95
R/D: CGanley/6/5/95
SChen/6/5/95
JShort/6/5/95
SZimmerman/6/6/95
RWolters/6/7/95
CResnick/6/7/95
NMorgenstern/6/7/95;6/8/95

Approval Dates:

18-998	-	12/24/85
19-221	-	10/31/86
19-309	-	2/9/88
19-558	-	12/29/87
19-778	-	2/16/89

APPROVABLE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-998/S-046
19-221/S-021
19-309/S-019
~~19-558/S-031~~
19-778/S-025

SEP 28 1995

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

Dear Dr. Bell:

Please refer to your May 10, 1995 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vasotec (enalapril) Tablets (NDA 18-998), Vaseretic (enalapril/hydrochlorothiazide) Tablets (NDA 19-221), Vasotec (enalaprilat) Intravenous (NDA 19-309), Prinivil (lisinopril) Tablets (NDA 19-558) and Prinzide (lisinopril/hydrochlorothiazide) Tablets (NDA 19-778).

We acknowledge receipt of your amendment dated August 24, 1995.

The supplemental applications, submitted in response to our January 27, 1995 letter, provide for final printed labeling revised as follows:

INDICATIONS AND USAGE:

NDA 18-998, 19-309, 19-558
In considering use of Vasotec/Vasotec I.V./Prinivil, it should be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, it should be noted that black patients receiving ACE inhibitor monotherapy have been reported to have a higher incidence of angioedema compared to non-blacks. (See **WARNINGS, Angioedema.**)

NDA 19-221 and 19-778
In considering use of Vaseretic/Prinzide, [redacted] (See **WARNINGS, Angioedema.**)

WARNINGS, Anaphylactoid and Possibly Related Reactions, Angioedema: a reference to the [redacted] section has been added.

ADVERSE REACTIONS, Angioedema: The phrase "with an incidence higher in black than in non-black patients" has been added to the first sentence of this subsection. The word [redacted] was deleted from this sentence in the Prinzide labeling.

You have responded to our letter, however, by proposing that instead of revising the **INDICATIONS AND USAGE** section as requested, you would revise the labeling under **WARNINGS** and **ADVERSE REACTIONS** as follows:

Under the single entity products (Vasotec, Vasotec I.V. and Prinivil), addition of the following paragraph to the **WARNINGS** section:

[redacted]

Addition of a heading for the next paragraph, "Patients with a history of angioedema," addition of a dependent clause in the angioedema section of the **ADVERSE REACTIONS** section stating that angioedema has a higher incidence in black than in non-black patients, and addition of the word [redacted]

Under the combination products (Vaseretic and Prinzide), you proposed adding the following paragraph to the **WARNINGS** section:

[redacted]

The additional revisions proposed above were also proposed for the combination labeling.

We have reviewed your proposal, and have decided that to maintain consistency in class labeling, the revisions should be made as we have originally requested. We have no objection to your reversing the order of the sentences in the statement used for the single entity products. The statements that you proposed for addition to the **WARNINGS** section may be used; they must, however, be placed in the **INDICATIONS AND USAGE** section.

The addition of the heading, [redacted] is acceptable. The addition of the clause in the **ADVERSE REACTIONS** section stating that angioedema has a higher incidence in black than in non-black patients is also acceptable, but because this is a restatement of what will be stated under **INDICATIONS AND USAGE**, is not needed.

The addition of the word ——— to describe the incidence of angioedema, under **WARNINGS** and **ADVERSE REACTIONS** in the Vasotec, Vaseretic, Vasotec I.V. and Prinivil labeling, however, is **NOT** acceptable. Also, please remove the word ——— from these sections in the Prinzide labeling. This was apparently a carry over from the original approval of this application and there are no data to indicate that the incidence of angioedema is ——— for Prinzide than it is for any other ACE inhibitor.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the FPL may be required. Please submit fifteen copies of the printed labeling to each application 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 an amendment, 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.

These changes may not be implemented until you have been notified in writing that these supplemental applications are approved.

Should you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
Telephone: (301) 594-5300

Sincerely yours,

R J 6/19/95

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
HFC-130/JAllen
HFD-80
HFD-110
HFD-110/CSO
HFD-110/GBuehler;6/5/95
sb/6/5/95;6/8/95;6/8/95
R/D: CGanley/6/5/95
SChen/6/5/95
JShort/6/5/95
SZimmerman/6/6/95
RWolters/6/7/95
CResnick/6/7/95
NMorgenstern/6/7/95;6/8/95

Approval Dates:
18-998 - 12/24/85
19-221 - 10/31/86
19-309 - 2/9/88
19-558 - 12/29/87
19-778 - 2/16/89

APPROVABLE

6/9/95

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-309/S-019

Approved Labeling

MERCK & CO., INC.
West Point, PA 19486, USA

INJECTION

VASOTEC® I.V.

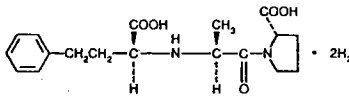
(ENALAPRILAT)

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASOTEC I.V. should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

DESCRIPTION

VASOTEC* I.V. (Enalaprilat) is a sterile aqueous solution for intravenous administration. Enalaprilat is an angiotensin converting enzyme inhibitor. It is chemically described as (*S*)-1-[*N*-(1-carboxy-3-phenylpropyl)-L-alanyl]-L-proline dihydrate. Its empirical formula is $C_{18}H_{24}N_2O_5 \cdot 2H_2O$ and its structural formula is:



Enalaprilat is a white to off-white, crystalline powder with a molecular weight of 384.43. It is sparingly soluble in methanol and slightly soluble in water.

Each milliliter of VASOTEC I.V. contains 1.25 mg enalaprilat (anhydrous equivalent); sodium chloride to adjust tonicity; sodium hydroxide to adjust pH; water for injection, q.s.; with benzyl alcohol, 9 mg, added as a preservative.

CLINICAL PHARMACOLOGY

Enalaprilat, an angiotensin-converting enzyme (ACE) inhibitor when administered intravenously, is the active metabolite of the orally administered pro-drug, enalapril maleate. Enalaprilat is poorly absorbed orally.

Mechanism of Action

Intravenous enalaprilat, or oral enalapril, after hydrolysis to enalaprilat, inhibits ACE in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. Although the latter decrease is small, it results in small increases of serum potassium. In hypertensive patients treated with enalapril alone for up to 48 weeks, mean increases in serum potassium of approximately 0.2 mEq/L were observed. In patients treated with enalapril plus a thiazide diuretic, there was essentially no change in serum potassium. (See PRECAUTIONS.) Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of enalaprilat remains to be elucidated.

While the mechanism through which enalaprilat lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, enalaprilat has antihypertensive activity even in patients with low-renin hypertension. In clinical studies, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to enalaprilat monotherapy than non-black patients.

Pharmacokinetics and Metabolism

Following intravenous administration of a single dose, the serum concentration profile of enalaprilat is polyexponential with a prolonged terminal phase, apparently representing a small fraction of the administered dose that has been bound to ACE. The amount bound does not increase with dose, indicating a saturable site of binding. The effective half-life for accumulation of enalaprilat, as determined from oral administration of multiple doses of enalapril maleate, is approximately 11 hours. Excretion of enalaprilat is primarily renal with more than 90 percent of an administered dose recovered in the urine as unchanged drug within 24 hours. Enalaprilat is poorly absorbed following oral administration.

The disposition of enalaprilat in patients with renal insufficiency is similar to that in patients with normal renal function until the glomerular filtration rate is 30 mL/min or less. With glomerular filtration rate ≤30 mL/min, peak and trough enalaprilat levels increase, time to peak concentration increases and time to steady state may be delayed. The effective half-life of enalaprilat is prolonged at this level of renal insufficiency. (See DOSAGE AND ADMINISTRATION.) Enalaprilat is dialyzable at the rate of 62 mL/min.

Studies in dogs indicate that enalaprilat does not enter the brain, and that enalapril crosses the blood-brain barrier poorly, if at all. Multiple doses of enalapril maleate in rats do not result in accumulation in any tissues. Milk in lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. Radioactivity was found to cross the placenta following administration of labeled drug to pregnant hamsters.

Pharmacodynamics

VASOTEC I.V. results in the reduction of both supine and standing systolic and diastolic blood pressure, usually with no orthostatic component. Symptomatic postural hypotension is therefore infrequent, although it might be anticipated in volume-depleted patients (see WARNINGS). The onset of action usually occurs within fifteen minutes of administration with the maximum effect occurring within one to four hours. The abrupt withdrawal of enalaprilat has not been associated with a rapid increase in blood pressure.

The duration of hemodynamic effects appears to be dose-related. However, for the recommended dose, the duration of action in most patients is approximately six hours.

Following administration of enalapril, there is an increase in renal blood flow; glomerular filtration rate is usually unchanged. The effects appear to be similar in patients with renovascular hypertension.

INDICATIONS AND USAGE

VASOTEC I.V. is indicated for the treatment of hypertension when oral therapy is not practical.

VASOTEC I.V. has been studied with only one other antihypertensive agent, furosemide, which showed approximately additive effects on blood pressure. Enalapril, the pro-drug of enalaprilat, has been used extensively with a variety of other antihypertensive agents, without apparent difficulty except for occasional hypotension.

In using VASOTEC I.V., consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that VASOTEC I.V. does not have a similar risk. (See WARNINGS.)

In considering use of VASOTEC I.V., it should be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, it should be noted that black patients receiving ACE inhibitor monotherapy have been reported to have a higher incidence of angioedema compared to non-blacks. (See WARNINGS, *Angioedema.*)

CONTRAINDICATIONS

VASOTEC I.V. is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor.

WARNINGS

Hypotension

Excessive hypotension is rare in uncomplicated hypertensive patients but is a possible consequence of the use of enalaprilat especially in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis. Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic, reduce the diuretic dose or increase salt intake cautiously before initiating therapy with VASOTEC I.V. in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, *Drug Interactions,* ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.) In patients with heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential for an excessive fall in blood pressure especially in these patients, therapy should be followed closely whenever the dose of enalaprilat is adjusted and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including VASOTEC I.V.) may be subject to a variety of adverse reactions, some of them serious.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalaprilat. This may occur at any time during treatment. In such cases VASOTEC I.V. should be promptly discon-

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tinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also INDICATIONS AND USAGE and CONTRAINDICATIONS).

Anaphylactoid reactions during desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid reactions during membrane exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption (a procedure dependent upon devices not approved in the United States).

Neutropenia/Agranulocytosis

Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis in similar rates. Marketing experience has revealed several cases of neutropenia, or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis, and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASOTEC I.V. as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, VASOTEC I.V. should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of oral enalapril were seen in studies of pregnant rats, and rabbits. On a mg/kg basis, the doses used

INJECTION
VASOTEC® I.V.
(ENALAPRILAT)

Circular Number 7875725

INJECTION
VASOTEC® I.V.
(ENALAPRILAT)

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VASOTEC® I.V.
(ENALAPRILAT)

VASOTEC® I.V. (Enalaprilat)

were up to 333 times (in rats), and 50 times (in rabbits) the maximum recommended human dose.

PRECAUTIONS

General

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril or enalaprilat, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients receiving enalapril. These increases were almost always reversible upon discontinuation of enalapril or enalaprilat and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalaprilat has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalaprilat and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials receiving enalapril. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing agents or potassium supplements, which should be used cautiously, if at all, with VASOTEC I.V. (See *Drug Interactions.*)

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Drug Interactions

Hypotension – Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalaprilat. The possibility of hypotensive effects with enalaprilat can be minimized by administration of an intravenous infusion of normal saline, discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalaprilat. If it is necessary to continue the diuretic, provide close medical supervision for at least one hour after the initial dose of enalaprilat. (See WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC I.V. appears to be augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC I.V. has been used concomitantly with digitalis, beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC I.V. attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been done with VASOTEC I.V.

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 orally for 106 weeks to rats at doses up to 90 mg/kg/day (150 times** the maximum daily human oral dose). Enalapril has also been administered for 94 weeks to male and female mice at oral doses up to 90 and 180 mg/kg/day, respectively (150 and 300 times** the maximum oral daily dose for humans), and showed no evidence of carcinogenicity.

VASOTEC I.V. was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril showed no drug-related changes in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, the micronucleus test with mice, and in an *in vivo* cytogenic study using mouse bone marrow. There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg enalapril/kg/day.

Pregnancy

Pregnancy Categories C (first trimester) *and D* (second and third trimesters). See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

Nursing Mothers

Enalapril and enalaprilat are detected in human milk in trace amounts. Caution should be exercised when VASOTEC I.V. is given to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

VASOTEC I.V. has been found to be generally well tolerated in controlled clinical trials involving 349 patients (168 with hypertension, 153 with congestive heart failure and 28 with coronary artery disease). The most frequent clinically significant adverse experience was hypotension (3.4 percent), occurring in eight patients (5.2 percent) with congestive heart failure, three (1.8 percent) with hypertension and one with coronary artery disease. Other adverse experiences occurring in greater than one percent of patients were: headache (2.9 percent) and nausea (1.1 percent).

Adverse experiences occurring in 0.5 to 1.0 percent of patients in controlled clinical trials included: myocardial infarction, fatigue, dizziness, fever, rash and constipation.

Angioedema: Angioedema has been reported in patients receiving enalaprilat, with an incidence higher in black than in non-black patients. Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with enalaprilat should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Cough: See PRECAUTIONS, *Cough.*

Enalapril Maleate

Since enalapril is converted to enalaprilat, those adverse experiences associated with enalapril might also be expected to occur with VASOTEC I.V.

The following adverse experiences have been reported with enalapril and, within each category, are listed in order of decreasing severity.

Body As A Whole: Syncope, orthostatic effects, anaphylactoid reactions (see WARNINGS, *Anaphylactoid reactions during membrane exposure*), chest pain, abdominal pain, asthenia.

Cardiovascular: Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; orthostatic hypotension; angina pectoris; palpitation.

Digestive: Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice) (see WARNINGS, *Hepatic Failure*), melena, diarrhea, vomiting, dyspepsia, anorexia, glossitis, stomatitis, dry mouth.

Hematologic: Rare cases of neutropenia, thrombocytopenia and bone marrow depression.

Musculoskeletal: Muscle cramps.

Nervous/Psychiatric: Depression, vertigo; confusion, ataxia, somnolence, insomnia, nervousness, peripheral neuropathy (e.g., paresthesia, dysesthesia).

Respiratory: Bronchospasm, dyspnea, pneumonia, bronchitis, cough, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection, pulmonary infiltrates.

Skin: Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, pemphigus, herpes zoster, erythema multiforme, urticaria, pruritus, alopecia, flushing, diaphoresis, photosensitivity.

Special Senses: Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), urinary tract infection, flank pain, gynecomastia, impotence.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Hypotension: Combining the results of clinical trials in patients with hypertension or congestive heart failure, hypotension (including postural hypotension, and other orthostatic effects) was reported in 2.3 percent of patients following the initial dose of enalapril or during extended therapy. In the hypertensive patients, hypotension occurred in 0.9 percent and syncope occurred in 0.5 percent of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.1 percent of hypertensive patients. (See WARNINGS.)

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

**Based on patient weight of 50 kg

Clinical Laboratory Test Findings

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2 percent of patients with essential hypertension treated with enalapril alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.)

Hematology: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with enalapril but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril cannot be excluded.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred (see WARNINGS, *Hepatic Failure*).

OVERDOSAGE

In clinical studies, some hypertensive patients received a maximum dose of 80 mg of enalaprilat intravenously over a fifteen minute period. At this high dose, no adverse effects beyond those as associated with the recommended dosages were observed.

The intravenous LD_{50} of enalaprilat is 3740-5890 mg/kg in female mice.

The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution.

Enalaprilat may be removed from general circulation by hemodialysis and has been removed from neonatal circulation by peritoneal dialysis.

DOSAGE AND ADMINISTRATION

FOR INTRAVENOUS ADMINISTRATION ONLY

The dose in hypertension is 1.25 mg every six hours administered intravenously over a five minute period. A clinical response is usually seen within 15 minutes. Peak effects after the first dose may not occur for up to four hours after dosing. The peak effects of the second and subsequent doses may exceed those of the first.

No dosage regimen for VASOTEC I.V. has been clearly demonstrated to be more effective in treating hypertension than 1.25 mg every six hours. However, in controlled clinical studies in hypertension, doses as high as 5 mg every six hours were well tolerated for up to 36 hours. There has been inadequate experience with doses greater than 20 mg per day.

In studies of patients with hypertension, VASOTEC I.V. has not been administered for periods longer than 48 hours. In other studies, patients have received VASOTEC I.V. for as long as seven days.

The dose for patients being converted to VASOTEC I.V. from oral therapy for hypertension with enalapril maleate is 1.25 mg every six hours. For conversion from intravenous to oral therapy, the recommended initial dose of Tablets VASOTEC (Enalapril Maleate) is 5 mg once a day with subsequent dosage adjustments as necessary.

Patients on Diuretic Therapy

For patients on diuretic therapy the recommended starting dose for hypertension is 0.625 mg administered intravenously over a five minute period; also see below, *Patients at Risk of Excessive Hypotension.* A clinical response is usually seen within 15 minutes. Peak effects after the first dose may not occur for up to four hours after dosing, although most of the effect is usually apparent within the first hour. If after one hour there is an inadequate clinical response, the 0.625 mg dose may be repeated. Additional doses of 1.25 mg may be administered at six hour intervals.

For conversion from intravenous to oral therapy, the recommended initial dose of Tablets VASOTEC (Enalapril Maleate) for patients who have responded to 0.625 mg of enalaprilat every six hours is 2.5 mg once a day with subsequent dosage adjustment as necessary.

Dosage Adjustment in Renal Impairment

The usual dose of 1.25 mg of enalaprilat every six hours is recommended for patients with a creatinine clearance >30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤30 mL/min (serum creatinine ≥3 mg/dL), the initial dose is 0.625 mg. (See WARNINGS.)

If after one hour there is an inadequate clinical response, the 0.625 mg dose may be repeated. Additional doses of 1.25 mg may be administered at six hour intervals.

For dialysis patients, see below, *Patients at Risk of Excessive Hypotension.*

For conversion from intravenous to oral therapy, the recommended initial dose of Tablets VASOTEC (Enalapril Maleate) is 5 mg once a day for patients with creatinine clearance >30 mL/min and 2.5 mg once daily for patients with creatinine clearance ≤30 mL/min. Dosage should then be adjusted according to blood pressure response.

Patients at Risk of Excessive Hypotension

Hypertensive patients at risk of excessive hypotension include those with the following concurrent conditions or characteristics: heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology (see WARNINGS). Single doses of enalaprilat as low as 0.2 mg have produced excessive hypotension in normotensive patients with these diagnoses. Because of the potential for an extreme hypotensive response in these patients, therapy should be started under very close medical supervision. The starting dose should be no greater than 0.625 mg administered intravenously over a period of no less than five minutes and preferably longer (up to one hour).

Patients should be followed closely whenever the dose of enalaprilat is adjusted and/or diuretic is increased.

Administration

VASOTEC I.V. should be administered as a slow intravenous infusion, as indicated above. It may be administered as provided or diluted with up to 50 mL of a compatible diluent.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use whenever solution and container permit.

Compatibility and Stability

VASOTEC I.V. as supplied and mixed with the following intravenous diluents has been found to maintain full activity for 24 hours at room temperature:

5 percent Dextrose Injection
0.9 percent Sodium Chloride Injection
0.9 percent Sodium Chloride Injection in 5 percent Dextrose
5 percent Dextrose in Lactated Ringer's Injection
McGaw ISOLYTE*** E.

HOW SUPPLIED

No. 3508 — VASOTEC I.V., 1.25 mg per mL, is a clear, colorless solution and is supplied in vials containing 1 mL and 2 mL.

NDC 0006-3508-01, 1 mL vials
(6505-01-356-8505, 1 mL vial)
NDC 0006-3508-04, 2 mL vials
(6505-01-305-6988, 2 mL vial).

Storage

Store below 30°C (86°F).

Dist. by:
MERCK & CO., INC., West Point, PA 19486, USA

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-309/S-019

Administrative/Correspondence

CSO Review of Labeling

SEP 28 1995

NDA: 18-998/S-046 Vasotec (enalapril maleate) Tablets
19-221/S-021 Vaseretic (enalapril maleate/HCTZ) Tablets
19-309/S-019 Vasotec (enalaprilat) I.V.
19-558/S-031 Prinivil (lisinopril) Tablets
19-778/S-025 Prinzide (lisinopril/HCTZ) Tablets

Date of submissions: August 24, 1995

Date of receipt: August 25, 1995

Applicant: Merck Research Laboratories

Background: On January 27, 1995, we issued a Supplement Request Letter to all approved ACE inhibitors, asking that the package inserts be changed to add language to the INDICATIONS AND USAGE section similar to the following:

> In considering use of Tradename, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. [redacted]

Merck responded with supplements dated May 10, 1995, that proposed making revisions to the WARNINGS and ADVERSE REACTIONS sections of the labeling. We issued an approvable letter dated June 19, 1995, that stated that Merck should make the change in the INDICATIONS AND USAGE section as originally requested; however, they could use the revised wording that they had proposed. We also allowed the use of a new subheading [redacted] for the ADVERSE REACTIONS section. We also asked the firm to remove the word [redacted] from the WARNINGS and ADVERSE REACTIONS sections of the labeling.

Review: These supplements provide for final printed labeling revised as follows:

INDICATIONS AND USAGE:

NDA 18-998, 19-309, 19-558

In considering use of Vasotec/Vasotec I.V./Prinivil, it should be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, it should be noted that black patients receiving ACE inhibitor monotherapy have been reported to have a higher incidence of angioedema compared to non-blacks. (See WARNINGS, Angioedema.)

NDA 19-221 and 19-778

In considering use of Vaseretic/Prinzide, [redacted] (See WARNINGS, Angioedema.)

WARNINGS, Anaphylactoid and Possibly Related Reactions, Angioedema: a reference to the [redacted] section has been added.

ADVERSE REACTIONS, Angioedema: The phrase "with an incidence higher in black than in non-black patients" has been added to the first sentence of this subsection. The word ____ was deleted from this sentence in the Prinzide labeling.

[redacted]

It is not clear why the sentences [redacted] and [redacted] under INDICATIONS AND USAGE specify ACE inhibitor monotherapy, since angioedema was seen in patients on ACE inhibitor/HCTZ combination products. In his memo dated December 9, 1994, Dr. Norman Stockbridge notes that for benazepril, 7 subjects (4 caucasian, 2 black, 1 other) developed angioedema on benazepril/HCTZ, and in this database black patients comprised 15% of the subjects. There is no mention of the rates of angioedema seen with other combination products.

I suggest that we ask the firm to delete the word "monotherapy" from these sentences at the time of the next printing and add an "s" to "ACE inhibitor;" [redacted] and "In considering use of Vaseretic/Prinzide, it should be noted that black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks."

Recommendation: I will prepare an approval letter for these supplements.

Kathleen F. Bongiovanni 9-11-95

Kathleen F. Bongiovanni

cc: 18-998/S-046
19-221/S-021
19-309/S-019
19-558/S-031
19-778/S-025
HFD-110 (all)
HFD-111/KBongiovanni
HFD-111/SBenton
kb/9/8/95.