CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-998/S040

Trade Name: Vasotec

Generic Name: Enalpril Maleate

Sponsor: Merck Research Laboratories

Approval Date: October 21, 1993

Indications: The treatment of hypertension.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S040

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S040

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-998/S-040
19-221/S-018
19-309/S-016

OCT 21 1993

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

Dear Dr. Kraft:

We acknowledge the receipt on August 16, 1993 of your August 13, 1993 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), Vaseretic (enalapril maleate/ hydrochlorothiazide) Tablets (NDA 19-221), and Vasotec I.V. (enalaprilat) Injection (NDA 19-309).

The supplemental applications provide for draft labeling revised as follows:

NDA 18-998, 19-221, and 19-309
ADVERSE REACTIONS [Enalapril maleate]:
Skin: "pemphigus" has been added;
Miscellaneous: "myositis" has been added;
Clinical Laboratory Test Findings, Hematology: the wording in the last sentence of this subsection has been revised from "A few cases of hemolysis have been reported in patients with G-6-PD deficiency in which a causal relationship cannot be excluded" to "Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril has not been established."

NDA 19-221
PRECAUTIONS, Drug Interactions, Cholestyramine and colestipol resins: The wording of this subsection has been changed to "Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively."

We have completed the review of these supplemental applications including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted draft labeling. Accordingly, the supplemental applications are approved effective on the date of this letter. The labeling, however, must be revised as follows:

1. **ADVERSE REACTIONS, Clinical Laboratory Test Findings, Hematology:** Please revise the wording in the final clause of the last sentence of this subsection to read "a causal relationship to enalapril cannot be excluded."

These revisions are terms of the supplemental NDA approval. Marketing the products before making the revisions, exactly as requested, in the products' final printed labeling (FPL) may render the products misbranded and unapproved new drugs.

When available, please submit twelve copies of the FPL to each NDA, seven of which are mounted on heavy weight paper or similar material. For administrative purposes, the submissions of FPL should be designated an "FPL Supplement" to the approved supplemental NDAs. Approval of the supplement by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drugs become available, further revision of that labeling may be required.

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
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

RJL 10/21/93

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-110
HFD-110/CSO
HFD-80
HFD-232 (with labeling)
HFD-110/KBongiovanni;9/23/93
sb/9/15/93;9/22/93;9/27/93
R/D: CGanley/9/15/93;10/13/93
SChen/9/20/93;10/13/93
NMorgenstern/9/20/93;10/13/93

Approval Date: 18-998 - December 24, 1985
19-221 - October 31, 1986
19-309 - February 9, 1988

APPROVAL K Bongiovanni 10-18-93

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S040

LABELING

7576641

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

TABLETS

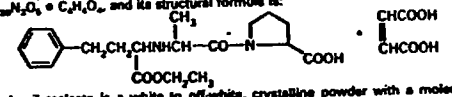
VASOTEC®

(ENALAPRIL MALEATE)

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 should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality*.

DESCRIPTION

VASOTEC* (Enalapril Maleate) is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat. Enalapril maleate is chemically described as (*S*)-1-[*N*-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (*Z*)-2-butenedioate salt (1:1). Its empirical formula is $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$, and its structural formula is:



Enalapril maleate is a white to off-white, crystalline powder with a molecular weight of 492.53. It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol.

Enalapril is a pro-drug; following oral administration, it is bioactivated by hydrolysis of the ethyl ester to enalaprilat, which is the active angiotensin converting enzyme inhibitor.

Enalapril maleate is supplied as 2.5 mg, 5 mg, 10 mg, and 20 mg tablets for oral administration. In addition to the active ingredient enalapril maleate, each tablet contains the following inactive ingredients: lactose, magnesium stearate, starch, and other ingredients. The 2.5 mg, 10 mg and 20 mg tablets also contain iron oxides.

CLINICAL PHARMACOLOGY

Mechanism of Action

Enalapril, after hydrolysis to enalaprilat, inhibits angiotensin-converting enzyme (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. The beneficial effects of enalapril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. 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 VASOTEC alone for up to 48 weeks, mean increases in serum potassium of approximately 0.2 mEq/L were observed. In patients treated with VASOTEC 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 VASOTEC remains to be elucidated.

While the mechanism through which VASOTEC lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, VASOTEC is antihypertensive even in patients with low-renin hypertension. Although VASOTEC was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to enalapril monotherapy than non-black patients.

Pharmacokinetics and Metabolism

Following oral administration of VASOTEC, peak serum concentrations of enalapril occur within about one hour. Based on urinary recovery, the extent of absorption of enalapril is approximately 60 percent. Enalapril absorption is not influenced by the presence of food in the gastrointestinal tract. Following absorption, enalapril is hydrolyzed to enalaprilat, which is a more potent angiotensin converting enzyme inhibitor than enalapril; enalaprilat is poorly absorbed when administered orally. Peak serum concentrations of enalaprilat occur three to four hours after an oral dose of enalapril maleate. Excretion of VASOTEC is primarily renal. Approximately 94 percent of the dose is recovered in the urine and feces as enalaprilat or enalapril. The principal components in urine are enalaprilat, accounting for about 40 percent of the dose, and intact enalapril. There is no evidence of metabolites of enalapril, other than enalaprilat.

The serum concentration profile of enalaprilat exhibits 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 following multiple doses of enalapril maleate is 11 hours.

The disposition of enalapril and 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 following multiple

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doses of enalapril maleate 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 enalapril crosses the blood-brain barrier poorly, if at all; enalaprilat does not enter the brain. Multiple doses of enalapril maleate in rats do not result in accumulation in any tissues. Milk of 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 and Clinical Effects

Hypertension: Administration of VASOTEC to patients with hypertension of severity ranging from mild to severe results in a reduction of both supine and standing blood pressure usually with no orthostatic component. Symptomatic postural hypotension is therefore infrequent, although it might be anticipated in volume-depleted patients. (See WARNINGS.)

In most patients studied, after oral administration of a single dose of enalapril, onset of antihypertensive activity was seen at one hour with peak reduction of blood pressure achieved by four to six hours.

At recommended doses, antihypertensive effects have been maintained for at least 24 hours. In some patients the effects may diminish toward the end of the dosing interval (see DOSAGE AND ADMINISTRATION).

In some patients achievement of optimal blood pressure reduction may require several weeks of therapy.

The antihypertensive effects of VASOTEC have continued during long term therapy. Abrupt withdrawal of VASOTEC has not been associated with a rapid increase in blood pressure.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. Following administration of VASOTEC, 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.

When given together with thiazide-type diuretics, the blood pressure lowering effects of VASOTEC are approximately additive.

In a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving VASOTEC. In this study there was no evidence of a blunting of the antihypertensive action of VASOTEC.

Heart Failure: In trials in patients treated with digitalis and diuretics, treatment with enalapril resulted in decreased systemic vascular resistance, blood pressure, pulmonary capillary wedge pressure and heart size, and increased cardiac output and exercise tolerance. Heart rate was unchanged or slightly reduced, and mean ejection fraction was unchanged or increased. There was a beneficial effect on severity of heart failure as measured by the New York Heart Association (NYHA) classification and on symptoms of dyspnea and fatigue. Hemodynamic effects were observed after the first dose, and appeared to be maintained in uncontrolled studies lasting as long as four months. Effects on exercise tolerance, heart size, and severity and symptoms of heart failure were observed in placebo-controlled studies lasting from eight weeks to over one year.

Heart Failure, Mortality Trials: In a multicenter, placebo-controlled clinical trial (SOLVD), from more than 39,000 patients screened, 2569 patients with all degrees of symptomatic heart failure and ejection fraction ≤35 percent were randomized to placebo or enalapril and followed for up to 55 months. Use of enalapril was associated with an 11 percent reduction in all-cause mortality and a 30 percent reduction in hospitalization for heart failure. Diseases that excluded patients from enrollment in the study included severe stable angina (>2 attacks/day), hemodynamically significant valvular or outflow tract obstruction, renal failure (creatinine >2.5 mg/dL), cerebral vascular disease (e.g., significant carotid artery disease), advanced pulmonary disease, malignancies, active myocarditis and constrictive pericarditis. The mortality benefit associated with enalapril does not appear to depend upon digitalis being present.

In another multicenter, placebo-controlled trial (CONSENSUS) limited to patients with NYHA Class IV congestive heart failure and radiographic evidence of cardiomegaly, use of enalapril was associated with improved survival. The results are shown in the following table.

	SURVIVAL (%)	
	Six Months	One Year
VASOTEC (n = 127)	74	64
Placebo (n = 126)	56	48

In both trials, patients were also usually receiving digitalis, diuretics or both.

INDICATIONS AND USAGE

Hypertension

VASOTEC is indicated for the treatment of hypertension.

VASOTEC is effective alone or in combination with other antihypertensive agents, especially thiazide-type diuretics. The blood pressure lowering effects of VASOTEC and thiazides are approximately additive.

Heart Failure

VASOTEC is indicated for the treatment of symptomatic congestive heart failure, usually in combination with diuretics and digitalis. In these patients VASOTEC improves symptoms, increases survival, and decreases the frequency of hospitalization (see CLINICAL PHARMACOLOGY, *Heart Failure, Mortality Trials* for details and limitations of survival trials).

In using VASOTEC 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 does not have a similar risk. (See WARNINGS.)

CONTRAINDICATIONS

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

WARNINGS

Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including VASOTEC. In such cases VASOTEC should be promptly discontinued 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 CONTRAINDICATIONS).

Hypotension

Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Patients with heart failure given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.) 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 (except in patients with heart failure), reduce the diuretic dose or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril 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 excessive 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 of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

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 at 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.

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 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 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 enalapril were seen in studies of pregnant rats, and rabbits. On a mg/kg basis, the doses used 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 VASOTEC, 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. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

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

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69®) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials. 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. In clinical trials in heart failure, hyperkalemia was observed in 3.8 percent of patients but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See *Drug Interactions.*)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of 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.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

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 enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

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

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

Agents Increasing Serum Potassium: VASOTEC 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. Potassium sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

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 VASOTEC 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

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

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as 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/kg/day of enalapril.

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 is given to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

For the most part, adverse experiences were mild and transient in nature. In clinical trials, discontinuation of therapy due to clinical adverse experiences was required in 3.3 percent of patients with hypertension and in 5.7 percent of patients with heart failure. The frequency of adverse experiences was not related to total daily dosage within the usual dosage ranges. In patients with hypertension the overall percentage of patients treated with VASOTEC reporting adverse experiences was comparable to placebo.

HYPERTENSION

Adverse experiences occurring in greater than one percent of patients with hypertension treated with VASOTEC in controlled clinical trials are shown below. In patients treated with VASOTEC, the maximum duration of therapy was three years; in placebo treated patients the maximum duration of therapy was 12 weeks.

	VASOTEC (n = 2314) Incidence (discontinuation)	Placebo (n = 230) Incidence
Body As A Whole		
Fatigue	3.0 (<0.1)	2.6
Orthostatic Effects	1.2 (<0.1)	0.0
Asthenia	1.1 (0.1)	0.9
Digestive		
Diarrhea	1.4 (<0.1)	1.7
Nausea	1.4 (0.2)	1.7
Nervous/Psychiatric		
Headache	6.2 (0.3)	9.1
Dizziness	4.3 (0.4)	4.3
Respiratory		
Cough	1.3 (0.1)	0.9
Skin		
Rash	1.4 (0.4)	0.4

HEART FAILURE

Adverse experiences occurring in greater than one percent of patients with heart failure treated with VASOTEC are shown below. The incidences represent the experiences from both controlled and uncontrolled clinical trials (maximum duration of therapy was approximately one year). In the placebo treated patients, the incidences reported are from the controlled trials (maximum duration of therapy is 12 weeks). The percentage of patients with severe heart failure (NYHA Class IV) was 29 percent and 43 percent for patients treated with VASOTEC and placebo, respectively.

*Based on patient weight of 50 kg

	VASOTEC (n = 673) Incidence (discontinuation)	Placebo (n = 339) Incidence
Body As A Whole		
Orthostatic Effects	2.2 (0.1)	0.3
Syncope	2.2 (0.1)	0.9
Chest Pain	2.1 (0.0)	2.1
Fatigue	1.8 (0.0)	1.8
Abdominal Pain	1.6 (0.4)	2.1
Asthenia	1.6 (0.1)	0.3
Cardiovascular		
Hypotension	6.7 (1.9)	0.6
Orthostatic Hypotension	1.6 (0.1)	0.3
Angina Pectoris	1.5 (0.1)	1.8
Myocardial Infarction	1.2 (0.3)	1.8
Digestive		
Diarrhea	2.1 (0.1)	1.2
Nausea	1.3 (0.1)	0.6
Vomiting	1.3 (0.0)	0.9
Nervous/Psychiatric		
Dizziness	7.9 (0.6)	0.6
Headache	1.8 (0.1)	0.9
Vertigo	1.6 (0.1)	1.2
Respiratory		
Cough	2.2 (0.0)	0.6
Bronchitis	1.3 (0.0)	0.9
Dyspnea	1.3 (0.1)	0.4
Pneumonia	1.0 (0.0)	2.4
Skin		
Rash	1.3 (0.0)	2.4
Urogenital		
Urinary Tract Infection	1.3 (0.0)	2.4

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.6 to 1.0 percent of patients with hypertension or heart failure in clinical trials are listed below and, within each category, are in order of decreasing severity.

Body As A Whole: Anaphylactoid reactions (see PRECAUTIONS, *Hemodialysis Patients*).

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; palpitation.

Digestive: Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular (proven on rechallenge) or cholestatic (jaundice)), melena, anorexia, dyspepsia, constipation, glossitis, stomatitis, dry mouth.

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

Musculoskeletal: Muscle cramps.

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

Respiratory: Bronchospasm, 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), 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.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9 percent and syncope occurred in 0.5 percent of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1 percent of hypertensive patients. In heart failure patients, hypotension occurred in 6.7 percent and syncope occurred in 2.2 percent of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9 percent of patients with heart failure. (See WARNINGS.)

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

Cough: See PRECAUTIONS, *Cough.*

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 VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were

observed in about 11 percent of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2 percent of patients.

Hematology: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in either hypertension or congestive heart failure patients treated with VASOTEC 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 has not been established.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

OVERDOSAGE

Limited data are available in regard to overdosage in humans.

The oral LD_{50} of enalapril is 2000 mg/kg in mice and rats.

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

Hypertension

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment

The usual dose of enalapril 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 first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Renal Status	Creatinine-Clearance mL/min	Initial Dose mg/day
Normal Renal Function	>80 mL/min	5 mg
Mild Impairment	≤80 >30 mL/min	5 mg
Moderate to Severe Impairment	≤30 mL/min	2.5 mg
Dialysis Patients*	—	2.5 mg on dialysis days**

*See PRECAUTIONS, *Hemodialysis Patients*

**Dosage on nondialysis days should be adjusted depending on the blood pressure response.

VASOTEC® (Enalapril Maleate)

Heart Failure

VASOTEC is indicated for the treatment of symptomatic congestive heart failure, usually in combination with diuretics and digitalis.

The recommended starting dose is 2.5 mg administered once or twice daily. The usual therapeutic dosing range is 5 to 20 mg daily, given as a single dose or two divided doses; the majority of patient experience in clinical studies has been with twice daily dosing. Dosage may be adjusted depending upon clinical response (see WARNINGS). In the placebo-controlled studies which demonstrated improved survival, the dose of VASOTEC was titrated upward as tolerated by the patient. The maximum daily dose administered in clinical trials was 40 mg.

After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*) If possible, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatremia

In patients with heart failure who have hyponatremia (serum sodium less than 130 mEq/L) or with serum creatinine greater than 1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, *Heart Failure,* WARNINGS and PRECAUTIONS, *Drug Interactions.*) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

HOW SUPPLIED

No. 3411 — Tablets VASOTEC, 2.5 mg, are yellow, biconvex barrel shaped, scored, compressed tablets with code MSD 14 on one side and VASOTEC on the other. They are supplied as follows:

NDC 0006-0014-94 unit of use bottles of 90 (with desiccant)
NDC 0006-0014-68 bottles of 100 (with desiccant)
NDC 0006-0014-28 unit dose packages of 100
NDC 0006-0014-96 unit of use bottles of 180 (with desiccant)
NDC 0006-0014-87 bottles of 10,000 (with desiccant).

No. 3412 — Tablets VASOTEC, 5 mg, are white, barrel shaped, scored, compressed tablets, with code MSD 712 on one side and VASOTEC on the other. They are supplied as follows:

NDC 0006-0712-94 unit of use bottles of 90 (with desiccant)
NDC 0006-0712-68 bottles of 100 (with desiccant)
(6505-01-236-8880, 5 mg 100's)
NDC 0006-0712-28 unit dose packages of 100
NDC 0006-0712-96 unit of use bottles of 180 (with desiccant)
NDC 0006-0712-87 bottles of 10,000 (with desiccant).

No. 3413 — Tablets VASOTEC, 10 mg, are salmon, barrel shaped, compressed tablets, with code MSD 713 on one side and VASOTEC on the other. They are supplied as follows:

NDC 0006-0713-94 unit of use bottles of 90 (with desiccant)
NDC 0006-0713-68 bottles of 100 (with desiccant)
(6505-01-236-8881, 10 mg 100's)
NDC 0006-0713-28 unit dose packages of 100
NDC 0006-0713-96 unit of use bottles of 180 (with desiccant)
NDC 0006-0713-87 bottles of 10,000 (with desiccant).

No. 3414 — Tablets VASOTEC, 20 mg, are peach, barrel shaped, compressed tablets, with code MSD 714 on one side and VASOTEC on the other. They are supplied as follows:

NDC 0006-0714-94 unit of use bottles of 90 (with desiccant)
NDC 0006-0714-68 bottles of 100 (with desiccant)
(6505-01-227-0545, 20 mg 100's)
NDC 0006-0714-28 unit dose packages of 100
NDC 0006-0714-87 bottles of 10,000 (with desiccant).

Storage

Store below 30°C (86°F) and avoid transient temperatures above 50°C (122°F). Keep container tightly closed. Protect from moisture.

Dispense in a tight container, if product package is subdivided.

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

Issued July 1993

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S040

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CSO Review of Labeling

NDA: 18-998/S-040 Vasotec (enalapril maleate) Tablets
19-221/S-018 Vaseretic (enalapril maleate/HCTZ) Tablets
19-309/S-016 Vasotec (enalaprilat) I.V.

Date of submissions: August 13, 1993

OCT 21 1993

Date of receipt: August 16, 1993

Applicant: Merck Research Laboratories

Background: Merck has submitted final printed labeling for Special Supplements - Changes Being Effected. to update the PRECAUTIONS and/or ADVERSE REACTIONS sections. In the cover letters for the supplements, Merck states that the changes will become effective on or about October 1, 1993.

Review:

NDA 18-998, 19-221, and 19-309

ADVERSE REACTIONS [Enalapril maleate]:
Skin: "pemphigus" has been added;
Miscellaneous: "myositis" has been added;
Clinical Laboratory Test Findings, Hematology: the wording in the last sentence of this subsection has been revised from "A few cases of hemolysis have been reported in patients with G-6-PD deficiency in which a causal relationship cannot be excluded." to "Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril has not been established."

The revision in the wording of the last sentence of the Clinical Laboratory Test Findings, Hematology subsections includes changes other than those described in the "Summary of Revisions" submitted with these supplements, which lists the change as " revision of wording to include 'hemolytic anemia.'" The change to the last phrase, from " a causal relationship cannot be excluded" to " a causal relationship to enalapril has not been established" was neither mentioned in the text nor supported. In a discussion with Dr. Lipicky on September 23, 1993, he said that we should approve the supplements on draft, asking them to change the phrase back in their final printed labeling.

NDA 19-221

PRECAUTIONS, Drug Interactions, Cholestyramine and colestipol resins: For consistency with the FDA letter to NDA 11-835 dated September 17, 1993, the wording of this subsection has been changed to "Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively."

Recommendation: I will prepare an acknowledge and approval-on-draft letter for these supplements, asking them to change the last phrase in the last sentence in ADVERSE REACTIONS, Clinical Laboratory Test Findings, Hematology subsection to "a causal relationship to enalapril cannot be excluded."

Kathleen F. Bongiovanni 9-23-93