

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**18-998/S025**

***Trade Name:*** Vasotec Tablets

***Generic Name:*** Enalapril Maleate

***Sponsor:*** Merck Sharp and Dohme Research Laboratories

***Approval Date:*** February 6, 1991

***Indications:*** The treatment for hypertension.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**18-998/S025**

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**18-998/S025**

**APPROVAL LETTER**

FEB - 6 1991

NDA 18-998/S-025  
19-221/S-007  
19-309/S-008  
19-558/S-010  
19-778/S-004

Merck Sharp and Dohme Research Laboratories  
Attention: Elliott T. Berger, Ph.D.  
Sunneytown Pike  
West Point, PA 19486

Dear Dr. Berger:

We acknowledge the receipt on December 11, 1990 of your December 7, 1990 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), Vasotec (enalapril maleate/HCTZ) Tablets (NDA 19-221), Vasotec (enalaprilat) IV (NDA 19-309), Prinivil (lisinopril) Tablets (NDA 19-558), and Prinivil (lisinopril/HCTZ) Tablets (NDA 19-778).

We also acknowledge receipt of your amendments to all of the above supplemental new drug applications, dated January 18, 1991.

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

NDA 18-998, 19-221, 19-309, 19-558, 19-778:

**WARNINGS, Angioedema:**

The sentence "In such cases DRUG NAME should be promptly discontinued and the patient carefully observed until the swelling disappears" has been changed to "In such cases DRUG NAME should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred."

The following phrase has been deleted from the end of the last sentence: "should be promptly administered" and replaced with: "and/or measures necessary to ensure a patient airway, should be promptly provided."

**PRECAUTIONS:**

A new subsection, Cough, has been added:

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.

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

ADVERSE REACTIONS, Cardiovascular:

The phrase "including atrial tachycardia and bradycardia" was added after "rhythm disturbances;"

Digestive: the phrase "[proven on rechallenge]" was added after "hepatitis hepatocellular."

Skin: the word hyperhidrosis was changed to diaphroesis.

NDA 19-221, 19-309, 19-558, 19-778:

WARNINGS:

A new subsection, Fetal and Neonatal Morbidity and Mortality, has been added.

PRECAUTIONS: The Pregnancy Category has been changed to D.

NDA 19-221 and 19-309:

PRECAUTIONS, Nursing Mothers:

The following has been deleted: "It is not known whether enalapril is secreted in human milk;" and "Milk of lactating rats contains radioactivity following administration of 14 C enalapril maleate." The following has been added: "Enalapril and enalaprilat are detected in human milk in trace amounts."

ADVERSE REACTIONS: A new subsection, Fetal and Neonatal Morbidity and Mortality, has been added.

OVERDOSAGE: The following has been added: "and has been removed from neonatal circulation by peritoneal dialysis."

NDA 19-221:

WARNINGS: A new subsection, Pregnancy, Enalapril-Hydrochlorothiazide, has been added.

NDA 19-778:

WARNINGS: A new subsection, Pregnancy, Lisinopril-Hydrochlorothiazide, has been added.

ADVERSE REACTIONS, Other adverse reactions that have been reported with the individual components are listed below, Lisinopril: A new subsection, Body as a Whole: Malaise, has been added.

In addition, minor editorial changes have been made to all the labeling.

We have completed the review of these supplemental applications and they are approved.

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

Should you have any questions, please contact:

Ms. Kathleen Bongiovanni  
Consumer Safety Officer  
Telephone: (301) 443-4730

Sincerely yours,

*RJ 2/6/91*

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

HFD-110

HFD-110/CSO

HFD-80/DDIR

HFD-100

HFD-232 (with labeling)

HFD-730

HFD-110/KBongiovanni

sb/1/31/91;2/6/91/0800Q

R/D: CGanley/1/31/91

SCheon/1/31/91

CGraham/2/1/91

NMorgenstern/2/1/91

*K. Bongiovanni  
2-6-91*

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

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*APPLICATION NUMBER:*

**18-998/S025**

**LABELING**

Labeling: Work copy  
 NDA No: 18-998 No. 11-2291  
 Reviewed by: K. S. ... 1-31-91

NDA 18-998

A.H.F.S. Categories: 24:04, 24:08

7575824

TABLETS

**MSD**

**VASOTEC**<sup>®</sup>

(ENALAPRIL MALEATE, MSD)

APPROVED

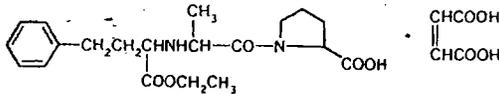
FEB - 6 1991

VASOTEC<sup>®</sup>  
(Enalapril Maleate, MSD)

VASOTEC<sup>®</sup>  
(Enalapril Maleate, MSD)

**DESCRIPTION**

VASOTEC<sup>®</sup> (Enalapril Maleate, MSD) 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-lethoxycarbonyl]-3-phenylpropyl-L-alanyl]-L-proline, (Z)-2-butenedioate salt (1:1). Its empirical formula is C<sub>20</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub> • C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>, 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 80 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 focus 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  $\leq$  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 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.

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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 <sup>14</sup>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.

A Scandinavian multicenter trial compared the effects of enalapril and placebo on mortality in 253 patients with severe heart failure (NYHA Class IV) and radiographic evidence of cardiomegaly who were maintained on therapy with diuretics and digitalis. Other vasodilators were used as needed. In the enalapril group, the reduction in all-cause mortality was 40 percent after six months and 31 percent after one year. There was an improvement in NYHA classification, a reduction in heart size, and a lessened need for concomitant vasodilator therapy in the enalapril group.

**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 as adjunctive therapy in the management of heart failure, in patients who are not responding adequately to diuretics and digitalis.

In patients with severe heart failure, VASOTEC improves survival. In a multicenter placebo-controlled trial in patients with severe heart failure (New York Heart Association Class IV) and radiographic evidence of cardiomegaly who were maintained on therapy with diuretics and digitalis, patients who received VASOTEC had improved survival compared to placebo. (See CLINICAL PHARMACOLOGY.)

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

VASOTEC is to be used with diuretics and digitalis.

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.

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(Enalapril Maleate, MSD)  
CIVILIAN

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.)

**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. Foreign 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, including VASOTEC, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

Enalapril crosses the human placenta. When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and/or death in the newborn. Oligohydramnios has also been reported, presumably representing decreased renal function in the fetus; limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine growth retardation have been reported in association with oligohydramnios. Patients who do require ACE inhibitors during the second and third trimesters of pregnancy should be apprised of the potential hazards to the fetus, and frequent ultrasound examinations should be performed to look for oligohydramnios. If oligohydramnios is observed, VASOTEC should be discontinued unless it is considered life-saving for the mother.

Other potential risks to the fetus/neonate exposed to ACE inhibitors include: intra-uterine growth retardation, prematurity, patent ductus arteriosus; fetal death has also been reported. It is not clear, however, whether these reported events are related to ACE inhibition or the underlying maternal disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

Infants exposed *in utero* 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.

Enalapril has been removed from the neonatal circulation by peritoneal dialysis and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril, but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day but not at 30 mg/kg/day (50 times the maximum human dose).

If VASOTEC is used during pregnancy or if the patient becomes pregnant while taking VASOTEC, the patient should be apprised of the potential hazards to the fetus.

VASOTEC®  
(Enalapril Maleate, MSD)

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. Dose 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.)

**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.

**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.)

**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, methylglucoside, 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.

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(Enalapril Maleate, MSD)

**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* cytogenetic 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 Category D.** 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
<b>Body As A Whole</b>		
Fatigue	3.0 (<0.1)	2.6
Orthostatic Effects	1.2 (<0.1)	0.0
Asthenia	1.1 (0.1)	0.9
<b>Digestive</b>		
Diarrhea	1.4 (<0.1)	1.7
Nausea	1.4 (0.2)	1.7
<b>Nervous/Psychiatric</b>		
Headache	5.2 (0.3)	9.1
Dizziness	4.3 (0.4)	4.3
<b>Respiratory</b>		
Cough	1.3 (0.1)	0.9
<b>Skin</b>		
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.

	VASOTEC (n=673) Incidence (discontinuation)	Placebo (n=339) Incidence
<b>Body As A Whole</b>		
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
<b>Cardiovascular</b>		
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
<b>Digestive</b>		
Diarrhea	2.1 (0.1)	1.2
Nausea	1.3 (0.1)	0.5
Vomiting	1.3 (0.0)	0.9

\*Based on patient weight of 50 kg

VASOTEC®  
(Enalapril Maleate, MSD)

	VASOTEC (n=673) Incidence (discontinuation)	Placebo (n=339) Incidence
<b>Nervous/Psychiatric</b>		
Dizziness	7.9 (0.6)	0.6
Headache	1.8 (0.1)	0.9
Vertigo	1.6 (0.1)	1.2
<b>Respiratory</b>		
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
<b>Skin</b>		
Rash	1.3 (0.0)	2.4
<b>Urogenital</b>		
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 0.5 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.

**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, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, dyspepsia, constipation, glossitis, stomatitis, dry mouth.

**Musculoskeletal:** Muscle cramps.

**Nervous/Psychiatric:** Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

**Respiratory:** Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection.

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

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

**Urogenital:** Renal failure, oliguria, renal dysfunction (see PRECAUTIONS AND DOSAGE AND ADMINISTRATION), impotence.

A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgias/arthritis, myalgia, 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:** In infants exposed *in utero* to ACE inhibitors the following adverse experiences have been reported: Fetal and neonatal death, renal failure, hypoplastic lung development, hypotension, hyperkalemia, skull hypoplasia, limb contractures, craniofacial deformities, intrauterine growth retardation, prematurity and patent ductus arteriosus (see WARNINGS, *Fetal/Neonatal Morbidity and Mortality*).

**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.

**Hemoglobin and Hematocrit:** 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.

**Other (Causal Relationship Unknown):** In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported. A few cases of hemolysis have been reported in patients with G6PD deficiency.

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

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**VASOTEC®**  
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**OVERDOSAGE**

Limited data are available in regard to overdosage in humans. The oral LD<sub>50</sub> 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  $\geq 30$  mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance  $\leq 30$  mL/min (serum creatinine  $\geq 3$  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	$\leq 80$ $>30$ mL/min	5 mg
Moderate to Severe Impairment	$\leq 30$ mL/min	2.5 mg
Dialysis Patients		2.5 mg on dialysis days*

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

**Heart Failure**

VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and

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(Enalapril Maleate, MSD)

until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions*.) If possible, the dose of the 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. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice daily dosing. In addition, patients in the mortality trial received therapy twice daily (see below). Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

In a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 - 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects*.)

**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 014 on one side and VASOTEC on the other. They are supplied as follows:

NDC 0006-0014-68 bottles of 100 (with desiccant)  
NDC 0006-0014-28 unit dose packages of 100.

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 0006-0712-68 bottles of 100 (with desiccant)  
(6505-01-236-8880, 5 mg 100's)  
NDC 0006-0712-28 unit dose packages of 100.

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 0006-0713-68 bottles of 100 (with desiccant)  
(6505-01-238-8881, 10 mg 100's)  
NDC 0006-0713-28 unit dose packages of 100.

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 0006-0714-68 bottles of 100 (with desiccant)  
(6505-01-237-0545, 20 mg 100's)  
NDC 0006-0714-28 unit dose packages of 100.

**Storage**

Store below 30°C (85°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.

**MSD** MERCK SHARP & DOHME  
DIV OF MERCK & CO., INC., WEST POINT, PA 19386, USA

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**18-998/S025**

**MEDICAL REVIEW**

JAN 25 1991

Medical Officer Review

NDA #: 18-998  
Sponsor: MSDRL  
Drug: Vasotec  
Type of Submission: Labeling change  
Date Submitted: 1/22/91  
Date of Review: 1/25/91  
Medical Officer # : 11D

Content

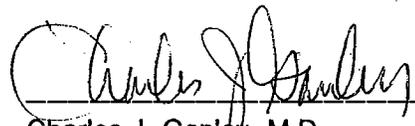
The sponsor submits revised final labeling that we had requested based on labeling changes submitted 12/11/91. (see attached)

Conclusions

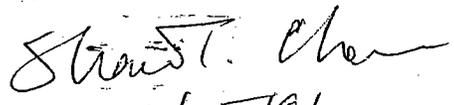
The labeling changes are consistent with our requests.

Regulatory Action

None required.

  
\_\_\_\_\_  
Charles J. Ganley, M.D.

cc: orig  
HFD-110  
HFD-110/c.ganley  
HFD-110/cso  
HFD-110/s.chen

Concurred  
  
1/25/91

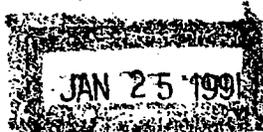
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       § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling

Medical Officer Review



NDA #: 18-998  
Sponsor: MSDRL  
Drug: Vasotec  
Type of Submission: Labeling change  
Date Submitted: 12/11/90  
Date of Review: 1/25/90  
Medical Officer #: 11D

Content

The proposed labeling change for enalapril includes revisions in the contraindications, warnings, precautions and adverse events sections as outlined in the attached documents.

Conclusions

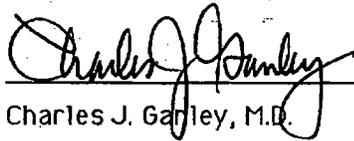
The proposed labeling was discussed among Drs. Chen, Graham and Ganley. The following conclusions have been agreed upon.

The sponsor has not provided sufficient information to justify the exclusion of patients with any history of angioedema as they have done in the contraindications section. We have discussed this issue previously, in reference to all ACEI, and concluded that a statement \_\_\_\_\_

\_\_\_\_\_ is not supported by the medical literature cited. The statement \_\_\_\_\_ is redundant and should not be included.

Regulatory Action

Prior to submitting the proposed labeling change, the sponsor had already printed several million copies of the proposed labeling. The sponsor was permitted to use these package inserts but had to submit new labeling instituting the changes listed above.

  
Charles J. Ganley, M.D.

- cc: orig
- HFD-110
- HFD-110/c.ganley
- HFD-110/cso
- HFD-110/s.chen
- HFD-110/c.graham

*Concurred*  
*Shaw T. Chen*  
*1/25/91*

7 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**18-998/S025**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

SUMMARY OF LABELING REVISIONS  
Tablets VASOTEC  
(Enalapril Maleate, MSD)

The following revisions have been made to the circular for Tablets VASOTEC:

1) CONTRAINDICATIONS

The contraindication concerning ACE inhibitors and angioedema has been revised, based on a review of the literature, as follows:

From: VASOTEC is contraindicated in patients ... and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor.

TO: VASOTEC is contraindicated in patients ... and in patients with a history of angioedema.

Publications:

- Orfan, N., Patterson, R., Dykewicz, M.S.: Severe angioedema related to ACE inhibitors in patients with a history of idiopathic angioedema, JAMA. 264: 1287-1289, Sept. 1990.
- Shepherd, G.M.: Possible contraindication of angiotension converting enzyme inhibitors in patients with hereditary angioedema, Am. J. Med. 88: 446, April 1990.
- Slater, E.E., Merrill, D.D.; Guess, H.A.; Roylance, P.J.; Cooper, W.D.; Inman, W.H.; Ewan, P.W.: Clinical profile of angioedema associated with angiotensin converting enzyme inhibition, JAMA 260: 967-970, Aug. 1988.

2) WARNINGS

- a) Angioedema - This section has been expanded based on good medical care and literature: 1) to ensure that appropriate therapy and monitoring are provided until complete resolution of symptoms has occurred because relapse of angioedema has been reported in some patients; and 2) that when there is airway obstruction emergency therapy including any measures necessary to ensure a patient airway should be promptly provided.

Publication:

Giannoccaro, P.J.; Wallace, G. J.; Higginson, L.A.J.; Williams, W.L.: Fatal angioedema associated with enalapril, Can, J. Cardiol. 5: 335-336, Oct. 1989.

3) PRECAUTIONS

- a) Cough - This new subsection has been added based on information contained in the report on the effects of ACE inhibitors on pulmonary function including cough, submitted to the FDA on 8/2/89, for inclusion in the NDA for Tablets VASOTEC (NDA 18-998).

## 4) ADVERSE REACTIONS

The paragraph listing those experiences occurring since enalapril was marketed has been revised as follows:

- a) Cardiovascular - the currently labeled experience "rhythm disturbances" has been expanded to include "atrial tachycardia" and "bradycardia". This revision is based on review of over 80 reports coded tachycardia or bradycardia, and specifies a possible cause for the disturbance which is possibly secondary to hypotension or abnormal serum potassium levels.
- b) Digestive - Based on an FDA letter dated 2/13/90, the qualifier "proven on rechallenge" has been included to the experience hepatocellular hepatitis.
- c) Skin - Based on a dictionary terminology change, the term for the experience "hyperhidrosis" has been updated to the term "diaphoresis".

RECORD OF TELEPHONE CONVERSATION

18-998

December 27, 1990

DEC 27 1990

Elliott T. Berger, Ph.D.  
Merck Sharp & Dohme Research Laboratories  
NDA ✓ 18-998/S-025  
19-221/S-007  
19-309/S-008  
19-558/S-010  
19-778/S-004

Background: On December 11, 1990 we received the above labeling supplements that provide for the addition of the new pregnancy wording (except Vasotec, already changed) and changes to the WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and CONTRAINDICATIONS sections. Drs. Graham, Ganley, and S. Chen disagreed with the CONTRAINDICATIONS change. Merck agreed to separate out that change and to submit it as a second supplement. Drs. Graham, Ganley and S. Chen and I met today to discuss the other changes. I phoned Dr. Berger to inform him of our decisions.

Phone Call:

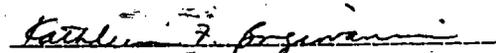
WARNINGS, Angioedema:

Please delete \_\_\_\_\_ from the first addition to this subsection. The event seems to be a continuation of an episode, not a relapse; the statement is supported by only one case.

Instead of the proposed additional sentence, for brevity please change the existing sentence to: "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 measures necessary to ensure a patent airway, should be promptly provided."

The other changes are acceptable.

Dr. Berger agreed to present the above changes to his labeling committee.

  
Kathleen Bongiovanni

cc:  
NDA 18-998/S-025  
19-221/S-007  
19-309/S-008  
19-558/S-010  
19-778/S-004  
HFD-110  
HFD-111/KBongiovanni  
HFD-110/CGraham  
HFD-110/CGanley  
HFD-110/SChen

2 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

FEB 6 1991

CSO Review of Labeling

NDA: ~~18-998/015~~ Vasotec (enalapril maleate) Tablets  
 19-221/S-007 Vaseretec (enalapril maleate/HCTZ) Tablets  
 19-309/S-008 Vasotec (enalaprilat) IV  
 19-558/S-010 Prinivil (lisinopril) Tablets  
 19-778/S-004 Prinzide (lisinopril/HCTZ) Tablets

Date of submissions: December 7, 1990

Amendments: January 18, 1991

Applicant: Merck Sharp & Dohme Research Laboratories

Merck submitted Special Supplements: Changes Being Effected dated December 7, 1990 for their five ACE inhibitor NDAs. These supplements included final printed labeling revised under CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS as follows:

All Applications:

**CONTRAINDICATIONS:** The sentence "DRUG NAME 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." has been changed to "DRUG NAME is contraindicated in patients who are hypersensitive to [any component of] this product and in patients with a history of angioedema."

**WARNINGS, Angioedema:** The sentence "In such cases DRUG NAME should be promptly discontinued and the patient carefully observed until the swelling disappears." has been changed to "In such cases DRUG NAME should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of symptoms has occurred"

The following sentence was added: "Other appropriate emergency therapy including any measures necessary to ensure a patent airway should be promptly provided."

**PRECAUTIONS:** A new subsection, Cough, has been added: 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.

In addition, minor editorial changes have been made.

18-998. 19-221. 19-309

**ADVERSE REACTIONS, Cardiovascular:** the phrase "including atrial tachycardia and bradycardia" was added after "rhythm disturbances";

**Digestive:** the phrase "[proven on rechallenge]" was added after "hepatitis (hepatocellular"

Skin: the word hyperhidrosis was changed to diaphoresis.

19-221, 19-309, 19-558, 19-778:

WARNINGS: A new subsection, Fetal and Neonatal Morbidity and Mortality, has been added.

PRECAUTIONS: The Pregnancy Category has been changed to D.

19-221 and 19-309:

PRECAUTIONS, Nursing Mothers: The following portions have been deleted: "It is not known whether enalapril is secreted in human milk;" and "Milk of lactating rats contains radioactivity following administration of 14 C enalapril maleate." The following has been added: "Enalapril and enalaprilat are detected in human milk in trace amounts."

ADVERSE REACTIONS: A new subsection, Fetal and Neonatal Morbidity and Mortality, has been added.

OVERDOSAGE: The following has been added: "and has been removed from neonatal circulation by peritoneal dialysis."

19-221:

WARNINGS: A new subsection, Pregnancy, Enalapril-Hydrochlorothiazide, has been added.

19-778:

WARNINGS: A new subsection, Pregnancy, Lisinopril-Hydrochlorothiazide, has been added.

ADVERSE REACTIONS, Other adverse reactions that have been reported with the individual components are listed below, Lisinopril: A new subsection, Body as a Whole: Malaise, has been added.

Drs. Lipicky, Graham, Ganley, and S. Chen disagreed with the CONTRAINDICATION change. Dr. Graham spoke with Merck by telephone and requested that the justification for this change be submitted in a separate supplement. The other changes were reviewed in a meeting between Drs. Graham, Ganley, S. Chen, and me, and I called the firm and asked them to do the following (see Record of Telephone Conversation 12-27-90):

WARNINGS, Angioedema:

Please delete \_\_\_\_\_ from the first addition to this subsection. The event seems to be a continuation of an episode, not a relapse; the statement is supported by only one case.

Instead of the proposed additional sentence, for brevity please change the existing sentence to: "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 measures necessary to ensure a patent airway, should be promptly provided."

The other changes are acceptable.

Merck responded by amending their supplements with final printed labeling revised to retain the CONTRAINDICATIONS statement as it was, and to change the other subsections as we requested. They also added the following changes:

WARNINGS, Angioedema: \_\_\_\_\_ has been changed to "sustained resolution of signs and symptoms."

These supplements are scheduled to become effective on or about February 1, 1991.

Conclusion: Merck has submitted supporting information for the above changes. The changes to the labeling are allowable under 21 CFR 314.70 (c)(2)(i), Supplements for changes that may be made before FDA approval. I will prepare acknowledge and approval letters for Dr. Lipicky's signature.

cc: NDA 18-998/S-025  
19-221/S-007  
19-309/S-008  
19-558/S-010  
19-778/S-004  
HFD-111  
HFD-111/KBongiovanni  
HFD-110/SBenton

  
Kathleen Bongiovanni 1-31-91