CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-998/S022

Trade Name: Vasotec

Generic Name: Enalaprilat

Sponsor: Merck Sharp & Dohme Research Laboratories

Approval Date: June 11, 1987

Indications: The treatment of hypertension.

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 18-998/S-022

JUN 11 1990

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

Dear Dr. Berger:

Please refer to your February 23, 1990 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Vasotec (enalapril maleate) Tablets.

We also acknowledge receipt of your amendment dated April 24, 1990.

The supplemental application provides for final printed labeling revised in the INDICATIONS AND USAGE section, Heart Failure subsection. The second paragraph has been replaced with the following:

> 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

We have completed the review of this supplemental application and it is 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.

Sincerely yours,

Robert Temple

Robert Temple, M.D.
Director
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-100/RTemple
HFD-110/KBongiovanni
sb/5/4/90;5/23/90/00040
R/D: CGanley/5/10/90
CGraham/5/10/90
RTemple/5/22/90
NMorgenstern/5/22/90

K. Bongiovanni 5-29-90
C. Ganley 5/29/90
CGraham 5/30/90

Approval Date: December 24, 1985

APPROVAL

Gellessinger 6/4/90
G Buehler for 5/31/90
Acting

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S022

LABELING

Labeling Revised
NDA No. 18-998 Rec'd 7-2-90
Reviewed by

NDA 18-998

JUN 1 1990

7575820

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

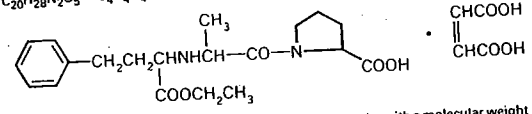
TABLETS

MSD | VASOTEC®
(ENALAPRIL MALEATE, MSD)

VASOTEC®
(Enalapril Maleate, MSD)

DESCRIPTION

VASOTEC* (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-(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 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.

VASOTEC®
(Enalapril Maleate, MSD)

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.

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.

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 the patient carefully observed until the swelling disappears. 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) should be promptly administered.** (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.

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.)

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*.)

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.

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(Enalapril Maleate, MSD)

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, 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 Category C. 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).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

Human Experience: There are no adequate and well-controlled studies of enalapril in pregnant women. However, data are available that show enalapril crosses the human placenta. Because the risk of fetal toxicity with the use of ACE inhibitors has not been clearly defined (see below), VASOTEC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Post-marketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. 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 with the administration of fluids and pressors as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors but it is not clear whether they are related to ACE inhibition, maternal hypertension or the underlying prematurity.

*Based on patient weight of 50 kg

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.

Nursing Mothers

Milk in lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, 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	5.2 (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.

	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

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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; atrial fibrillation; palpitation.

Digestive: Ileus, pancreatitis, hepatitis (hepatocellular 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, hyperhidrosis.

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, arthralgia/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.)

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.

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.

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).

7575820

VASOTEC®
(Enalapril Maleate, MSD)

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*

*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 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*.)

VASOTEC®
(Enalapril Maleate, MSD)

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)
(6505-01-236-8881, 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 (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.

MSD MERCK SHARP & DOHME
DIV OF MERCK & CO., INC., WEST POINT, PA 19486, USA

Issued April 1990

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S022

MEDICAL REVIEW

Medical Officer Review

MAR 9 1990

NDA #: 18-998/SLR-022
Sponsor: Merck Sharp and Dohme Research Labs
Drug: Vasotec (enalapril maleate, MSD)
Type of Submission: Supplemental New Drug Application Draft Labeling
Date of Submission: 2/27/90
Date of Review: 3/8/90
Reviewer: Charles J. Ganley, M.D.

On 2/27/90, MSDRL submitted a proposal for a "mortality" indication in severe heart failure. The rational for this change is based on the approval of Tenormin IV/Tenormin tablets for reduction in cardiovascular mortality. The indications section from Tenormin labeling is as follows.

INDICATIONS AND USAGE

Acute Myocardial Infarction: TENORMIN is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows. (See DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS.) In general, there is no basis for treating patients like those who were excluded from the ISIS-1 trial (blood pressure less than 100 mg Hg systolic, heart rate less than 50 bpm) or have other reasons to avoid beta blockade. As noted above, some subgroups (eg, elderly patients with systolic blood pressure below 120 mm Hg) seemed less likely to benefit.

DOSAGE AND ADMINISTRATION

Acute Myocardial Infarction: In patients with definite or suspected acute myocardial infarction, treatment with TENORMIN I.V. Injection should be initiated as soon as possible after the patient's arrival in the hospital and after eligibility is established. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized. Treatment should begin with the intravenous administration of 5 mg TENORMIN over 5 minutes followed by another 5 mg intravenous injection 10 minutes later. TENORMIN I.V. Injection should be administered under carefully controlled conditions including monitoring of blood pressure, heart rate, and electrocardiogram. Dilutions of TENORMIN I.V. Injection in Dextrose Injection USP, Sodium Chloride Injection USP, or Sodium Chloride and Dextrose Injection may be used. These admixtures are stable for 48 hours if they are not used immediately.

In patients who tolerate the full intravenous dose (10 mg), TENORMIN Tablets 50 mg should be initiated 10 minutes after the last intravenous dose followed by another 50 mg oral dose 12 hours later. Thereafter, TENORMIN can be given orally either 100 mg once daily or 50 mg twice a day for a further 6-9 days or until discharge from the hospital. If bradycardia or hypotension requiring treatment or any other untoward effects occur, TENORMIN should be discontinued. (See full prescribing information prior to initiating therapy with TENORMIN Tablets.)

At the time of approval, MSDRL felt that they were denied a "reduced mortality" indication because the claim was based on a single mortality study and this was consistent with past FDA policy. With the recent labeling change based on a single mortality trial that gave Tenormin an indication for use in acute myocardial infarction to reduce cardiovascular mortality, they feel that the policy is inconsistent. It is for this reason that they propose the following changes in the indications and usage section of the Vasotec package insert.

Current Labeling

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 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 a 40 percent reduction in mortality after six months and a 31 percent reduction after one year. (See CLINICAL PHARMACOLOGY.)

VASOTEC is to be used with diuretics and digitalis.

Proposed Labeling

[redacted]

contention by MSDRL that only one mortality study contributed to this claim of reduced mortality for Tenormin in acute MI is not true. In memorandum between Drs. Lipicky and Temple (memo dated 5/8/89 and 8/4/89), it is apparent that the Oxford/Wythenshawe 2 center trial may be considered a confirmatory mortality study in their view. In any event, this is a moot point since there was general agreement among advisory committee members that another placebo controlled mortality study in patients with class IV heart failure could not be done in light of the Consenses trial results. Thus, MSDRL has a legitimate complaint concerning the labeling for a mortality claim.

The proposed changes by MSDRL are inadequate to reflect the results of Consenses I. I disagree with the exclusion of the paragraph from the indications section describing the Consenses trial results and the use of the term [redacted] rather than patients with [redacted] In addition, I am reluctant to agree to terminology such as [redacted] in patients with diseases that are chronic, have a high associated mortality and require prolonged therapy. Mortality data from the Consenses trial has different implications than ISIS because it involves treatment of a chronic disease for a prolonged period of time. In fact, there is no data as to how long a patient should be treated to get the survival benefit. [redacted]

I propose that the labeling for Heart Failure should possibly be:

[redacted]

The numbers used in the survival table have to be confirmed by MSDRL and our statistics division.

Charles J. Ganley, M.D.

cc:
NDA 18-998/S-022
HFD-110
HFD-110/CSO
HFD-110/Dr. Graham

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S022

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

March 29,1990

Elliott T. Berger, Ph.D.
Merck, Sharp & Dohme Research Laboratories
NDA 18-998/S-022

Dr. Berger called to say that their labeling committee met and reviewed our proposed wording for a survival claim for Vasotec in CHF. We had suggested the following:

[redacted]

Merck agrees with the above, except they would like to add the words [redacted] to the underlined sentence; it would read:

[redacted]

cc: NDA 18-998/S-022
HFD 110
HFD 110/ESO

So, Merck thinks we have gone too far in our praise of enalapril. I find the [redacted] contradictory to the sentences that describe the study. They say enalapril [redacted] improve survival. My counterproposal is to leave the labelling as it now sits in the published 1990 PDR and, for a while anyhow, forget about a separate or partially separate [redacted] "claim. RK

Agree, but do we know why they want this change? Their proposal was to indicate it for survival, i.e. even more blunt than our version. Unless they have a persuasive reason I'd argue with your counterproposal, but do find out why they made it.

MINUTES
March 26, 1990
NDA 18-998/S-022 Vasotec (enalapril maleate) Tablets;

MAR 26 1990

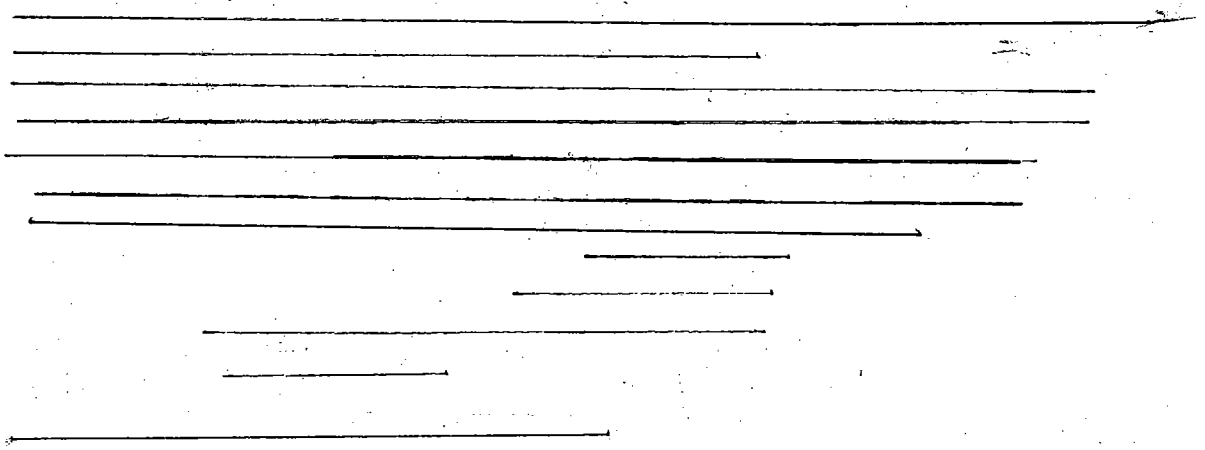
Between: Merck Sharp and Dohme Research Laboratories:

Dr. Elliott T. Berger	Director, Regulatory Affairs
Dr. David W. Blois	Executive Director, Regulatory Affairs
Ms. Marie A. Dray	Director, Government Agency Relations
Dr. John D. Irvin	Clinical Research
Dr. Sol Rajfer	Clinical Research
Dr. Janet Rush	Clinical Research
Dr. Mary Fisher	Clinical Research
Dr. Robert Davis	Biostatistics
Dr. Steve Snapinn	Biostatistics

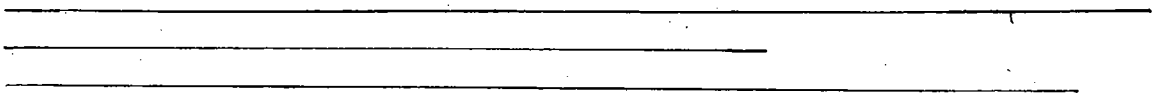
and FDA:

Dr. Robert Temple	HFD-100	Office Director
Dr. Raymond Lipicky	HFD-110	Division Director
Dr. Cheryl Graham	HFD-110	Deputy Director
Dr. Charles Ganley	HFD-110	Medical Officer
Dr. Shaw Chen	HFD-110	Medical Officer
Dr. George Chi	HFD-713	Group Leader
Dr. James Hung	HFD-713	Statistician
Kathleen Bongiovanni	HFD-110	Consumer Safety Officer

Background: On February 23, 1990, Merck submitted a supplement to the NDA for Vasotec Tablets, providing for a revision to the INDICATIONS AND USAGE section of the package insert, replacing the paragraph describing the results of the CONSENSUS study under the subsection Heart Failure with an indication for the reduction of mortality in severe congestive heart failure. Dr. Ganley reviewed the submission (see MOR dated March 9, 1990) and recommended the following revision in place of the one Merck submitted:



Pre-meeting: Dr. Temple suggested the following changes to Dr. Ganley's wording (underlined for emphasis here):



[redacted]

Drs. Lipicky, Graham, and Ganley agreed with Dr.Temple's suggestion.

Meeting: We told Merck of our changes to their proposed wording, and provided them with a copy of Dr. Ganley's review with Dr. Temple's revisions. Merck will submit final printed labeling after the changes have been reviewed by their labeling committee.

Kathleen F. Bongiovanni 3-29-90
Kathleen F. Bongiovanni

cc: Orig. NDA 18-998/S-022
HFD-110
HFD-110/CSO
HFD-110/SBenton

R/D: CGanley 3/28/90

Attachment: Dr. Ganley's review with Dr. Temple's revisions

APR 12 1990

NDA 18-998

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

Dear Dr. Berger:

Please refer to your new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for Vasotec (enalapril maleate) Tablets.

We also refer to your correspondence dated February 23, 1990 that describes your plans to study the effect of i.v. enalaprilat followed by oral enalapril in the treatment of acute myocardial infarction (CONSENSUS II), and to the discussion held at the March 16, 1990 meeting on the reporting of serious adverse drug reactions.

Under 21 CFR 314.80 you are required to report each adverse drug event that is both serious and unexpected, regardless of source, as soon as possible but in any case within 15 working days of initial receipt of the information. Your reporting responsibilities once the Safety Monitoring Committee has reported serious and unexpected adverse drug events to you will be covered by normal procedures.

What to have the Safety Monitoring Committee report to you is somewhat more difficult to define. Certainly, we do not think reporting of every death is required. In fact, reporting of every death is contrary to the best interests of the study, you, and FDA's Adverse Drug Reporting system.

You have a Safety Monitoring Committee and among the responsibilities of that committee is an ongoing assessment of the safety of the trial. I am totally comfortable with that committee making all judgments with respect to what to report to you.

Since your trial is a mortality trial and one can expect death to be a common event (which until the results of the trial are analyzed, cannot be reasonably attributed to the presence or absence of either of the drugs being tested), death should not be considered a "serious and unexpected event." Certainly the committee will have developed a means for ensuring that the trial is still able to be morally and ethically continued because the primary hypothesis had not been adequately tested. Neither Merck, nor the FDA should play a role in that decision-making process.

Thus, "serious and unexpected," for purposes of your trial, should be within the context of acute renal failure, pancreatitis, hepatitis, agranulocytosis, stroke, etc., where the circumstances are such that your committee thinks a treatment relationship cannot be excluded and/or when the frequency of such events has had a meaningful (another committee judgment) increase.

When reporting these "serious and unexpected" events, there is no reason to break the blind. Presumably, your committee will have access to a patient belonging to group A or B. That is good enough for reporting purposes. Only when events in one group reach a magnitude that would conceivably lead to an alteration in the trial's procedures, design, or perhaps its termination, would it be necessary to know the identity of the treatment a patient was receiving.

We expect that the committee would, on a quarterly basis, submit to you and you would then submit to us a report on "serious and unexpected" events tabulated by groups A and B. In addition to the tabulation, we would expect some summarizing statements that reflect the committee's deliberations regarding the reports received.

We are open to discussion if this letter suggests procedures that complicate the conduct of the trial or affront your perceived responsibilities to our Agency.

Sincerely yours,

RL 4/12/80

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

I have read this letter regarding reporting of 15 day reports to FDA associated with the protocol "Enalapril Post-MI Mortality Study (CONSENSUS II)," and concur with the overall recommendation. I think that, before submission of individual patient reports to FDA by Merck, the blind for those patients should be broken (by Merck or your Safety Committee). This does not pertain to the quarterly reports. For quarterly reports only "groups A and B" need to be identified.

Gerald A. Faich, M.D., MPH
Director
Office of Epidemiology and Biostatistics
Center for Drug Evaluation and Research

cc:
Orig. NDA
HFD-80/DDIR
HFD-110
HFD-110/CSO
HFD-110/Consensus II
HFD-700/GFaich
HFD-110/KBongiovanni
sb/4/2/90;4/9/90/5239S
R/D: RLipicky
NMorgenstern/4/6/90

K Bongiovanni 4-9-90

4/9/90

GENERAL CORRESPONDENCE