CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-998/S024

Trade Name: Vasotec Tablets

Generic Name: Enalapril Maleate

Sponsor: Merck Sharp and Dohme Research Laboratories

Approval Date: October 5, 1990

Indications: The treatment for hypertension.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S024

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Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S024

APPROVAL LETTER

NOV 28 1990

NDA 18-998/S-024

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

Dear Dr. Berger:

Please refer to your April 24, 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 November 14, 1990.

The supplemental application provides for final printed labeling revised to include the following changes:

WARNINGS: a new subsection, Fetal/Neonatal Morbidity and Mortality has been added;

PRECAUTIONS: the Pregnancy Category has been changed to D; the subsection on Nursing Mothers has been updated;

ADVERSE REACTIONS: a new subsection, Fetal/Neonatal Morbidity and Mortality, has been added;

OVERDOSAGE: the phrase "and has been removed from neonatal circulation by peritoneal dialysis" has been added.

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,

RL 11/28/90

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/11/20/90;11/28/90/0584Q
R/D: SZimmerman/11/27/90
RWolters/11/27/90
CGanley/11/27/90
SChen/11/27/90
CGraham/11/27/90
NMorgenstern/11/27/90

K. Borgova 11-28-90

APPROVAL Approval Date: October 31, 1986

Approval Date: October 31, 1986

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S024

APPROVABLE LETTER

OCT - 5 1990

NDA 18-998/S-024

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

Dear Dr. Berger:

Please refer to your April 24, 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 September 18, 1990.

The supplemental application provides for draft labeling revised to include the following changes:

WARNINGS, Fetal/Neonatal Morbidity and Mortality: Information previously under PRECAUTIONS, Pregnancy has been relocated to this subsection. Information on human experience has been updated.

PRECAUTIONS: The Pregnancy Category has been changed from C to D. The subsection Nursing Mothers has been updated.

ADVERSE REACTIONS, Fetal/Neonatal Morbidity and Mortality: This subsection has been added.

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

The WARNINGS, Fetal/Neonatal Morbidity and Mortality subsection should be modified as in the enclosed marked-up draft labeling.

In addition, all previous revisions as reflected in the most recently approved package insert must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

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

Please submit twelve copies of the printed labeling, seven of which are individually mounted on heavy weight paper or similar material.

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

Should you have any questions, please contact:

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

Sincerely yours,

RK 10/4/90

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

Enclosure

cc:
Original NDA
HFD-110
HFD-110/CSO
HFD-80/DDIR
HFD-110/KBongiovanni
sb/9/25/90;9/25/90;10/5/90/0413Q
R/D: CGanley/10/2/90
SChen/10/3/90
CGraham/10/3/90
NMorgenstern/10/4/90

K. Bongiovanni 10-5-90

APPROVABLE

1 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling

NDA 18-998/S-024

[redacted] 10 [redacted]

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

Dear Dr. Berger:

Please refer to your April 24, 1990 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Vasotec (enalapril maleate) Tablets.

The supplemental application provides for draft labeling revised to include the following changes:

1. PRECAUTIONS: The Pregnancy Category has been changed from C to D.

2. WARNINGS: Information previously under PRECAUTIONS, Pregnancy, has been relocated to this section. Information on Human Experience has been updated.

We have completed the review of this supplemental application as submitted with draft labeling. Before this supplement may be approved, however, it will be necessary for you to submit final printed labeling modified as in the enclosed draft labeling and as follows:

WARNINGS, Fetal/Neonatal Morbidity and Mortality

Add a more complete listing of potential risks to the fetus and neonate to this subsection, including intrauterine growth retardation, fetal and neonatal death, and possible increased incidence of patent ductus arteriosus.

ADVERSE REACTIONS

Update this section to include the frequency and rates, if known, of fetal/neonatal morbidity and mortality.

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

Please submit twelve copies of the printed labeling, seven of which are individually mounted on heavy weight paper or similar material.

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

Should you have any questions, please contact:

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

Sincerely yours,

R F 8/10/90

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

Enclosure

cc:
Original NDA
HFD-110
FD-110/CSO
HFD-80/DDIR
K. Bongiovanni 8-8-90
HFD-110/KBongiovanni/6/28/90;7/31/90
clb/6/28/90;6/29/90;7/3/90;7/31/90;sb/8/3/90;8/8/90/3093C
R/D: CGanley/7/24/90
CGraham/7/26/90
CResnick/7/30/90
NMorgenstern/7/30/90;8/3/90

APPROVABLE

2 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/S024

LABELING

ORGINAL

NDA 18-998 11-15-90 NDA 18-998

Reviewed by: [signature] 11-28-90

1

APPROVED

NOV 28 1990

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

7575821

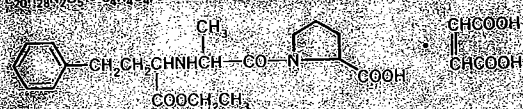
TABLETS

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.

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[redacted]

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.

[redacted]

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.

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 intrauterine 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.

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

[redacted]

VASOTEC®
(Enalapril Maleate, MSD)

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.

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

*Based on patient weight of 50 kg

[redacted]

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 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
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

[redacted]

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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.)

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.

OVERDOSAGE

Limited data are available in regard to overdosage in humans.

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

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

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

DOSAGE AND ADMINISTRATION

Hypertension

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

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

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage

[redacted]

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

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

Dosage Adjustment in Hypertensive Patients with Renal Impairment

The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤30 mL/min (serum creatinine ≥3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

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

*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.)

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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)
(6505-01-236-8881, 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 packaged is subdivided.

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

Issued November 1990

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S024

MEDICAL REVIEW

Medical Officer Review

IND #: 18998/SLR-024

Drug: Vasotec (enalapril, MSD)

Sponsor: Merck Sharp and Dohme Research Laboratories

Type of Submission: Labeling for use in pregnancy

Date Received: 4/26/90

Date Review Completed: 6/21/90

Medical Reviewer #: 11-D

The sponsor has submitted the following information to support proposed changes in the labeling of Vasotec for use in pregnancy.

1. Listing of enalapril cases
2. Listing of lisinopril cases
3. Listing of captopril cases
4. Listing of enalapril + captopril cases
5. Consultant's report regarding skull ossification defects
6. Bibliography of enalapril use in human pregnancy
7. Bibliography of lisinopril use in human pregnancy
8. Bibliogrpahy of captopril use in human pregnancy
9. Bibliography of enalapril + captopril use in human pregnancy

Currently, MSDRL has knowledge of the following numbers of cases in which women were treated with one or more angiotensin converting enzyme inhibitors during pregnancy.

Enalapril	70
Lisinopril	8
Captopril	61
Enalapril + Captopril	4

The listings are known reports of the use of ACE inhibitors during pregnancy.

Summary of Consultants Report

The consultant addressed questions pertaining to deformations or malformations in neonates born to mothers receiving ACE inhibitors.

Hypoplasia of the calvarial bones, especially the occipital and parietal bones, has occurred in some neonates after maternal use of ACE inhibitors. The calvaria bones are membranous bones. They require a high oxygen tension for growth and subsequently have a high degree of vascularity. The etiology of this defect is unclear but one could hypothesize that hypotension during pregnancy is the cause. Vertex craniotabes (prolonged vertex positioning results in compression and resorption of the top of the calvaria) was a possibility, however, in one case the autopsy was performed by a pediatrician/pathologist/embryologist and the defect was hypoplasia.

Descriptions of dysmorphic facies are poorly described . Craniofacial deformations (small mandible, ear anomalies, abnormalities of the nose) are part of Potter sequence. Potter's sequence is the result of oligohydramnios.

There were two reports describing different anomalies associated with first trimester involvement. Anencephaly associated with the use of lisinopril and a lower extremity ending at mid-thigh associated with the use of captopril. In the opinion of the consultant, the case of anencephaly was probably a spontaneous event. The case of the lower extremity abnormality may very well be a malformation which occurred during embryogenesis. It could also be a disruption from amniotic bands, resulting in a peromelic limb (2nd or 3rd trimester). There was one case of malformation, a microscopically abnormal kidney with a paucity of tubules, increased mesenchymal tissue, and glomerular maldevelopment. Not enough information was given but this could represent a second trimester arrest of development.

Recommendations of ————

* Women receiving ACE inhibitors who want to become pregnant should have their physician change their medication. Only if they are unresponsive to other medications should the women remain on ACE inhibitors.
* Indicate that calvarial hypoplasia has been a feature in some cases.

The company provides summary information of the pregnancies in which the fetus was exposed to enalapril for varying periods of time (at the request of Dr. Cheryl Graham, M.D.).

Category I: Children born to mothers who were on enalapril when they became pregnant and subsequently discontinued therapy within the first 12 weeks of pregnancy.

No. of cases: 30

Outcomes:

Normal infants	11*
Spontaneous abortion	7
Elective abortion	3
Intrauterine death	3
Cough, infant	1
Unknown	5

*Note: In many instances, the company reports the outcome as "presumably normal".

Category II: Children born to mothers who were on enalapril when they became pregnant and continued enalapril therapy at least into the second trimester.

No. of cases: 18

Outcomes:

Normal infants	6
Hyperkalemia	1
Anuria	7
Premature birth, placental abruptio	1
Ossification defects (included under other outcomes also)	3
Renal tubular dysplasia, anuria	1
Stillbirth	1
Unknown	1

Cateory III: Chidren born to women who were not receiving enalapril at conception, but received enalapril at some point during the pregnancy.

No. of cases: 25

Outcomes:

Normal infants	15
Anuria	8
Intrauterine death	1
Polycystic kidney	1

From the individual case reports and references in the medical literature, the following conclusions about the use of ACE inhibitors in pregnancy can be made.

(1) The risks to the fetus are unknown when the mother is taking an ACE inhibitor at the time of conception and during the first trimester.

(2) Use of ACE inhibitors during the second and third trimester of pregnancy can cause oligohydramnios resulting in growth retardation, hypoplastic lung development and craniofacial deformations (potter's sequence).

(3) If ACE inhibitors are used during the third trimester and are used during the days prior to delivery, renal insufficiency with anuria or oliguria can occur.

(4) Some neonates with renal insufficiency due to maternal use of ACE inhibitors have responded to treatment with peritoneal dialysis.

(5) Neonatal calvarial hypoplasia has been reported with the use of ACE inhibitors during pregnancy.

After reviewing the data and references in the medical literature supplied by the sponsor, I propose the following information should be included in the warnings section of the labeling for all ACE inhibitors. How it should be incorporated into the labeling can be decided by the company on an individual basis.

1)

2)

3)

4)

5)

The revised labeling for Vasotec is presented on the following pages.

2 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling

In general, I agree with the revised labeling. The only additions should include: 1) ———

——— 2) ultrasound examinations should be performed on pregnant women receiving vasotec to detect oligohydramnios (guideline #3).

Charles J. Ganley, M.D.

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

Medical Officer Review

NDA #: 18-998
Drug: enalapril maleate
Sponsor: MSDRL
Type of Submission: Revised labeling
Date Received: 9/19/90
Date Review Completed: 9/21/90
Medical Reviewer #: 11-D

The sponsor submits revised labeling in response to a our letter dated 8/10/90 (see attached). The sponsor has addressed all of our concerns adequately. However, on 9/14/90 Dr. Lipicky raised a contradiction in the labeling. These statements are from the revised labeling:

1) [redacted]

2) "Patients who do require ACE inhibitors during the second and third trimester of pregnancy should be apprised of the potential hazard to the fetus, and frequent ultrasounds should be performed to look for oligohydramnios."

3) " If Vasotec is used during pregnancy or if the patient becomes pregnant while taking Vasotec, the patient should be appraised of the potential hazard to the fetus".

The contradiction arises in that the labeling states that enalapril [redacted] *and then goes on to describe what should be done when enalapril is used during pregnancy. The problem arises with the statement* [redacted] *This statement should not be allowed in the labeling because it contradicts the pregnancy category D classification that the drug will now have in the labeling (and which the company had requested). Pregnancy category D acknowledges the potential risk to the fetus but it also concludes that* [redacted] *Pregnancy category D permits the clinician to make a judgement on an individual basis as to whether the drug should be used in pregnancy. By allowing the sponsor to include the recommendation that enalapril* [redacted] *they are limiting the clinician from making a clinical judgement.*

In addition, the statement "If oligohydramnios is observed, vasotec should be discontinued". This statement also limits the clinician from making a clinical decision whether to continue or stop the medication. This statement [redacted]

Conclusion:

The labeling will be acceptable if the following sentences [redacted]
from paragraph 1: [redacted]
from paragraph 2: If oligohydramnios is observed, vasotec should be discontinued

Charles J. Ganley, M.D.

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

Medical Officer Review

IND #: 18-998/S-024
Drug: Vasotec
Sponsor: MSDRL
Type of Submission: Final Printed Labeling/Pregnancy
Date Received: 11/15/90
Date Review Completed: 11/26/90
Medical Reviewer #: 11-D

The sponsor provides final labeling for the use of Vasotec during pregnancy. The changes had been agreed upon by the Cardio-Renal Division prior to this submission. (See attached for changes)

Charles J. Ganley, M.D.

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

concurred
S.T. Chen
11/28/90

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/S024

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NOV 1990

RECORD OF TELEPHONE CONVERSATION
November 5, 1990
NDA 18-998/S-024 Vasotec (enalapril maleate) Tablets: Pregnancy Labeling
Elliott T. Berger, Ph.D.
Merck Sharp & Dohme Research Laboratories
(215)834-2310

Elliott Berger FAXed in the attached revised wording on 11-2-90. Dr. Graham thought that it was acceptable. Today I showed it to Drs. Lipicky, Ganley, and S. Chen and they agreed that it was acceptable. I called Dr. Berger and he agreed to send in final printed labeling as soon as possible.

Kathleen Bongiovanni 11-5-90

cc: NDA 18-998/S-024
HFD-110
HFD-111/KBongiovanni
HFD-110/CGraham
HFD-110/SChen
HFD-110/CGanley

CSO Review of Labeling

NDA 18-998/SLR-024 (Change to Pregnancy Category D)

Date of submission: April 24, 1990 (AE letter issued 8-10-90)
September 18, 1990 (second AE letter issued 10-5-90)
November 14, 1990 AF

Applicant: Merck Sharp & Dohme Research Laboratories

Drug Name: Vasotec (enalapril maleate) Tablets

Date of Review: November 15, 1990

Background: In our October 5, 1990 approvable letter for this supplement, we asked Merck to revise the WARNINGS, Fetal/Neonatal Morbidity and Mortality subsection according to enclosed marked-up draft. The draft included (among other revisions) the sentence "If oligohydramnios is observed, [redacted] Merck FAXed in a counterproposal on 11-2-90 that replaced the above sentence with "If oligohydramnios is observed, VASOTEC should be discontinued unless it is considered life-saving for the mother." After Drs. Lipicky, Ganley, and S. Chen agreed that it was acceptable, I called Dr. Berger (see Telecon 11-5-90) who agreed to send us final printed labeling as soon as possible.

Review: This submission contains the final printed labeling for this supplement. Changes to the labeling include:

WARNINGS: the addition of a new subsection, Fetal/Neonatal Morbidity and Mortality;

PRECAUTIONS: the Pregnancy Category has been changed to D; the subsection on Nursing Mothers has been updated;

ADVERSE REACTIONS: the addition of a new subsection, Fetal/Neonatal Morbidity and Mortality;

OVERDOSAGE: the addition of the phrase "and has been removed from neonatal circulation by peritoneal dialysis."

Conclusion: Merck has made all of the changes that were asked for and agreed to in the earlier stages of this supplement review. I will prepare an approval letter for Dr. Lipicky's signature.

Kathleen F. Bongiovanni

cc: NDA 18-998/S-024
HFD-110
HFD-110/KBongiovanni
HFD-110/SBenton

(1)

TELECOPIER MESSAGE

PANAFAX (215) 834 - 2335

MERCK SHARP & DOHME RESEARCH LABORATORIES

REGULATORY AFFAIRS AND REGULATORY LIAISON

BLUE BELL, PA

TO: Ms. C. Graham

LOCATION: FDA **PHONE:** fax: 301-443-9283

FROM: DR. ELLIOTT T. BERGER

LOCATION: BLUE BELL **PHONE:** 215 - 834-2310

2

TOTAL ~~NUMBER OF~~ PAGES INCLUDING COVER SHEET

11/2/90

DATE

7 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling

OCT - 5 1990

CSO Review of Labeling

NDA 18-998/SLR-024

Date of submission: April 24, 1990 (AE letter issued 8-10-90)
September 18, 1990

Applicant: Merck Sharp & Dohme

Drug Name: Vasotec (enalapril maleate) Tablets

Date of Review: September 24, 1990

Background:
In our August 10, 1990 approvable letter we asked Merck to modify their proposed labeling as follows:

WARNINGS, Fetal/Neonatal Morbidity and Mortality
Add a more complete list of potential risks to the fetus and neonate to this subsection, including intrauterine growth retardation, fetal and neonatal death, and possible increased incidence of patent ductus arteriosus.

ADVERSE REACTIONS
Update this section to include the frequency and rates, if known, of fetal/neonatal morbidity and mortality.

Current Submission:
Merck responded with the September 18, 1990 submission containing draft labeling modified as follows:

WARNINGS, Fetal/Neonatal Morbidity and Mortality

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. [redacted]

(Note the deletion of the phrase [redacted]

WARNINGS, Nursing Mothers: Information on lactating rats has been replaced with the following:

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

ADVERSE REACTIONS: A new subsection has been added:
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, hypotension, hyperkalemia, skull hypoplasia, limb contractures, craniofacial deformities, intrauterine growth retardation, prematurity and patent ductus arteriosus (see WARNINGS, Fetal/Neonatal Morbidity and Mortality).

Review:
Merck has responded to our requests for modified labeling. In the interim, Drs. Lipicky and Ganley discussed the proposed labeling and would like the following additional change:
WARNINGS, Fetal/Neonatal Morbidity and Mortality:
In the first paragraph, insert "including VASOTEC" after "ACE inhibitors" and delete ————

In the second paragraph, Drs. Temple, Lipicky, Ganley, and S. Chen met and decided to ask for a modification of the sentence: "If oligohydramnios is observed, VASOTEC should be discontinued" to "If oligohydramnios is observed, ————

Upon further review, Dr. Ganley suggested the following changes:
WARNINGS, Fetal/Neonatal Morbidity and Mortality:
In the second paragraph, second sentence, add " and death" after "...skull hypoplasia"; in the third sentence, add "hypoplastec lung development, and intrauterine growth retardation" after "craniofacial deformities."

Move the third paragraph ("Infants exposed...") to after the current forth paragraph ("Other potential risks..."). In the paragraph beginning "Other potential risks...", delete ———— from the first sentence.

I will prepare another approvable letter asking for the additional changes outlined above to be submitted as FPL. I will check with Dr. Ganley on the acceptability of the submitted changes.

Kathleen F. Bongiovanni 10-2-90
Kathleen F. Bongiovanni

cc: NDA 18-998/S-024
HFD-110
HFD-111/KBongiovanni
HFD-110/CGanley
HFD-110/CGraham
HFD-111/SBenton

DATE: 24 September 1990

NOTE TO: R.Lipicky

SUBJECT: Pregnancy Labeling for VASOTEC, NDA 18-998/S-024

In discussions with Dr. Ganley (see MOR dated 21Sep90) you recommended that two sentences in Merck's proposed labeling ——— I agree that the statement ——— is contradictory to classification in Category "D" and ——— However, I **disagree** ——— of the statement "If oligohydramnios is observed, VASOTEC should be discontinued." The reasons for this position are stated below.

Oligohydramnios, unlike polyhydramnios, is associated with a relatively small number of fetal abnormalities, all of which involve fetal renal function. Renal agenesis and excretory obstruction are the two most common findings according to obstetrical textbooks. In the case of oligohydramnios associated with maternal ACE inhibitor use, there have been at least two cases reported to DESS in which oligohydramnios was reversible upon discontinuation of the ACE inhibitor. In the 25 cases of neonatal anuria reported to this Division in a 13 April 1990 Update from DESS, there were fourteen cases in which pre-existing oligohydramnios was reported. Nine of these infants died soon after birth (64%). In the remaining 11 cases in which oligohydramnios was either not reported (10) or did not occur (1) there were two deaths (18%). Certainly there could be a reporting bias here, but it is also possible that the presence of oligohydramnios is associated with more severe fetal renal dysfunction and a worse outcome.

The association between oligohydramnios and maternal ACE inhibitor use is certainly not common, since there are many cases on record where pregnant women have received ACE inhibitors throughout pregnancy without developing oligohydramnios. In general these women delivered healthy infants. However, in those cases where oligohydramnios does occur, its association with more serious neonatal outcomes is compelling. Furthermore, there are cases of neonatal anuria in which enalapril concentrations were measured starting shortly after delivery. In these infants there was a decrease in enalapril levels after dialysis, with a concurrent increase in functional ACE and the return of renal function.

Discontinuing the use of VASOTEC in a pregnant women with oligohydramnios would seem to be an appropriate recommendation for labeling. I do not agree with Dr. Chen's recommendation that the occurrence of oligohydramnios be cause for a re-assessment of the situation. It may be, however, ——— I don't think this is a decision that should be left to the clinician. There is no evidence that continuation of treatment will result in a better

outcome for either the mother or the infant, and there are plenty of therapeutic alternatives for controlling maternal hypertension.

In the case of serious life-threatening adverse events that we know (based on the best possible evidence) to be drug-related, we don't usually leave the decision to terminate therapy up to "clinical discretion." We recommend discontinuation. A recent labeling revision in which immediate discontinuation of the drug was recommended was for labetalol in the WARNING section regarding Hepatic Injury ——— laboratory evidence of liver injury ———

I strongly recommend that the sentence regarding discontinuation of VASOTEC in the presence of oligohydramnios ———
As suggested above, this recommendation might be further expanded by including a recommendation ———

Cheryl Graham

cc:
C.Ganley
S.Chen
K.Bongiovanni

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Minutes of an Internal Meeting
September 28, 1990
NDA 18-998/S-024 Vasotec (enalapril maleate) Tablets

Attending:	Robert Temple, M.D.	HFD-100	Office Director
	Raymond Lipicky, M.D.	HFD-110	Division Director
	Shaw Chen, M.D., Ph.D.	HFD-110	Group Leader/Medical
	Charles Ganley, M.D.	HFD-110	Medical Officer
	Kathleen Bongiovanni	HFD-111	Consumer Safety Officer

Background: see attached: Medical Officer's Review 9-21-90, C. Ganley
Memo to Drs. Graham and Ganley from Dr. Chen, 9-21-90
Note to Dr. Lipicky from Dr. Graham, 9-24-90

Merck submitted a supplement to change the pregnancy category to D for Vasotec Tablets. There was some discussion about how to word the second paragraph of the WARNINGS, Fetal/Neonatal Morbidity and Mortality subsection, specifically if the sentence "If oligohydramnios is observed, VASOTEC should be discontinued" ———— Drs. Lipicky, Graham, Chen, and Ganley agreed to meet with Dr. Temple for his opinion. (Note: Dr. Graham could not attend the meeting due to illness.)

Meeting: Dr. Lipicky presented both arguments. Dr. Temple thought that there should be a qualified version of the sentence included in the labeling, such as
"If oligohydramnios is observed, VASOTEC should ———— or
"If oligohydramnios is observed, VASOTEC should ———— ', or
"If oligohydramnios is observed, ————

We agreed and the meeting was adjourned.

Dr. Lipicky came up with the following recommendation:
"If oligohydramnios is observed, ————
————

I will prepare an approvable letter for the supplement, including the above sentence in our changes.

Kathleen F. Bongiovanni 10-2-90
Kathleen F. Bongiovanni

cc: NDA 18-998/S-024
HFD-110
HFD-111/KBongiovanni
HFD-110/CGraham
HFD-110/SChen
HFD-110/CGanley
HFD-111/SBenton

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEMORANDUM

Date: 09/21/90

To: C. Graham, C. Ganley

From: S. T. Chen

Subject: Labeling Change/NDA 18-998

I agree that there is a contradiction in the labeling. But I am not completely comfortable with ——— of the two sentences as proposed. There is a philosophical dilemma here: how much we tell the clinician to do and how much we leave to their judgement. I guess it depends a lot on the specific clinical data and it is a conflict not easily resolved. Instead of ——————————————— I would put some warning at the end of first paragraph. As for the second sentence, I suggest the following substitution:

"If oligohydramnios is observed, ———————————————

Again, it can probably be argued that this really doesn't say too much and the clinician does not need this advice. But it implies that oligohydramnios is a indicator with clinical consequences in this situation.

CSO Review of Labeling

AUG 10 1990

NDA 18-998/SLR-024

Date of submission: April 24, 1990

Applicant: Merck Sharp & Dohme

Drug Name: Vasotec (enalapril maleate) Tablets

Date of Review: June 26, 1990

Background: On October 19, 1989 we issued a letter to the holders of all ACE inhibitors asking for quarterly reports summarizing their reported cases of neonatal anuria. Merck responded with a report dated April 9, 1990. Merck's conclusions in this report were:

> There is conclusive evidence to establish that ACE inhibitors can cause fetal hypotension and anuria when used during the second and third trimesters. This can result in oligohydramnios and fetal compression leading to limb contractures and dysmorphic facies. Hypoplastic calvaria also appear to be caused by maternal use of an ACE inhibitor but the mechanism for this is unknown. The relationship of ACE inhibitor use to other defects which have been observed in single cases is not clearly delineated at this time. It is recommended that ACE inhibitors not be used during pregnancy. If an ACE inhibitor is used during pregnancy or if a patient becomes pregnant while taking an ACE inhibitor, the patient should be apprised of the potential hazard to the fetus.

Current Submission: Based on their findings, Merck has submitted a supplement that provides for a revision of the Pregnancy Category from C to D. The included annotated paste-up of the package circular for Vasotec Tablets has been revised to relocate the information on the use of enalapril in pregnancy, including the [redacted] subsection, to the WARNINGS section in conformance with Category D of the pregnancy labeling regulations.

In addition, Merck has reworded the [redacted] subsection as follows (new portions in italics, deleted portions in brackets):

[redacted]

[redacted]

Recommendation: Charles Ganley, M.D., medical officer, has reviewed this supplement (see MOR dated June 21, 1990) and suggested the following changes:
1) Add a more complete listing of potential risks, including intrauterine growth retardation, fetal [redacted] and possible increased incidence of patent ductus arteriosus.
2) Include wording similar to the following: [redacted]

I discussed the proposed labeling with Charles Resnick, Ph.D., and we came up with the following recommendations:
1) The subheadings under the WARNINGS section all deal with specific problems; for enalapril these subheadings include Angioedema, Hypotension, and Neutropenia/Agranulocytosis. Merck has proposed putting the information on use in pregnancy under the subheading [redacted] Dr. Resnick suggests using a subheading that describes the adverse experiences, such as Fetal/Neonatal Morbidity and Mortality.
2) The subsection should begin with the sentence "ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women; [redacted] followed by the human experience data, followed by the applicable animal data. The sentence "If VASOTEC is used during pregnancy or if the patient becomes pregnant while taking VASOTEC, the patient should be apprised of the potential hazard to the fetus" should be moved to after the description of the human and pertinent animal data, as described in 21 CFR 201.57 (f)(6)(d).
3) The sentence [redacted] should be deleted, since ACE inhibitors cross the human placenta and this information is included in the labeling.

In addition, the ADVERSE REACTIONS section should be updated to include the frequency and the rates, if known, of fetal/neonatal morbidity and mortality (21 CFR 201.57 (e)).

Conclusion: I recommend that we issue an approvable letter to Merck for this supplemental application, including all of the above modifications.

Kathleen F. Bongiovanni

cc: NDA 18-998/S-024
HFD-110
HFD-110/KBongiovanni
HFD-110/CGanley
HFD-110/CGraham
HFD-110/SBenton