CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-309/S008

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 19-309/S-008

Trade Name: Vasotec I.V. Injection

Generic Name(s): (enalaprilat)

Sponsor: Merck Sharp and Dohme Research Laboratories

Agent:

Approval Date: February 6, 1991

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-309/S-008

Approval Letter(s)

FEB - 6 1991

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

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

Dear Dr. Berger:

We acknowledge the receipt on December 11, 1990 of your December 7, 1990 supplemental new drug applications submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Vasotec (enalapril maleate) Tablets (NDA 18-998), Vaseretic (enalapril maleate/HCTZ) Tablets (NDA 19-221), Vasotec (enalaprilat) IV (NDA 19-309), Prinivil (lisinopril) Tablets (NDA 19-558), and Prinzide (lisinopril/HCTZ) Tablets (NDA 19-778).

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

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

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

WARNINGS, Angioedema:

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

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

PRECAUTIONS:

A new subsection, Cough, has been added:

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

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

ADVERSE REACTIONS, Cardiovascular:

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

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

Skin: the word hyperhidrosis was changed to diaphroesis.

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

WARNINGS:

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

PRECAUTIONS: The Pregnancy Category has been changed to D.

NDA 19-221 and 19-309:

PRECAUTIONS, Nursing Mothers:

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

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

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

NDA 19-221:

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

NDA 19-778:

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

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

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

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

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

Should you have any questions, please contact:

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

Sincerely yours,

RL 2/6/91

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

cc:
Original NDA
HFD-110
HFD-110/CSO
HFD-80/DDIR
HFD-100
HFD-232 (with labeling)
HFD-730
HFD-110/KBongiovanni KBongiovanni 2-6-91
sb/1/31/91;2/6/91/08000
R/D: CGanley/1/31/91
SChen/1/31/91
CGraham/2/1/91
NMorgenstern/2/1/91

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

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-309/S-008

Approved Labeling

Labeling: Original NDA 19-309

NDA No: 19-309 Rc'd. 1-22-91

Reviewed by: K. Bangaram 1-31-91

FEB - 6 1991

7494611

A.H.F.S. Category: 24:08

INJECTION

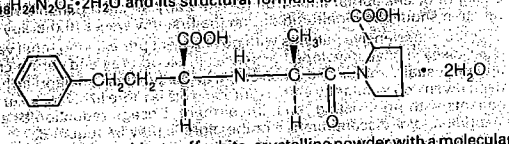
APPROVED

MSD | VASOTEC® I.V.
(ENALAPRILAT, MSD)

VASOTEC® I.V.
(Enalaprilat, MSD)

DESCRIPTION

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



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

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

CLINICAL PHARMACOLOGY

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

Mechanism of Action

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

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

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

Pharmacokinetics and Metabolism

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

*Registered trademark of MERCK & CO., INC.

VASOTEC® I.V.
(Enalaprilat, MSD)

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

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

Pharmacodynamics

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

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

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

INDICATIONS AND USAGE

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

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

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

CONTRAINDICATIONS

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

WARNINGS

Hypotension

Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalaprilat use in severely salt/volume-depleted persons such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients with severe heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely whenever the dose of enalaprilat is adjusted and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline.

A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema

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

Neutropenia/Agranulocytosis

Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis in similar rates. 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 I.V., 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 I.V. 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.

No reproductive or teratogenicity studies have been performed with VASOTEC I.V. Radioactivity was found to cross the placenta following oral administration of labeled enalapril to pregnant hamsters.

Studies with oral enalapril showed no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day. 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.

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.

If VASOTEC I.V. is used during pregnancy or if the patient becomes pregnant while taking VASOTEC I.V. 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 converting enzyme inhibitors, including enalapril or enalaprilat, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

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

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

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

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

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

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

Drug Interactions

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

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

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

Pregnancy

Pregnancy 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 I.V. is given to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

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

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

Enalapril Maleate

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

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

Body As A Whole: Syncope, orthostatic effects, chest pain, abdominal pain, asthenia.

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

Digestive: Ileus, pancreatitis, hepatitis (hepatocellular [proven on rechallenge] or cholestatic [jaundice]), melena, diarrhea, vomiting, dyspepsia, anorexia, glossitis, stomatitis, dry mouth.

Musculoskeletal: Muscle cramps.

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

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

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

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

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

*Based on patient weight of 50 kg.

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 enalapril (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 enalapril should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

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

Fetal/Neonatal Morbidity and Mortality: 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 enalapril alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.)

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 hypertensive patients treated with enalapril but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

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

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

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

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

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

DOSAGE AND ADMINISTRATION

FOR INTRAVENOUS ADMINISTRATION ONLY

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

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

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

7494611

VASOTEC® I.V.
(Enalaprilat, MSD)

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

Patients on Diuretic Therapy

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

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

Dosage Adjustment in Renal Impairment

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

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

For dialysis patients, the initial dose should be 0.625 mg q.6.h.

VASOTEC® I.V.
(Enalaprilat, MSD)

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

Administration

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

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

Compatibility and Stability

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

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

HOW SUPPLIED

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

NDC 0006-3508-01, 1 mL vials
NDC 0006-3508-04, 2 mL vials.

Storage

Store below 30°C (86°F).

*Registered trademark of American Hospital Supply Corporation

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

Issued December 1990

Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-309/S-008

Medical Review(s)

Medical Officer Review

NDA #: 19-309
Sponsor: MSDRL
Drug: Vasotec I.V.
Type of Submission: Labeling change
Date Submitted: 1/22/91
Date of Review: 1/25/91
Medical Officer # : 11D

Content

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

Conclusions

The labeling changes are consistent with our requests.

Regulatory Action

None required.

Charles J. Ganley, M.D.

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

Concurred
Shiew T. Chen
1/25/91

8 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

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-309/S-008

Administrative/Correspondence

8.1

FEB 6 1991

CSO Review of Labeling

NDA:	18-998/S-025	Vasotec (enalapril maleate) Tablets
	19-221/S-007	Vaseretic (enalapril maleate/HCTZ) Tablets
	19-309/S-008	Vasotec (enalaprilat) IV
	19-558/S-010	Prinivil (lisinopril) Tablets
	19-778/S-004	Prinzide (lisinopril/HCTZ) Tablets

Date of submissions: December 7, 1990

Amendments: January 18, 1991

Applicant: Merck Sharp & Dohme Research Laboratories

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

All Applications:

CONTRAINDICATIONS: The sentence "DRUG NAME is contraindicated in patients who are hypersensitive to [any component of] this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor." has been changed to "DRUG NAME is contraindicated in patients who are hypersensitive to [any component of] this product and in patients with a history of angioedema."

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

———————

The following sentence was added: ———————

———————

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

In addition, minor editorial changes have been made.

18-998, 19-221, 19-309

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

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

Skin: the word hyperhidrosis was changed to diaphoresis.

19-221, 19-309, 19-558, 19-778:
WARNINGS: A new subsection, Fetal and Neonatal Morbidity and Mortality, has been added.

PRECAUTIONS: The Pregnancy Category has been changed to D.

19-221 and 19-309:
PRECAUTIONS, Nursing Mothers: The following portions have been deleted: "It is not known whether enalapril is secreted in human milk;" and "Milk of lactating rats contains radioactivity following administration of 14 C enalapril maleate." The following has been added: "Enalapril and enalaprilat are detected in human milk in trace amounts."

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

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

19-221:
WARNINGS: A new subsection, Pregnancy, Enalapril-Hydrochlorothiazide, has been added.

19-778:
WARNINGS: A new subsection, Pregnancy, Lisinopril-Hydrochlorothiazide, has been added.

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

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

WARNINGS, Angioedema:
Please delete

Instead of the proposed additional sentence, for brevity please change the existing sentence to: "Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and measures necessary to ensure a patent airway, should be promptly provided."

The other changes are acceptable.

Merck responded by amending their supplements with final printed labeling revised to retain the CONTRAINDICATIONS statement as it was, and to change the other subsections as we requested. They also added the following changes:
WARNINGS, Angioedema: ———————————— has been changed to "sustained resolution of signs and symptoms."

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

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

Kathleen Bongiovanni 1-31-91
Kathleen Bongiovanni

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

19.309

RECORD OF TELEPHONE CONVERSATION

December 27,1990

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

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

Phone Call:
WARNINGS, Angioedema:
Please delete ——————————————— from the first addition to this subsection. The event seems to be a continuation of an episode, not a relapse; the statement is supported by only one case.

Instead of the proposed additional sentence, for brevity please change the existing sentence to: "Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and measures necessary to ensure a patent airway, should be promptly provided."

The other changes are acceptable.

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

Kathleen J. Bongiovanni
Kathleen Bongiovanni

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