CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-998/S011

Trade Name: Vastoec

Generic Name: Enalapril maleate

Sponsor: Merck Sharp & Dohme Research Laboratories

Approval Date: April 25, 1988

Indications: The treatment of hypertension.

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APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S011

APPROVAL LETTER

39.1

NDA 18-998/S-001
/S-011

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

APR 25 1988

Dear Dr. Berger:

We acknowledge receipt on February 13, 1986 and February 22, 1988 of your supplemental new drug applications dated February 7, 1986 (S-001) and February 16, 1988 (S-011), respectively. These supplements were submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Vasotec (enalapril maleate) Tablets.

Your February 7 supplmental application provides for final printed labeling revised to include a 5 mg unit dose package in the How Supplied section. Except for its inclusion in the labeling, this unit dose package was reviewed and approved on December 24, 1985. Moreover, subsequent labeling submitted with your June 2, 1986 supplemental application (S-004) included the 5 mg unit dose package; this was approved on October 3, 1986. Consequently no further action is required and we are retaining this application in our file.

The February 13 supplemental application provides for changes in the Description, Warning, Precaution, and Adverse Reaction sections. These changes include:

The addition of the statement, "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" to the Warnings section.

Revision of the Precautions section, changing the phrase "agents to treat hypokalemia" to "potassium-sparing agents, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with Vasotec."

Reformatting of the Adverse Reaction section.

The addition of 18 adverse reactions (myocardial infarction, cerebrovascular accident, ileus, pancreatitis, hepatitis or cholestatic jaundice, constipation, depression, confusion, bronchospasm, rhinorrhea, photosensitivity, alopecia, flushing, taste alteration, tinnitus, glossitis, symptom complex- which may include fever, myalgia and arthralgia; elevated ESR. Rash or dermatologic manifestations may occur, and hyponatremia).

Deletion of the word "rarely" from the statement concerning elevation in liver enzymes and/or serum bilirubin.

Other minor editorial changes.

We have completed the review of this supplmental application (S-011) and it is approved. Our letter of December 24, 1985 detailed the conditions relating to the approval of this application.

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. Gwyn Reis
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

RJL 4/26/88

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-232 (with labeling)
HFD-110/GReis/3/24/88
sb/3/24/88/0678S
R/D: SZimmerman/3/25/88
GReis/3/25/88
RWolters/3/29/88
CGraham/4/7/88

S-001 - ACKNOWLEDGE AND RETAIN
S-011 - APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S011

LABELING

Labeling: Orig
NDA No: 18-998 Orig 2-22-88
Reviewed by: Sonya Rao 3/25/88

NDA 18-998

APR 25 1988

358410

APPROVED

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

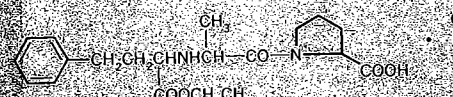
TABLETS

MSD | VASOTEC®
(ENALAPRIL MALEATE, MSD)

VASOTEC®
(Enalapril Maleate, MSD)

DESCRIPTION

VASOTEC® (Enalapril Maleate, MSD) is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor. The chemical described as enalaprilat is N-[1-(S)-carboxy-3-phenylpropyl]-L-alanyl-L-proline, (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 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, talc, magnesium stearate, starch, and other ingredients. The 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. 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, the 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 enalaprilat 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 potent angiotensin converting enzyme inhibitor. Oral administration of enalaprilat is poorly absorbed. Intravenously administered enalaprilat has a biphasic serum decay curve with a terminal elimination half-life of approximately 11 hours. Peak serum concentration of enalaprilat after oral administration of enalapril maleate is observed within 1 hour. Excretion of enalapril is primarily renal. Approximately 94 percent of the dose

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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 renal function ≤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.

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

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.

INDICATIONS AND USAGE

VASOTEC is indicated for the treatment of hypertension.

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.)

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.

assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.

Pregnancy

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

There are no adequate and well-controlled studies in pregnant women. VASOTEC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2677 patients.

The most frequent clinical adverse experiences in controlled trials were: headache (4.8 percent), dizziness (4.6 percent) and fatigue (2.8 percent). For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0 percent of patients. In clinical trials, the overall frequency of adverse experiences was not related to total daily dosage within the range of 10 to 40 mg. The overall percentage of patients treated with VASOTEC reporting adverse experiences was comparable to placebo.

Adverse experiences occurring in greater than one percent of patients treated with VASOTEC in controlled clinical trials are shown below.

	Percent of Patients in Controlled Studies	
	VASOTEC (n = 2677*) Incidence (discontinuation)	Placebo (n = 230) Incidence
Headache	4.8 (0.8)	9.1
Dizziness	4.6 (0.4)	4.3
Fatigue	2.8 (<0.1)	2.6
Diarrhea	1.6 (0.2)	1.7
Rash	1.5 (0.3)	0.4
Hypotension	1.4 (0.3)	0.4
Cough	1.3 (0.2)	0.9
Nausea	1.3 (0.2)	1.7
Orthostatic Effects	1.3 (<0.1)	0.0

*Includes 363 patients treated for congestive heart failure receiving concomitant digoxin and diuretic therapy.

Clinical adverse experiences occurring since the drug was marketed or in 0.5 to 1.0 percent of patients in the controlled trials are listed below and, within each category, are in order of decreasing severity.

Cardiovascular: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS: *Hypotension*); syncope; orthostatic hypotension; palpitations; chest pain.

Gastrointestinal System: Ileus, pancreatitis; hepatitis or cholestatic jaundice; abdominal pain; vomiting; dyspepsia; constipation.

Nervous System/Psychiatric: Depression; confusion; somnolence; insomnia; nervousness; paresthesia.

Renal: Renal failure; oliguria; renal dysfunction (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

Respiratory: Bronchospasm; dyspnea; rhinorrhea.

Other: Muscle cramps, hyperhidrosis, impotence, pruritus, asthenia, photosensitivity, alopecia, flushing; taste alteration, tinnitus, glossitis.

A symptom complex has been reported which may include fever, myalgia and arthralgia; an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

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: 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.)

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.)

Hemaglobin 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 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.

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

OVERDOSAGE

Limited data are available in regard to overdosage in humans.

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

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

Enalaprilat may be removed from general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION

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 (break the 5 mg tablet) should be used under medical supervision for at least one hour to determine whether excess hypotension will occur. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*)

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

Concomitant administration of VASOTEC with potassium supple-

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CONTRAINDICATIONS

VASOTEC is contraindicated in patients who are hypersensitive to this product.

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 was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril 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 congestive 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 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 hypotension occurs, the patient should be placed in 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.

Neutropenia/Agranulocytosis

Another angiotensin converting enzyme inhibitor has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

PRECAUTIONS

General

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

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

Some 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 VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril 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.)

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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. 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 medical supervision for at least one hour after the initial dose. (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 and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC may attenuate 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at a dose up to 90 mg/kg/day (150 times the maximum daily human dose). Enalapril has also been administered for 91 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

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ments, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in 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.

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HOW SUPPLIED

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 red, 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.

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

Issued December 1987

Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S011

MEDICAL REVIEW

Division of Cardio-Renal Drug Products
Medical Officer's Review

MAR 14 1988

39.1

Number: NDA 18-998/S-011
Drug Name: Vasotec®
Sponsor: MSD

Submission Type: Supplemental Application
Submission Date: 16 February 1988
Date of Receipt: 24 February 1988
Review Complete: 8 March 1988

Content:

This supplement contains numerous changes to the labeling of which the most important is the addition of 18 new adverse reactions to the Adverse Reaction Section of the labeling. A justification for each of these additions is included based on the case reports received by Merck since the approval of Vasotec. The strength of the evidence for including each of these 18 ADRs varies from a total of 2 cases for ileus (one was a positive rechallenge) to 46 cases for alopecia (five of which were temporally associated with enalapril initiation). The ADRs to be added to the appropriate paragraphs of the Adverse Reaction Section are: myocardial infarction; cerebrovascular accident; ileus; pancreatitis; hepatitis or cholestatic jaundice; constipation; depression; confusion; bronchospasm; rhinorrhea; photosensitivity; alopecia; flushing; taste alteration; tinnitus; glossitis; a sypmtom complex consisting of fever, myalgia and arthralgia, elevated ESR and skin manifestations; and hyponatremia.

In a conversation with the sponsor (E. Berger on 2 March 1988) it was determined that [redacted] The revisions in S-011 were submitted as "Changes Being Effected" with the revised label circulated starting 1 April 1988.

Assessment:

The additions and changes in the labeling are appropriate and acceptable.

Plan:

A letter to the sponsor should be prepared acknowledging the acceptability of these labeling changes and commending them for the format in which the justification for the changes was prepared.

Cheryl Fossum Graham, M.D.

cc:
Orig NDA 18-998
HFN-110
HFN-110/CSO
HFN-110/CGRAHAM
MM# N1899806/cfg/8mar88