CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-998/S039

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 18-998/S039

Trade Name: Vasotec

Generic Name: Enalapril Maleate

Sponsor: Merck Research Laboratories

Approval Date: January 14, 1994

Indications: The treatment of hypertension.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 18-998/S039

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 14 1994

NDA 18-998/S-039
19-221/S-016
19-309/S-014
19-558/S-021
19-778/S-015

Merck Research Laboratories
Attention: Patricia L. Kraft, Ph.D.
Sumneytown Pike
West Point, PA 19486

Dear Dr. Kraft:

Please refer to your May 26, 1993 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/hydrochlorothiazide) Tablets (NDA 19-221), Vasotec (enalaprilat) I.V. (NDA 19-309), Prinivil (lisinopril) Tablets (NDA 19-558) and Prinzide (lisinopril/hydrochlorothiazide) Tablets (NDA 19-778).

We also acknowledge receipt of your amendments to NDAs 18-998, 19-221, 19-309 and 19-558 dated December 14, 1993 and your amendment to NDA 19-778 dated December 16, 1993.

The supplemental applications provide for final printed labeling revised to include a new subsection, **WARNINGS, Hepatic Failure**:

> **WARNINGS, Hepatic Failure**: Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

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.

Sincerely yours,

RL 1/14/94

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

cc:
Original NDA
HF-2 (with labeling)
HFC-130/JAllen
HFD-110
HFD-110/CSO
HFD-80
HFD-230 (with labeling)
HFD-240 (with labeling)
HFD-638 (with labeling)
HFD-730 (with labeling)
HFD-110/KBongiovanni;1/4/94
sb/1/4/93;1/12/94
R/D: CGanley/1/4/94
SChen/1/4/94
GBuehler for NMorgenstern/1/7/94

Approval Date: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

APPLICATION NUMBER:

NDA 18-998/S039

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL

NDA ~~18-998~~/S-039
19-221/S-016
19-309/S-014
19-558/S-021
19-778/S-015

Merck Research Laboratories
Attention: Patricia L. Kraft, Ph.D.
West Point, PA 19486

Dear Dr. Kraft:

We acknowledge the receipt on June 1, 1993 of your May 26, 1993 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/ hydrochlorothiazide) Tablets (NDA 19-221), Vasotec (enalaprilat) I.V. (NDA 19-309), Prinivil (lisinopril) Tablets (NDA 19-558) and Prinzide (lisinopril/hydrochlorothiazide) Tablets (NDA 19-778).

The supplemental applications provide for draft labeling revised to include a new subsection, **WARNINGS, Hepatic Failure:**

> **WARNINGS, Hepatic Failure:** Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

We have completed the review of these supplemental applications as submitted with draft labeling. Before the supplements may be approved, however, it will be necessary for you to submit final printed labeling. The labeling should be identical in content to the draft copy. If additional information relating to the safety or effectiveness of these drugs becomes available before we receive the final printed labeling, revision of that labeling may be required.

To each application, 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 the applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the supplemental applications.

Should you have any questions, please contact:

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

Sincerely yours,

R L 7/1/93

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-110/KBongiovanni
sb/6/22/93;6/28/93
R/D: CGanley/6/24/93
NMorgenstern/6/25/93

K Bongiovanni 7.1.93

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

APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-998/S039

LABELING

MERCK & CO., INC.
West Point, PA 19486, USA

APPROVED JAN 14 1994 7432319

TABLETS

VASERETIC®

(ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE)

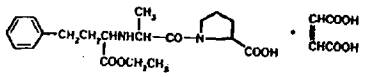
USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible. See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

DESCRIPTION

VASERETIC® (Enalapril Maleate-Hydrochlorothiazide) combines an angiotensin converting enzyme inhibitor, enalapril maleate, and a diuretic, hydrochlorothiazide.

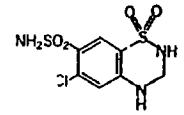
Enalapril maleate is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat. Enalapril maleate is chemically described as (*S*)-1-[*N*-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (*Z*)-2-butenedioate salt (1:1). Its empirical 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.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



It is a white, or practically white, crystalline powder with a molecular weight of 297.72, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

VASERETIC is available for oral use as tablets containing 10 mg of enalapril maleate, 25 mg of hydrochlorothiazide and the following inactive ingredients: iron oxides, lactose, magnesium stearate, starch and other ingredients.

CLINICAL PHARMACOLOGY

As a result of its diuretic effects, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, and decreases serum potassium. Administration of enalapril maleate blocks the renin-angiotensin-aldosterone axis and tends to reverse the potassium loss associated with the diuretic.

In clinical studies, the extent of blood pressure reduction seen with the combination of enalapril maleate and hydrochlorothiazide was approximately additive. The antihypertensive effect of VASERETIC was usually sustained for at least 24 hours.

Concomitant administration of enalapril maleate and hydrochlorothiazide has little, or no effect on the bioavailability of either drug. The combination tablet is bioequivalent to concomitant administration of the separate entities.

Enalapril Maleate

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 enalapril maleate alone for up to 48 weeks, mean increases in serum potassium of approximately 0.2 mEq/L were observed. In patients treated with enalapril maleate 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 enalapril remains to be elucidated.

While the mechanism through which enalapril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, enalapril is antihypertensive even in patients with low-renin hypertension. Although enalapril was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to enalapril maleate monotherapy than non-black patients. In contrast, hydrochlorothiazide was more

effective in black patients than enalapril. Concomitant administration of enalapril maleate and hydrochlorothiazide was equally effective in black and non-black patients.

Pharmacokinetics and Metabolism: Following oral administration of enalapril maleate, 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 enalaprilat and enalapril 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. 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 enalapril maleate 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 infrequent with enalapril alone but it can be anticipated in volume-depleted patients, such as patients treated with diuretics. In clinical trials with enalapril and hydrochlorothiazide administered concurrently, syncope occurred in 1.3 percent of patients. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

In most patients studied, after oral administration of a single dose of enalapril maleate, 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 of enalapril maleate monotherapy have been maintained for at least 24 hours. In some patients the effects may diminish toward the end of the dosing interval; this was less frequently observed with concomitant administration of enalapril maleate and hydrochlorothiazide.

Achievement of optimal blood pressure reduction may require several weeks of enalapril therapy in some patients.

The antihypertensive effects of enalapril have continued during long term therapy. Abrupt withdrawal of enalapril has not been associated with a rapid increase in blood pressure.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction produced by enalapril 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 enalapril maleate, 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.

In a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving enalapril maleate. In this study there was no evidence of a blunting of the antihypertensive action of enalapril maleate.

Hydrochlorothiazide

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure. Hydrochlorothiazide is a diuretic and antihypertensive. It affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. After oral use diuresis begins within two hours, peaks in about four hours and lasts about 6 to 12 hours. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

INDICATIONS AND USAGE

VASERETIC is indicated for the treatment of hypertension in patients for whom combination therapy is appropriate.

This fixed dose combination is not indicated for initial therapy. Patients already receiving a diuretic when enalapril is initiated, or given a diuretic and enalapril simultaneously, can develop symptomatic hypotension. In the initial titration of the individual entities, it is important, if possible, to stop the diuretic for several days before starting enalapril or, if this is not possible, begin enalapril at a low initial dose (see DOSAGE AND ADMINISTRATION). This fixed dose combination is not suitable for titration but may be substituted for the individual components if the titrated doses are the same as those in the combination.

In using VASERETIC, 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 enalapril does not have a similar risk. (See WARNINGS.)

CONTRAINDICATIONS

VASERETIC 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. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

General

Enalapril Maleate

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.

Syncope has been reported in 1.3 percent of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, *Drug Interactions*, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION.)

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 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 VASERETIC 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.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

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. 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.

Hepatic Failure: Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis, and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Hydrochlorothiazide

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions, Enalapril Maleate* and *Hydrochlorothiazide*).

Pregnancy

Enalapril-Hydrochlorothiazide

There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2) times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses; 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible. (See *Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality*, below.)

Enalapril Maleate

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERETIC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, VASERETIC should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure 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. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalaprilat, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats), and 50 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide

Teratogenic Effects: Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4 - 5.6 mg/kg/day (approximately 1 - 2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Nonteratogenic Effects: These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS

General

Enalapril Maleate

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 enalapril, 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 enalapril 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.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69®) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. 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 enalapril. (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

VASERETIC® (Enalapril Maleate-Hydrochlorothiazide)

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secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions, Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

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.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC 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

Enalapril Maleate

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 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 enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: Enalapril 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: Enalapril attenuates diuretic-induced potassium loss. 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.

Hydrochlorothiazide

When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—additive effect or potentiation.

Cholestyramine and colestipol resins—Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH—Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine)—possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC.

Non-steroidal Anti-inflammatory Drugs—In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution assay in rat hepatocytes or chromosomal aberrations in an *in vivo* mouse bone marrow assay.

Enalapril Maleate

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

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

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

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 μg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters). See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

Nursing Mothers

Enalapril and enalaprilat are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC no

*Based on patient weight of 50 kg

adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Generally, adverse experiences were mild and transient in nature. Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials are shown below.

	Percent of Patients in Controlled Studies	
	VASERETIC (n = 1580) Incidence (discontinuation)	Placebo (n = 230) Incidence
Dizziness	8.6 (0.7)	4.3
Headache	5.5 (0.4)	9.1
Fatigue	3.9 (0.8)	2.6
Cough	3.5 (0.4)	0.9
Muscle Cramps	2.7 (0.2)	0.9
Nausea	2.5 (0.4)	1.7
Asthenia	2.4 (0.3)	0.9
Orthostatic Effects	2.3 (< 0.1)	0.0
Impotence	2.2 (0.5)	0.5
Diarrhea	2.1 (< 0.1)	1.7

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain; *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia; *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth; *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo; *Skin:* Pruritus, rash; *Other:* Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 0.3 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, *Cough.*

Clinical Laboratory Test Findings

Serum Electrolytes: See PRECAUTIONS.

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 0.1 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium: 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 VASERETIC 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.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred (see WARNINGS, *Hepatic Failure*)

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.

Enalapril Maleate—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, *Hemodialysis Patients*); *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; hypotension; angina pectoris; *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular (proven on rechallenge) or cholestatic jaundice) (see WARNINGS, *Hepatic Failure*),melena, anorexia, glossitis, stomatitis, dry mouth; *Hematologic:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression, Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril has not been established. *Nervous System/Psychiatric:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia); *Urogenital:* Renal failure, oliguria, renal dysfunction, (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), flank pain, gynecomastia; *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection; *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pemphigus, alopecia, flushing, photosensitivity; *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality*

Hydrochlorothiazide — Body as a Whole: Weakness; *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia; *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions; *Musculoskeletal:* Muscle spasm; *Nervous System/Psychiatric:* Restlessness; *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; *Special Senses:* Transient blurred vision, xanthopsia.

OVERDOSAGE

No specific information is available on the treatment of overdosage with VASERETIC. Treatment is symptomatic and supportive. Therapy with VASERETIC should be discontinued and the patient observed closely. Suggested measures include induction of emesis and/or gastric lavage, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

Enalapril Maleate — 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.

Hydrochlorothiazide — The oral LD_{50} of hydrochlorothiazide is greater than 10 g/kg in both mice and rats. The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. THE FIXED COMBINATION IS NOT FOR INITIAL THERAPY. THE DOSE OF VASERETIC SHOULD BE DETERMINED BY THE TITRATION OF THE INDIVIDUAL COMPONENTS.

Once the patient has been successfully titrated with the individual components as described below, VASERETIC (one or two 10-25 tablets once daily) may be substituted if the titrated doses are the same as those in the fixed combination. (See INDICATIONS AND USAGE and WARNINGS.)

Patients usually do not require doses in excess of 50 mg of hydrochlorothiazide daily; when combined with other antihypertensive agents. Therefore, since each tablet of VASERETIC includes 25 mg of hydrochlorothiazide, the daily dosage of VASERETIC should not exceed two tablets. If further blood pressure control is indicated, additional doses of enalapril or other non-diuretic antihypertensive agents should be considered.

For enalapril monotherapy the recommended initial dose in patients not on diuretics is 5 mg of enalapril once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range of enalapril is 10 to 40 mg per day administered in a single dose or two divided doses. In some patients treated once daily, the antihypertensive effects 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 enalapril alone, a diuretic may be added.

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

If the diuretic cannot be discontinued an initial dose of 2.5 mg of enalapril 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.*)

Concomitant administration of VASERETIC with potassium supplements, potassium salt substitutes, or potassium sparing agents may lead to increases of serum potassium. (See PRECAUTIONS.)

Dosage Adjustment in Renal Impairment. The usual dose of VASERETIC is recommended for patients with a creatinine clearance >30 mL/min (serum creatinine of up to approximately 3 mg/dL).

When concomitant diuretic therapy is required in patients with severe renal impairment, a loop diuretic, rather than a thiazide diuretic is preferred for use with enalapril; therefore, for patients with severe renal dysfunction the enalapril maleate hydrochlorothiazide combination tablet is not recommended.

HOW SUPPLIED

No. 3418—Tablets VASERETIC 10-25, are rust, squared capsule-shaped, compressed tablets, coded MSD 720 on one side and VASERETIC on the other. Each tablet contains 10 mg of enalapril maleate and 25 mg of hydrochlorothiazide. They are supplied as follows:

NDC 0006-0720-68 bottles of 100 (with desiccant).

Storage: Store below 30° (86°F) and avoid transient temperatures above 50°C (122°F). Keep container tightly closed. Protect from moisture.

Dispense in a tight container, if product package is subdivided

Dist. by:
MERCK & CO., INC., West Point, PA 19486, USA

Issued July 1993

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-998/S039

CHEMISTRY REVIEW(S)

SLR (AP)
S016
14.1

DEC 22 1993

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 19-221
3. Name and Address of Applicant (City & State) Merck Research Laboratories West Point, PA 19486		4. Supplement(s) Number(s) Date(s) S-016 26 Mar 93
5. Drug Name Vaseretic	6. Nonproprietary Name Enalapril Maleate Hydrochlorothiazide	7. Amendments & Other (reports, etc) - Dates Amendment 14 Dec 93
8. Supplement Provides For: Revision of the Package Insert (PI).		
9. Pharmacological Category Antihypertensive	10. How Dispensed [X] Rx [ ] OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) TCM	13. Potency(ies) 10/25 mg	
14. Chemical Name and Structure		15. Records/Reports Current [ ] Yes [ ] No Reviewed [ ] Yes [ ] No

16. Comments

The PI is revised to include a section on hepatic failure in the Warnings section. The revision is made to comply with the Agency's letter of 17 Feb 93. The amendment provides FPL in compliance with the Agency's letter of 1 Jul 93.

The revised PI is dated 7/93.

17. Conclusions and Recommendations

The technical aspects of the labeling are unchanged.

APPROVAL is recommended as far as the technical aspects of the labeling are concerned.

18. REVIEWER

Name James H. Short	Signature James H. Short	Date Completed 21 Dec 93

Distribution:

[ ] Original Jacket [ ] Reviewer [ ] Division File [ ] CSO [ ] District

jhs/12/21/93/N19-221A.S16

R/D init:RWolters/

12-22-93

14.1

JAN 3 - 1994

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 19-221
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5. Drug Name Vaseretic	6. Nonproprietary Name Enalapril Maleate Hydrochlorothiazide	7. Amendments & Other (reports, etc) - Dates
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12. Dosage Form(s) TCM	13. Potency(ies) 10/25 mg	
14. Chemical Name and Structure		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. Comments

The Warnings, Angioedema and Precautions, Information for Patients sections have been revised to state that angioedema may occur at any time during treatment with angiotensin converting enzyme inhibitors. These changes will become effective about 1/1/94. An annotated draft is provided showing the changes as well as FPL.

The revised PI is dated 8/93.

17. Conclusions and Recommendations

The technical aspects of the labeling are unchanged.

APPROVAL is recommended as far as the technical aspects of the labeling are concerned.

18. REVIEWER

Name James H. Short Signature James H. Short Date Completed 3 Jan 94

Distribution:

☐ Original Jacket ☐ Reviewer ☐ Division File ☐ CSO ☐ District

jhs/1/3/94/N19-221.S19

R/D init:RWolters/ 1-3-94

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-998/S039

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CSO Review of Labeling 1994

NDA: 18-998/S-039 Vasotec (enalapril maleate) Tablets
19-221/S-016 Vaseretic (enalapril maleate/HCTZ) Tablets
19-309/S-014 Vasotec (enalaprilat) I.V.
19-558/S-021 Prinivil (lisinopril) Tablets
19-778/S-015 Prinzide (lisinopril/HCTZ) Tablets

Date of submissions: December 14, 1993 for all but 19-778/S-015; it was dated December 16, 1993

Date of receipt: December 15, 1993 for all but 19-778/S-015, it was received December 17, 1993

Applicant: Merck Research Laboratories

Background: Merck has submitted final printed labeling in response to our July 1, 1993 approvable letter. These supplements provide for final printed labeling revised to include a new subsection, WARNINGS, Hepatic Failure.

Review: The submitted final printed labeling includes the requested subsection:

WARNINGS, Hepatic Failure: Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

The cover letters for these amendments state that the firm received an approval letter dated July 1, 1993. This is an error; the July 1, 1993, letter is an approvable letter. I called Patricia Kraft's office on January 4, 1994, and spoke to her assistant, Marsha Fantini. I called this error to her attention.

Recommendation: I will prepare an approval letter for these supplements. These supplements fall under 21 CFR 314.70 (c)(2)(i), Supplements for changes that may be made before FDA approval.

Kathleen F. Bongiovanni 1-4-94

cc: 18-998/S-0349
19-221/S-016
19-309/S-014
19-558/S-021
19-778/S-015
HFD-110 (all)
HFD-111/KBongiovanni
HFD-111/SBenton
kb/1/4/94