CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20507/S001

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-998/S-057
19-221/S-025
19-309/S-022
19-558/S-036
19-778/S-029
20-507/S-001

FEB 17 1999

Merck Research Laboratories
Attention: Jeffrey R. White, M.D.
Sumneytown Pike, P.O. Box 4
BLA-20
West Point, PA 19486

Dear Dr. White:

Please refer to your supplemental new drug applications dated December 10, 1997, received December 12, 1997, submitted under section 505(b) 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), Prinzide (lisinopril/hydrochlorothiazide) Tablets (NDA 19-778), and Teczem (enalapril maleate/diltiazem maleate) Tablets (NDA 20-507).

We acknowledge receipt of your submissions dated January 21, 1999.

These supplemental new drug applications provide for final printed labeling revised as follows:

NDA 18-998, 19-221, 19-309, and 20-507:

CONTRAINDICATIONS: The phrase "and in patients with hereditary or idiopathic angioedema" has been added to the first sentence.

WARNINGS, Neutropenia/Agranulocytosis: The word referring to the number of cases of agranulocytosis reported, has been deleted from the third sentence.

PRECAUTIONS, General [, Enalapril Maleate]: A new subsection has been added: "Aortic Stenosis/Hypertrophic Cardiomyopathy: As with all vasodilators, enalapril should be given with caution to patients with obstruction in the outflow tract of the left ventricle."

PRECAUTIONS, Drug Interactions [, Enalapril Maleate]: A new subsection has been added: "Non-steroidal Anti-inflammatory Agents: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the coadministration of enalapril may result in a further deterioration of renal function. These effects are usually reversible."

ADVERSE REACTIONS, [Enalapril Maleate,] Respiratory: "eosinophilic pneumonitis" has been added.

OVERDOSAGE [, Enalapril Maleate]: A cross-reference, "(See WARNINGS, Anaphylactoid reactions during membrane exposure.)" has been added.

NDA 19-558 and 19-778:

CONTRAINDICATIONS: The phrase "and in patients with hereditary or idiopathic angioedema" has been added to the first sentence.

PRECAUTIONS, General [, Lisinopril]: A new subsection has been added: "Aortic Stenosis/Hypertrophic Cardiomyopathy: As with all vasodilators, lisinopril should be given with caution to patients with obstruction in the outflow tract of the left ventricle."

PRECAUTIONS, Drug Interactions [, Lisinopril]: A new subsection has been added: "Non-steroidal Anti-inflammatory Agents: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the coadministration of lisinopril may result in a further deterioration of renal function. These effects are usually reversible." The information formerly in the subsection "Indomethacin" now follows the above two sentences. The "Indomethacin" subheading has been deleted.

ADVERSE REACTIONS, [Lisinopril,] Special Senses: "taste disturbances" has been added.

OVERDOSAGE [, Lisinopril]: A cross-reference, "(See WARNINGS, Anaphylactoid reactions during membrane exposure.)" has been added.

NDA 18-998:
HOW SUPPLIED: Information on unit of use bottles of
has been deleted due to the discontinuation of production and sale of these items.

NDA 19-558
ADVERSE REACTIONS, Respiratory System: "eosinophilic pneumonitis" has been added.

NDA 19-778:
ADVERSE REACTIONS, Lisinopril, Respiratory: "eosinophilic pneumonitis" has been added.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in final printed labeling included in your January 21, 1999 submissions. Accordingly, the supplemental applications are approved effective on the date of this letter.

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

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
(301) 594-5334

Sincerely yours,

/S/ 2/17/99

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20507/S001

APPROVABLE LETTER

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Food and Drug Administration
Rockville MD 20857

OCT 28 1998

Merck Research Laboratories
Attention: Larry P. Bell, M.D.
Sumneytown Pike
West Point, PA 19486

Dear Dr. Bell:

Please refer to your supplemental new drug applications dated December 10, 1997, received December 12, 1997 submitted under section 505(b) 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), Prinzide (lisinopril/hydrochlorothiazide) Tablets (NDA 19-778), and Teczem (enalapril maleate/diltiazem maleate) Tablets (NDA 20-507).

We acknowledge receipt of your amendments dated May 20 and July 10, 1998.

The supplemental applications provide for draft labeling revised as follows:

NDA 18-998, 19-221, 19-309, and 20-507:
WARNINGS, Neutropenia/Agranulocytosis: The word referring to the number of cases of agranulocytosis reported, has been deleted from the third sentence.

NDA 18-998, 19-221, 19-309, 19-558, 19-778, and 20-507:
ADVERSE REACTIONS, Respiratory: "eosinophilic pneumonitis" has been added.

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PRECAUTIONS, General: A new subsection has been added: "Aortic Stenosis/Hypertrophic Cardiomyopathy: As with all vasodilators, [enalapril or lisinopril] should be given with caution to patients with obstruction in the outflow tract of the left ventricle."

PRECAUTIONS, Drug Interactions: A new subsection has been added: "Non-steroidal Anti-inflammatory Agents: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of [enalapril or lisinopril] may result in a further deterioration of renal function. These effects are usually reversible.

OVERDOSAGE: A cross-reference, "(See WARNINGS, Anaphylactoid reactions during membrane exposure.)" has been added.

NDA 19-558 and 19-778:
ADVERSE REACTIONS, Special Senses: "taste disturbances" has been added.

We have completed the review of these applications as submitted with draft labeling and they are approvable. Before the applications may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the draft labeling included in the December 10, 1997 submissions.

To each application, please submit 20 copies of the printed labels and other labeling, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

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

If you have any questions, please contact:

NDAs 18-998, 19-221, 19-309, 19-558, 19-778
Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
Telephone: (301) 594-5334

NDA 20-507
Mr. David Roeder
Regulatory Health Project Manager
Telephone: (301) 594-5313

Sincerely yours,

/S/ 10/28/97

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
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JAN -7 1998

Merck Research Laboratories
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Sumneytown Pike
West Point, PA 19486

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If you have any questions, please contact:

NDAs 18-998, 19-221, 19-309, 19-558, 19-778
Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
Telephone: (301) 594-5334

NDA 20-507
Mr. David Roeder
Regulatory Health Project Manager
Telephone: (301) 594-5313

Sincerely yours,

/S/ 11/7/97

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20507/S001

FINAL PRINTED LABELING

Prescribing Information as of February 1998

TECZEM®

(Enalapril Maleate/Diltiazem Malate Extended Release Tablets)

USE IN PREGNANCY

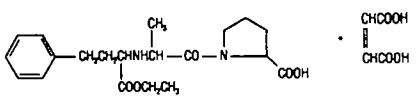
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, TECZEM should be discontinued as soon as possible. See WARNINGS, Pregnancy, Enalapril Maleate, Fetal/Neonatal/Morbidity and Mortality.

DESCRIPTION

TECZEM® (enalapril maleate/diltiazem malate extended release tablets) combines an angiotensin converting enzyme inhibitor, enalapril maleate, and a calcium ion influx inhibitor, diltiazem malate.

Enalapril maleate is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat.

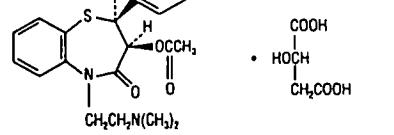
Enalapril maleate is chemically described as (*S*)-1-[*N*-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (*Z*)-2-butenedioate salt (1:1). Its empirical formula is $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$, and its structural formula is:



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.

Diltiazem malate is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem malate is described as (+)-(2*S*,3*S*)-5-[2-(Dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one acetate (ester), (*S*)-malate (1:1). Its empirical formula is $C_{22}H_{26}N_2O_4S \cdot C_4H_6O_5$ and the chemical structure is:



Diltiazem malate is a white to off-white crystalline powder and has a molecular weight of 548.61. It is moderately soluble in isotonic saline, water, and methanol, and slightly soluble in acetonitrile and ethanol.

TECZEM is formulated as a once-a-day extended release tablet containing 5 mg enalapril maleate and 219 mg diltiazem malate, which corresponds to a dose of 180 mg of diltiazem hydrochloride. In addition to the active ingredients, each TECZEM tablet contains the following inactive ingredients: cellulose acetates, hydroxypropylcellulose, hydroxypropylmethylcellulose, iron oxide (0.65 mg/tablet as elemental iron), magnesium stearate, polyethylene glycol, povidone, sodium bicarbonate, sodium hydrogen tartrate, stearic acid, sucrose, and titanium dioxide.

CLINICAL PHARMACOLOGY

The therapeutic effects of diltiazem are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle. Administration of enalapril maleate blocks the renin-angiotensin-aldosterone axis.

The antihypertensive effects of TECZEM have been evaluated principally from the results of three double-blind, placebo-controlled trials which randomized 1458 patients with mild to moderate hypertension. Enalapril doses studied in these three trials varied from 5 to 20 mg, once-a-day and diltiazem malate extended release tablet doses (expressed as hydrochloride equivalents) varied from 60 to 360 mg, once-a-day. Blood pressure reduction was significantly greater for TECZEM than for either of the components used alone.

Compared to placebo, the combination of enalapril (as an immediate release tablet) and diltiazem malate extended release tablets produced increasing reductions of blood pressure as the doses of each component increased. When enalapril 5 mg was combined with diltiazem doses ranging from 60 to 240 mg, the placebo-adjusted reductions of trough sitting systolic/diastolic blood pressure ranged from 4.5/3.6 to 11.8/7.1 mm Hg. In contrast, when enalapril 20 mg was combined with diltiazem doses ranging from 60 to 360 mg, the placebo-adjusted reductions of trough sitting systolic/diastolic blood pressure ranged from 8.5/7.7 to 13.2/10.6 mm Hg. Placebo-adjusted peak effects, measured 4 to 6 hours after dosing, were greater than those at trough, ranging from 11.3/8.3 to 19.8/15.3 mm Hg for sitting systolic/diastolic blood pressure. Standing systolic and diastolic blood pressures were similarly affected by combinations of enalapril and extended release diltiazem. These antihypertensive effects were sustained for 24 hours in most patients. In spite of substantial decreases in blood pressure, changes in pulse rate were generally not of clinical significance. In long-term therapy lasting up to one year, the antihypertensive effects were generally well-maintained on combination treatment.

Of 109 patients with severe hypertension (sitting diastolic blood pressure ≥ 115 mm Hg at the time of randomization) who were randomized to one of two treatment arms (enalapril 5 mg/diltiazem 120 mg or enalapril 5 mg/diltiazem 180 mg), the initial reductions from baseline in sitting systolic/diastolic blood pressure were 3.9/3.7 and 2.8/6.3 mm Hg, respectively. Following a doubling of the dose (to enalapril 10 mg/diltiazem 240 mg or enalapril 10 mg/diltiazem 360 mg) for patients whose blood pressures were not controlled, mean reductions from baseline in sitting systolic/diastolic blood pressures were 7.9/8.3 and 7.8/11.5 mm Hg, respectively. Overall, 24% of the patients were able to be maintained on the combination alone for the duration of the study (12 weeks), with an average reduction in sitting systolic/diastolic blood pressure of 15.0/16.3 mm Hg; the remaining patients required the addition of one or more antihypertensive agents.

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. The beneficial effects of enalapril in hypertension appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. Although the latter decrease is small, it results in small increases of serum potassium. In hypertensive patients treated with enalapril maleate alone for up to 48 weeks, mean increase in serum potassium of approximately 0.2 mEq/L was 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.

Pharmacokinetics and Metabolism: The pharmacokinetics of enalapril are not changed by the concurrent use of diltiazem. 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. (See WARNINGS.)

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. (See WARNINGS.) 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.

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.

Diltiazem Malate

Mechanism of Action: Diltiazem produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.

Hemodynamic and Electrophysiologic Effects: Like other calcium channel antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure in normotensive individuals, and in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. Such data have no predictive value with respect to effects in patients with poor ventricular function, and increased heart failure has been reported in patients with preexisting impairment of ventricular function. There are as yet few data on the interaction of diltiazem and beta-blockers in patients with poor ventricular function. Resting heart rate is usually slightly reduced by diltiazem.

Three placebo-controlled studies establish that diltiazem malate extended release tablets produce an antihypertensive effect both in the sitting and standing positions. In one trial (a placebo-controlled, parallel group, dose-ranging trial) the mean, trough reduction of sitting diastolic blood pressure was 3.2, 4.2, 3.6, and 7.6 mm Hg greater than placebo for the 120, 180, 240, and 480 mg once-daily diltiazem malate extended release tablet arms, respectively, and was sustained for 24 hours in most patients. Reduction of sitting diastolic blood pressure measured 4 to 6 hours after dosing, approximately peak effect, was 6.0, 6.3, 8.9, and 14.2 mm Hg greater than placebo for the 120, 180, 240, and 480 mg once-daily arms, respectively. Postural hypotension was infrequently noted upon suddenly assuming an upright position. The antihypertensive effect of diltiazem malate extended release tablets was sustained during long term therapy.

The antihypertensive effect of diltiazem malate extended release tablets was not significantly influenced by patient age or race; however, the antihypertensive effect was somewhat greater in females.

Diltiazem decreases vascular resistance, increases cardiac output (by increasing stroke volume), and produces a slight decrease or no change in heart rate. During dynamic exercise, increases in diastolic pressure are inhibited while maximum achievable systolic pressure is usually reduced. Chronic therapy with diltiazem produces no change or an increase in plasma catecholamines. No increased activity of the renin-angiotensin-aldosterone axis has been observed. Diltiazem reduces the renal and peripheral effects of angiotensin II. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in urinary sodium/potassium ratio.

Following administration of single oral doses of 300 mg diltiazem hydrochloride in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of diltiazem hydrochloride in patients in doses up to 540 mg/day has resulted in small increases in PR interval, and on occasion produces abnormal prolongation. (See WARNINGS.)

Pharmacokinetics and Metabolism: The pharmacokinetics of diltiazem are not changed by the concurrent use of enalapril. Diltiazem is well absorbed from the gastrointestinal tract and is subject to extensive first pass metabolism, giving a bioavailability, compared to intravenous administration of 40 - 50%. Following intravenous or oral administration of ^{14}C-diltiazem, approximately 71% of the radiolabel is excreted in urine and approximately 16% is excreted in feces.

Drugs that induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition.

Diltiazem is extensively metabolized with major metabolic pathways including deacetylation, N-demethylation, O-demethylation, and aromatic oxidation followed by conversion to glucuronide and sulfate conjugates. The major metabolites are N-desmethyldiltiazem (DMD) and desacetyldiltiazem (DAD), both of which are pharmacologically less active than diltiazem. Following oral doses of diltiazem, plasma concentrations of DAD or DMD are approximately 30% and 10%, respectively, of those for diltiazem. These metabolites are eliminated via biliary and urinary excretion. Less than 4% of a dose is excreted in urine as unchanged drug, and even smaller amounts in bile. Total radioactivity measurement following short intravenous administration in healthy volunteers suggests the presence of other unidentified metabolites which attain higher concentrations than those of diltiazem and are more slowly eliminated; apparent half-life of total radioactivity is about 20 hours compared to 2 to 5 hours for diltiazem. Diltiazem is 70 to 80% bound to plasma protein (α_1-acid glycoprotein and albumin) over the therapeutic range of plasma concentrations. In vitro studies have shown that therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin do not affect the protein binding of diltiazem.

Following oral administration of the extended release formulation of diltiazem malate, peak plasma concentrations of diltiazem increase with dose and occur an average of 9 to 16 hours after drug administration. Compared to the intravenous administration of 20 mg of diltiazem, diltiazem malate extended release tablets are approximately 40% bioavailable. Dose-dumping was not noted in any of the pharmacokinetic studies with diltiazem malate extended release tablets even when it was administered immediately following a high-fat breakfast.

Diltiazem malate extended release tablets, as other diltiazem preparations, exhibited non-linear pharmacokinetics. Steady state AUC, normalized for dose, showed increases of approximately 30% and 60% for the 240 and 360 mg, respectively, relative to the 120 mg dose. Additional non-linearity is anticipated at higher than 360 mg doses.

Mean AUC was slightly (approximately 16%) higher when diltiazem malate extended release tablets were given postprandially compared to fasting conditions. Release of diltiazem from diltiazem malate extended release tablets is dependent on gastrointestinal transit times. Release of 70% or more of diltiazem requires transit times of 10 hours or greater, shorter transit times result in proportionally less diltiazem released. A study in healthy elderly subjects (aged 65-77) showed an approximately 50% increase in mean AUC relative to young subjects following oral and intravenous administration due to slower elimination in the elderly. The bioavailability of diltiazem malate extended release tablets is unaffected by patient age.

INDICATIONS AND USAGE

TECZEM is indicated for the treatment of hypertension.

This fixed combination drug is not indicated for the initial therapy of hypertension. (See DOSAGE AND ADMINISTRATION.)

In using TECZEM, consideration should be given to the fact that an 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, Neutropenia/Agranulocytosis.)

In considering use of TECZEM, it should be noted that in controlled clinical trials, the addition of enalapril to a regimen of diltiazem had an effect on blood pressure that was notably less in black patients than in non-blacks. In addition, it should be noted that black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks. (See WARNINGS, Angioedema.)

CONTRAINDICATIONS

TECZEM is contraindicated in patients who are hypersensitive to any component of this product. Due to the enalapril component, TECZEM is contraindicated in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema. Due to the diltiazem component, TECZEM is also contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), and (4) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

General

Enalapril Maleate

Anaphylactoid and Possibly Related Reactions: Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including TECZEM) may be subject to a variety of adverse reactions, some of them serious.

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. This may occur at any time during treatment. In such cases TECZEM 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 INDICATIONS AND USAGE and CONTRAINDICATIONS.)

Anaphylactoid Reactions During Desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption (a procedure dependent upon devices not approved in the United States).

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with enalapril maleate alone. Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose or increase salt intake cautiously before initiating therapy with enalapril maleate in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of enalapril maleate, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of enalapril maleate or diuretic may be necessary.

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

Diltiazem Malate

Cardiac Conduction: Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second or third-degree AV block. Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

Congestive Heart Failure: Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Worsening of congestive heart failure has been reported in patients with pre-existing impairment of ventricular function. Experience with the use of diltiazem in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

Hypotension: Decreases in blood pressure associated with diltiazem therapy may occasionally result in symptomatic hypotension.

Acute Hepatic Injury: Mild elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been observed in clinical studies with diltiazem. Such elevations were usually transient and frequently resolved even with continued treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted after administration of diltiazem. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some. (See PRECAUTIONS).

Pregnancy

Enalapril-Diltiazem

There was no developmental toxicity in mice given up to 0.5/6 mg/kg/day of enalapril/diltiazem (approximately 3/0.9 times the maximum daily human dose of enalapril/diltiazem in the combination based on body weight, 0.25/0.079 times the maximum daily human dose based on body surface area) or in rats given up to 5/60 mg/kg/day of enalapril/diltiazem (approximately 30/9 times the maximum daily human dose of enalapril/diltiazem in the combination based on body weight, 5.7/1.6 times the maximum daily human dose based on body surface area). In rats given a high dose of 12.5/150 mg/kg/day of enalapril/diltiazem (83/22 times the maximum human dose of the combination based on body weight, 14.3/4 times the maximum daily human dose based on body surface area) there was a decrease in fetal weight, an increase in incidence of fetuses with visceral anomalies (thin diaphragm with protruding liver and dilated renal pelvis/ureter), and a decrease in pup survival. In mice given a high dose of 2.5/30 mg/kg/day of enalapril/diltiazem (17/4.5 times the maximum daily human dose of the combination based on body weight, 1.4/0.4 times the maximum daily human dose based on body surface area), there was an increase in post-implantation loss and a decrease in fetal weight.

When used in pregnant women during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, TECZEM 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 have 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 TECZEM 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 intra-amniotic environment.

If oligohydramnios is observed, TECZEM 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. Enalapril, 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 body surface area basis, the doses used were 57 times and 12 times, respectively, the maximum recommended human daily dose (MRHDD).

Diltiazem Malate

Reproduction studies have been conducted in mice, rats, and rabbits. Embryo and fetal lethality were observed in all three species, with doses of 200 or more mg diltiazem/kg/day in rats, 50 or more mg diltiazem/kg/day in mice, and 35 or more mg diltiazem/kg/day in rabbits. In rabbits and mice, these doses have also been associated with skeletal (primarily vertebral) malformations. On a mg/m^2 basis, these doses are similar to or lower than the maximum recommended human dose. Abnormalities of retina and tongue were associated with doses of 30 or more mg diltiazem/kg/day in a peri-post natal study in which only dead rat pups were examined for such anomalies. Prolonged gestation and dystocia leading to pup death/stillbirths occurred when rats were administered approximately 1.5 times (on a mg/m^2 basis) the daily recommended therapeutic dose immediately prior to, and throughout the period of parturition.

PRECAUTIONS

General

As with any other non-deformable material, caution should be used when administering TECZEM in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been reports of obstructive symptoms in patients with known strictures in association with the use of other non-deformable drug formulations.

Enalapril Maleate

Aortic Stenosis/Hypertrophic Cardiomyopathy: As with all vasodilators, enalapril should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

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.

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 hyper-

Administration of diltiazem hydrochloride concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area under the curve (53%) after a one-week course of cimetidine at 1,200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of diltiazem with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Cyclosporine: A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted, or discontinued. The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

Carbamazepine: Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40% to 72% increase) resulting in toxicity in some cases. Patients receiving these agents concomitantly should be monitored for a potential drug interaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Enalapril - Diltiazem

Carcinogenicity studies have not been conducted with enalapril in combination with diltiazem. Enalapril in combination with diltiazem was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril in combination with diltiazem 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. However, in an in vitro cytogenetics assay of enalapril in combination with diltiazem, increases in chromosomal aberrations were seen (including endoreduplication, a form of polyploidy), similar to increases seen when diltiazem malate was given alone. No evidence of impaired fertility was observed in studies in rats performed at oral dosages of 10/120 mg/kg/day of enalapril/diltiazem in females and 8/96 mg/kg/day in males. On a body surface area basis, these doses were 1/2.3 times and 9/2.5 times, respectively, the maximum recommended human daily dose. However, in the female fertility study a slight decrease in litter size due to preimplantation loss at 10/120 mg/kg/day was considered of uncertain relationship to treatment.

Enalapril Maleate

There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to male and female rats at doses up to 90 mg/kg/day or for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively. These doses are 26 times (in rats and female mice) and 13 times (in male mice) the maximum recommended human daily dose (MRHDD) when compared on a body surface area basis.

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 up to 90 mg/kg/day of enalapril (26 times the MRHDD when compared on a body surface area basis).

Diltiazem Malate

Oral administration of diltiazem hydrochloride to male and female rats for up to 104 weeks and to male mice for up to 92 weeks at doses up to 100 mg diltiazem/kg/day (approximately 2 and 1 times, respectively, the maximum recommended human dose (MRHD) of 480 mg/day on a mg/m² basis) revealed no evidence of a tumorigenic effect of diltiazem. In female mice receiving doses of 100 mg diltiazem/kg/day for 92 weeks, an increased incidence of benign ovarian granulosa cell tumor was observed. A similar effect was not apparent at doses as high as 200 mg diltiazem/kg/day administered for up to 78 weeks.

Diltiazem was negative in vitro for mutagenic effects in bacteria (Ames Test) and Chinese hamster lung cells and for induction of DNA strand breaks in rat hepatocytes (Alkaline Elution Assay). Diltiazem was also negative in vivo for chromosomal aberrations in mouse and Chinese hamster bone marrow, and for induction of micronuclei in Chinese hamster bone marrow. Diltiazem was, however, positive in vitro for induction of chromosomal aberrations in Chinese hamster ovary cells at concentrations approximately 500 times the human clinical plasma levels. No evidence of impaired fertility or reproductive performance was observed in studies in rats at doses of up to 30 mg/kg/day. However, decreased reproductive performance (mating) was observed at 100 mg/kg/day in studies in which males were treated at this dosage level.

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. Diltiazem is excreted in human milk. Concentrations of diltiazem in breast milk have been reported to approximate serum levels. If the use of TECZEM is deemed essential, an alternative method of infant feeding other than breast feeding should be instituted.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total number of patients who received enalapril maleate/diltiazem malate extended release tablets in clinical studies, 18% were 65 or older. Overall differences in effectiveness or safety were not observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Enalapril maleate/diltiazem malate combinations, including TECZEM, have been evaluated for safety in more than 1950 patients, including over 350 patients treated for one year or more. In clinical trials with enalapril maleate/diltiazem malate combinations, including TECZEM, no adverse experiences peculiar to this combination drug have been reported. Adverse experiences reported have been limited to those that have been previously reported with enalapril or diltiazem.

Generally, adverse experiences were mild and transient in nature. Discontinuation rates for adverse experiences reported in controlled trials were similar for enalapril maleate/diltiazem malate combinations, including TECZEM, and placebo-treated patients. All clinical adverse experiences, whether drug related or not, reported in greater than one percent of patients treated with enalapril maleate/diltiazem malate combinations, including TECZEM (in total daily doses up to 20 mg/360 mg, respectively), in controlled clinical trials, and the corresponding incidence of drug-related clinical adverse experiences, are shown below.

PERCENT OF PATIENTS IN CONTROLLED TRIALS

Body System Adverse Experience	All Adverse Experiences		Drug-Related Adverse Experiences*	
	Enalapril/Diltiazem Including TECZEM (N=1283) Incidence %	Placebo (N=260) Incidence %	Enalapril/Diltiazem Including TECZEM (N=1283) Incidence %	Placebo (N=260) Incidence %
Nervous				
Headache	7.2	13.5	2.7	4.6
Dizziness	3.2	3.5	1.9	1.2
Body as a Whole				
Edema/Swelling	3.4	4.6	2.3	2.3
Asthenia/Fatigue	3.0	2.3	2.0	0.4
Chest Pain	1.6	2.7	0.5	0.0
[illegible]	1.2	1.2	0.5	0.4

kalemia 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 enalapril. (See Drug Interactions.)

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with the use of ACE inhibitors, always resolving 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.

Diltiazem Malate

Diltiazem is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic changes. In dogs, sporadic and occasionally transient elevations of transaminase values occurred in a one-year oral toxicity study at doses of 10 to 20 mg/kg/day.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of diltiazem. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported with diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Information for Patients

Patients should be instructed to take TECZEM tablets whole and not to break, crush, or chew the tablets. Patients should also be instructed not to be concerned if they notice something in their stool that looks like a tablet. In TECZEM, the diltiazem component is contained within a nonabsorbable shell that has been specially designed to slowly release drug for the patient's body to absorb. When this process is completed, the empty tablet is eliminated from the body.

Angioedema: Angioedema, including laryngeal edema, may occur at any time during treatment with angiotensin converting enzyme inhibitors, including 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 TECZEM 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).

Non-steroidal Anti-Inflammatory Agents: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of enalapril may result in a further deterioration of renal function. These effects are usually reversible.

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.

Diltiazem Malate

Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with diltiazem. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of diltiazem with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Especially in patients with renal and/or hepatic impairment, dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, may require adjustment when starting or stopping concomitantly administered diltiazem to maintain optimum therapeutic blood levels.

The following interactions have been seen with diltiazem hydrochloride and can be anticipated to occur with the diltiazem malate salt.

Beta-blockers: Clinical trials with diltiazem suggest that concomitant use of diltiazem and beta-blockers is usually well-tolerated, but available data are not sufficient to predict the effects of concomitant treatment with beta-blockers in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Abdominal Pain	1.2	---	---	---
Respiratory				
Upper Respiratory Infection	5.4	7.3	0.0	0.0
Cough	3.4	2.3	2.3	0.4
Sinusitis	1.2	3.1	0.0	0.4
Influenza	1.2	1.2	0.0	0.0
Skin				
Rash	2.0	1.5	1.3	0.4
Digestive				
Diarrhea	2.1	2.3	0.5	0.8
Nausea	1.5	2.3	0.6	0.0
Musculoskeletal				
Back Pain	1.1	3.5	0.1	0.0

*Considered possibly, probably, or definitely related to study drug by investigators.

Clinical adverse experiences, regardless of drug relationship, reported in 0.5 to 1.0 percent of patients in controlled trials included: **Cardiovascular:** First-degree AV block; palpitation; **Digestive:** Constipation, dental infection, dental pain; **Musculoskeletal:** Joint swelling; **Nervous System/Psychiatric:** Depression, insomnia, somnolence, **Respiratory:** Bronchitis, nasal congestion, pharyngitis, sinus disorder; **Skin:** Flushing; **Urogenital:** Impotence

Clinical Laboratory Test Findings

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were reported infrequently. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit occurred infrequently in hypertensive patients treated with enalapril maleate/diltiazem malate combinations but were rarely of clinical importance unless another cause of anemia coexisted. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Other: In controlled clinical trials minor increases in serum potassium, alanine transaminase, aspartate transaminase, alkaline phosphatase, and/or bilirubin, and minor decreases in serum sodium, generally reversible upon discontinuation, were reported. (See WARNINGS and PRECAUTIONS.)

Other adverse experiences, regardless of drug relationship, that have been reported in clinical trials or postmarketing experience with the individual components include the following and they should be considered as potential adverse reactions for TECZEM.

Enalapril Maleate–Body as a Whole: Anaphylactoid reaction (See WARNINGS), orthostatic effects, symptoms suggestive of facial edema or angioedema (see WARNINGS), syncope; **Cardiovascular:** Angina pectoris; atrial fibrillation; cardiac arrest; hypotension; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, Hypotension); orthostatic hypotension; pulmonary edema; pulmonary embolism and infarction; rhythm disturbances including atrial tachycardia and bradycardia; **Digestive:** Anorexia, dry mouth, dyspepsia, glossitis, hepatic failure, hepatitis (hepatocellular (proven on rechallenge) or cholestatic jaundice) (See WARNINGS, Hepatic Failure), ileus, melena, pancreatitis, stomatitis, vomiting; **Hematologic:** Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril cannot be excluded. Rare cases of neutropenia, thrombocytopenia and bone marrow depression; **Musculoskeletal:** Muscle cramps; **Nervous System/Psychiatric:** Ataxia, confusion, nervousness, peripheral neuropathy (eg, paresthesia, dysesthesia), vertigo; **Respiratory:** Asthma, bronchospasm, dyspnea, pneumonia, pulmonary infiltrates, eosinophilic pneumonitis, rhinorrhea, sore throat and hoarseness; **Skin:** Alopecia, diaphoresis, erythema multiforme, exfoliative dermatitis, herpes zoster, pemphigus, photosensitivity, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria; **Special Senses:** Anosmia, blurred vision, conjunctivitis, dry eyes, taste alteration, tearing, tinnitus; **Urogenital:** Flank pain, gynecomastia, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), renal failure, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving enalapril, with an incidence higher in black than in non-black patients. Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with TECZEM should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

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.

Diltiazem Malate or Other Formulations of Diltiazem–Body as a Whole: Facial edema, fever, flu-like illness, orthostatic effects, pain, syncope, vasovagal reaction; **Cardiovascular:** Angina, arrhythmia, atrial fibrillation, AV block-second degree, AV block-third degree, bundle branch block, congestive heart failure, ECG abnormality, heart murmur, hypotension, myocardial infarction (not readily distinguishable from the natural history of the disease of the patients receiving diltiazem), myocardial ischemia, sinus bradycardia, tachycardia, ventricular extrasystoles; **Digestive:** Acid regurgitation, anorexia, dry mouth, dysgeusia, dyspepsia, flatulence, gingival hyperplasia, thirst, tongue edema, vomiting, weight gain; **Hematologic:** Hemolytic anemia, increased bleeding time, leukopenia, thrombocytopenia; **Metabolic:** Hyperglycemia, hyperuricemia, hypokalemia, increased creatine phosphokinase; **Musculoskeletal:** Arthralgia, foot pain, gout, knee pain, muscle cramp, osteoarticular pain, shoulder pain, stiffness, strain; **Nervous System/Psychiatric:** Abnormal dreams, amnesia, decreased libido, extrapyramidal symptoms, gait abnormalities, hallucinations, hypoesthesia, migraine, muscle weakness, nervousness, paresthesia, personality changes, tremor; **Respiratory:** Allergic rhinitis, dyspnea, epistaxis, pharyngeal edema; **Skin:** Alopecia, erythema multiforme, exfoliative dermatitis, leukocytoclastic vasculitis, petechiae, photosensitivity, pruritus, purpura, urticaria; **Special Senses:** Amblyopia, eye infection, eye irritation, eyelid edema, otitis media, retinopathy, tinnitus; **Urogenital:** Flank pain, hematuria, nocturia, polyuria, proteinuria, pyuria, sexual difficulties, urinary frequency, urinary tract infection.

OVERDOSAGE

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

Enalapril Maleate

Limited data are available in regard to overdosage of enalapril maleate in humans. The oral LD_{50} of enalapril is 2000 mg/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. Enalaprilat may be removed from general circulation by hemodialysis and has been removed from neonatal circulation by peritoneal dialysis. (See WARNINGS, Anaphylactoid reactions during membrane exposure.)

Diltiazem Malate

The oral LD_{50}'s of diltiazem malate in mice and rats range from 424 to 554 mg/kg and from 736 to 844 mg/kg, respectively. The intravenous LD_{50}'s in these species ranged from 40.6 to 44.1 and 39.9 to 40.2 mg/kg, respectively. The LD_{50}'s of the hydrochloride salt of diltiazem in mice and rats were comparable to that of the malate salt. The LD_{50} of the hydrochloride salt of diltiazem in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg.

The toxic dose in man is not known. Due to extensive metabolism, blood levels after a standard dose of diltiazem can vary over tenfold, limiting the usefulness of blood levels in overdose cases. There have been several reports of diltiazem hydrochloride overdose in doses ranging up to 10.8g. In the majority of the cases, patients recovered from the reported overdose. In the few cases with a fatal outcome, multiple drug ingestions were usually involved. No specific information is available on overdose in humans with diltiazem malate.

Events observed following diltiazem overdose included bradycardia, hypotension, heart block, and cardiac failure. Most reports of overdose described some supportive medical measure and/or drug treatment. Bradycardia frequently responded favorably to atropine as did heart block, although cardiac pacing was also frequently utilized to treat heart block. Fluids and vasopressors were used to maintain blood pressure, and in cases of cardiac failure, inotropic agents were administered. In addition, some patients received treatment with ventilatory support, gastric lavage, activated charcoal, GI0/or intravenous calcium. Evidence of the effectiveness of intravenous calcium administration to reverse the pharmacological effects of calcium channel blockers overdose was conflicting.

In the event of overdose or exaggerated response, appropriate supportive measures should be employed in addition to gastrointestinal decontamination. Diltiazem does not appear to be removed by peritoneal or hemodialysis. Based on the known pharmacological effects of diltiazem and/or reported clinical experience, the following measures may be considered:

Bradycardia: Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously

High-Degree AV Block: Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.

Cardiac Failure: Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.

Hypotension: Vasopressors (eg, dopamine or levarterenol bitartrate)

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

DOSAGE AND ADMINISTRATION

The recommended initial dose of enalapril maleate for hypertension in patients not receiving diuretics is 5 mg once a day. The usual dosage range of enalapril maleate for hypertension is 10 - 40 mg per day administered in a single dose or two divided doses. In some patients treated once daily with enalapril, 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. The recommended usual dosage range of controlled-release formulations of diltiazem for hypertension is 120 to 540 mg, once-a-day.

In clinical trials of enalapril maleate/diltiazem malate controlled release formulation, administered once daily, the antihypertensive effect of the combination generally increased as the dose of each ingredient was increased. In the combination trials, the doses studied were 1.25 to 20 mg of enalapril maleate and 60 to 360 mg of diltiazem malate (dosage expressed as diltiazem hydrochloride).

The adverse events (see WARNINGS and ADVERSE REACTIONS) of enalapril are generally independent of dose; those of diltiazem are a mixture of dose-dependent phenomena (primarily dizziness, AV block, sinus bradycardia, and to a lesser extent peripheral edema) and dose-independent phenomena, the former much more common than the latter. Therapy with any combination of enalapril and diltiazem will thus be associated with both sets of dose-independent adverse events.

Rarely, the dose independent adverse events associated with enalapril or diltiazem are serious.

To minimize dose independent adverse events, it is usually appropriate to begin therapy with TECZEM only after (a) a patient has failed to achieve the desired antihypertensive effect with one or the other monotherapy (see above) or (b) the dose of one or the other monotherapy cannot be increased further because of dose limiting side effects.

Replacement Therapy: For convenience, patients receiving enalapril and diltiazem as separate dosage forms may instead wish to receive tablets of TECZEM containing the same component doses.

Use in Renal Impairment: The usual regimens of therapy with TECZEM need not be adjusted as long as the patient's creatinine clearance is >30 mL/min/1.73m² (serum creatinine approximately ≤3 mg/dL or 265 µmol/L). In patients with more severe renal impairment, i.e., creatinine clearance ≤30 mL/min/1.73m² (serum creatinine >3 mg/dL or 265 µmol/L), titration of the individual components must be done prior to switching to TECZEM. (See PRECAUTIONS, Enalapril Maleate; Impaired Renal Function.)

HOW SUPPLIED

TECZEM
(Enalapril Maleate/Diltiazem Malate Extended Release Tablets)

Strength	Quantity	NDC Number	Description
5 mg enalapril maleate/180 mg diltiazem malate*	100 unit of use bottle (with desiccant)	0088-1765-47	Gold-hued, film-coated, capsule-shaped, extended release tablets coded TECZEM 5/180.

*Expressed as the corresponding diltiazem hydrochloride doses. (See DESCRIPTION.)

Storage: Store in a well-closed container at room temperature, 15-30°C (59-86°F). Protect from moisture.

Prescribing Information as of February 1998

Manufactured by:
Merck & Co., Inc.
West Point, PA 19486 USA
for
Hoechst Marion Roussel, Inc.
Kansas City, MO 64137 USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20507/S001

MEDICAL REVIEW(S)

LONGLOVANNE

SEP 23 1998

Division of Cardio-Renal Drug Products
Medical Officer Review

cc: 19-221/S-025
19-309/S-022
19-775/S-029
20-507/S-001
HFD-110 (all)
HFD-110/D Roeder

Name of Drug: Vasotec® Tablets (Enalapril Maleate).

NDA 18-998 (S-029)

Reviewer: Abraham Karkowsky, M.D., Ph.D

/S/

Date: September 17, 1998

Type of Review: Modification of Labeling to include PRECAUTIONS on the use of vasodilators in patients with aortic stenosis.

Summary:

Merck requested that a Precaution should be added about the use of Vasotec® in patients with Aortic Stenosis. In support of this request, Merck submitted eight publications as well as the U.S circulars for Capoten®, Norvasc®, Cardene® and Adalat®. Dr. Ganley who reviewed the same submission makes the point that the labeling for use in patients with aortic stenosis not only differs in exact wording but appears in different parts of the labeling under PRECAUTIONS, WARNINGS or CONTRAINDICATION with the different drugs.

None of the eight publications[1] contained data from controlled clinical studies. None were case studies in patients who had aortic stenosis and were treated with vasodilators. All were review articles.

The are several theoretical concerns why the use of afterload reducers in patients with aortic stenosis may be harmful. These concerns may be summarized as follows. As a result of vasodilatation, blood pools peripherally, venous return decreases and cardiac preload is compromised, leading to an overall decrease in cardiac output. A second putative mechanism for harm is that vasodilatation may result in inhomogeneous redistribution of blood flow, with a critical decrease in blood flow to either the coronary or cerebral circulations.

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[1] Cantley, PM, Hardwick,DJ and Norris CA. Stand-alone Doppler echocardiography in the assessment of elderly patients with possible aortic stenosis. *Cardiology in the Elderly* 3 (3); Jun 1995; p. 213-16.

Churchwell, AL. Indications for Surgical Treatment of Aortic Stenosis. *Heart Disease and Stroke* 3(6) ; Nov-Dec 1994 p.351-54.

Hess,OM, Vilari,B and Krayenbuehl, HP. Diastolic Dysfunction in Aortic Stenosis. *Circulation* 87 (5); May 1993; IV 73-76.

Opie, LH. Fundamental Role of Angiotensin-Converting Enzyme Inhibitors in the Management of congestive Heart Failure. *American Journal of Cardiology* 75(16); Jun 16 1995; p. 3F-6F.

Resnakov,L. Aortic Valve stenosis: Management in Children and Adults. *Postgrad. Med.* 93(6); May 1 1993; p. 107-10, 113-14, 117-22.

Swedberg, K and Sharpe N. The Value of Angiotensin Converting Enzyme Inhibitors for the Treatment of Patients with Left Ventricular Dysfunction, Heart Failure or After Acute Myocardial Infarction. *European Heart Journal* 17(9); Sept 1996; p 1306-11

Braunwald, E. Valvular Heart Disease In: *Heart Disease: A Textbook of Cardiovascular Medicine.*4th ed. Philadelphia: WBSaunders, 1992: 1035-43.

Fuster, Vshub,C Guiliani, ER, McGoon, DC. Acquired Valvular Heart Disease. In: Brandenburg, RO, Fuster, V, Guiliani, ER Mcgoon DC, ed. Cardiology: *Fundamentals and Practice.* Chicago Year Book Medical Publishers, 1987: 1271-88.

It seems counterintuitive, given the relative lack of data specific for any one of the vasodilators, that their labeling should differ. The position and wording of any Precautions should be the same.

Excluding vasodilators in patients with aortic stenosis is not necessarily a conservative tact to take. A broad cautionary statement would likely limit the use of these drugs, even where these drugs were known to have a positive morbidity or mortality outcome for patients whose concurrent underlying medical conditions is amenable to treatment with afterload reducers.

A recent article[2] questions whether the use of ACE-inhibitors in a patient population with aortic stenosis is harmful. Two published case series are cited[3],[4]. In the first (Martinez –Sanchez et al.), there were a total of 22 patients with a mean aortic gradient of 93 mm Hg. Patients were given modest doses of Captopril (12.5 mg x1 dose then 8 mg id for 48 hours). In the second study (Grace et al.,) eight patients with a range of aortic gradients of 64-96 mm Hg were given low doses of Captopril (6.25 mg then 12.5 mg tid). These subjects were monitored hemodynamically. In neither of the two patient series were any subjects acutely harmed by the initial dosing with Captopril. Contrary to expectation, cardiac output increased substantially (41%) in the Martinez-Sanchez series. Six of the eight patients enrolled in the Grace et al., series, averaged a 21% increase in cardiac output (the other two subjects apparently had no change in cardiac output). Any comfort from the two series must be tempered by the fact that the series were small, unblinded and uncontrolled.

The authors of the *Lancet* article queried the Committee on Safety of Medicines in the United Kingdom and medical advisors of pharmaceutical companies, which produce ACE-inhibitors. They found no cases of ACE-inhibitor related hypotenisve reactions in patients with aortic stenosis.

Mr. Mike Johnston of REB queried our SRS/AER of adverse outcomes in patients treated with ACE-inhibitors who had aortic stenosis. The query was, however, limited to those patients whose aortic stenosis was listed under adverse events. The search system could not sort the data base by concurrent medical problems. Nevertheless, ten reports were pulled.

1. This was an 83 y/o male with a history of CHF was being treated with Lisinopril as part of the ATLAS trial and had a syncopal episode. The duration of exposure to Lisinopril is not stated. Concurrent medications include Trombyl, Zyloric, Impugan, Zaroxylyn, Lancrist, Suscard. Aortic Stenosis is listed as part of the adverse events
2. This was a 67 y/o male with a history of CHF who was treated with Lisinopril for 8 months as part of the ATLAS study who died suddenly. Concurrent medication included Digitoxin, Furosemide, Verapamil and Warfarin sodium.
3. This was a 67 y/o male with a history of CHF, ischemic heart disease, myocardial infarction and carcinoma of the bladder. The patient was treated for approximately 2 years with Lisinopril. The patient developed severe left ventricular dysfunction with aortic stenosis and died. Concurrent medication included Aspirin, Diltiazem, Frusemide, Glyceryl trinitrate, and isosorbide dinitrate .
4. This was a 94 year old female with a history of aortic valve disease, acute cor pulmonale, cataracts and osteoporosis. The patient apparently went into renal failure and developed hypotension and pulmonary edema. The event occurred on the same day as Lisinopril was started. It is, however, unclear if the event occurred as a result of Lisinopril treatment or the Lisinopril treatment was started to reduce afterload, and treat the pulmonary edema. The relationship of Lisinopril to the event was considered as suspect, but imputed as doubtful by

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[2] Cox, NLT, Abdul-Hamid, AR, Mulley, GP. *Lancet* 352 111-12, 1998.

[3] Martinez-Sanchez,C, Henne, O, Areco,A. et al., Hemodynamic Effects of Oral Captopril in Patients with Severe Aortic Stenosis. *Arch Inst Cardiol. Mex*, 1996, 66: 322-30

[4] Grace,AA, Brooks, NH, Schofield, PM, Beneficial Effects of Angiotensin Converting Enzyme Inhibitors in Severe Symptomatic Stenosis. *Eur. Heart J* 1991: 12 (suppl) 129 (abstr).

the French Method of Imputability. Concurrent medication also included furosemide, amoxacillin trihydrate, KCl and Cethexonium chloride.

5. This was an 80 year old white male patient with a history of emphysema, diabetes mellitus, heart disease, heart failure, MI, renal disease, CABG, hypertension and cardiovascular disease. This subject had previously taken Accupril during a phase IV study that started 6/94. The patient voluntarily discontinued therapy on 11/96. On 5 Nov 1996(it is unclear if this was after the patient stopped taking Accupril) the patient suffered a non-transmural MI. Marked aortic stenosis and low EF < 0.2 as well as cardiac hypokinesis and akenesis were noted on ECHO. The patient was discharged, only to be shortly readmitted. This patient died approximately 1 month later of what appears to be worsening CHF. Concomitant medications include Alupent, Azmacort, Cardiazem Colchicine, Cozaar and Insulin.
6. Unstated age and gender patient took Accupril . The adverse event was listed as left ventricular hypertrophy and aortic regurgitation. A follow up report indicates the patient was a 65 year old female. The adverse event was not regurgitation, but cough.
7. This was a 75 year old female had decease in renal function in response to Accupril 10 mg. The MedWatch report does not suggest that the patient had aortic stenosis but aortic insufficiency.
8. This was a 69 year old male. The event was abdominal aortic occlusion. The patient did not apparently have aortic valvular stenosis.
9. This was an elderly female who had pre-existing aortic stenosis. After Capoten, the valvular function decreased.
10. This was a 68 year old male with a history of depression, aortic valve stenosis, hypertension and gastric ulcer. The patient was started on Enalapril 2.5 mg daily and titrated to 5 mg daily. The aortic stenosis worsened shortly after the start of the Enalalrpil (within the month), and he underwent aortic valve prosthesis placement. the patient had a GI bleed during

In summary, the published data is far from convincing either in establishing a safe profile or an alarming adverse outcomes for the use of afterload reducers in patients with aortic stenosis. The spontaneous adverse events reports are poorly documented with an unknown denominator. Several of these reports, however, are not inconsistent with the theoretical risks outlined by the sponsor.

I would like to propose the following labeling under PRECAUTIONS:

In patients with aortic stenosis, the potential benefit of treatment should be balanced against the theoretical risks of diminished cardiac output as well as compromised coronary and cerebral perfusion. Caution should be exercised in the use of _____, particularly, in patient with critical or flow-limited aortic stenosis.

An alternate suggestion would be to truncate the above:

Caution should be exercised in the use of _____, particularly, in patient with critical or flow-limited aortic stenosis.

cc NDA 19-998
CSO
File

/S/

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20507/S001

ADMINISTRATIVE DOCUMENTS

FEB 17 1999

RHPM Review of Labeling

NDA: 18-998/S-057 Vasotec (enalapril maleate) Tablets
19-221/S-025 Vaseretic (enalapril maleate/HCTZ) Tablets
19-309/S-022 Vasotec (enalaprilat) I.V.
19-558/S-036 Prinivil (lisinopril) Tablets
19-778/S-029 Prinzide (lisinopril/HCTZ) Tablets
20-507/S-001 Teczem (enalapril maleate/diltiazem maleate) Tablets

Date of submissions: January 21, 1999 (AF)

Date of receipt: January 25, 1999

Applicant: Merck Research Laboratories

Background: On September 19, 1997, we issued a supplement request letter to Merck, recommending that the ADVERSE REACTIONS section of the package inserts of ACE-inhibitor products be revised to include eosinophilic pneumonitis.

On May 20, 1997, I called Larry Bell, M.D.'s office and, based on Dr. Ganley's May 14, 1997 MOR of a D report to NDA 18-998 dated April 16, 1997, asked that the word be deleted from the sentence,

in the WARNINGS, Neutropenia/Agranulocytosis subsection of the labeling for enalapril-containing products.

Merck responded with labeling supplements dated December 10, 1997. They amended these supplements with documents dated May 20 and July 10, 1998, providing requested information to support the PRECAUTIONS, Aortic Stenosis/Hypertrophic Cardiomyopathy statement. We issued an approvable letter on October 28, 1998, asking for final printed labeling identical to the draft labeling included in the December 10, 1997 submission.

Review: Merck has submitted final printed labeling revised as follows:

NDA 18-998, 19-221, 19-309, and 20-507:

CONTRAINDICATIONS: The phrase "and in patients with hereditary or idiopathic angioedema" has been added to the first sentence.

WARNINGS, Neutropenia/Agranulocytosis: The word ' referring to the number of cases of agranulocytosis reported, has been deleted from the third sentence.

PRECAUTIONS, General [, Enalapril Maleate]: A new subsection has been added: "Aortic Stenosis/Hypertrophic Cardiomyopathy: As with all vasodilators, enalapril should be given with caution to patients with obstruction in the outflow tract of the left ventricle."

PRECAUTIONS, Drug Interactions [, Enalapril Maleate]: A new subsection has been added: "Non-steroidal Anti-inflammatory Agents: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the coadministration of enalapril may result in a further deterioration of renal function. These effects are usually reversible."

ADVERSE REACTIONS, [Enalapril Maleate,] Respiratory: "eosinophilic pneumonitis" has been added.

OVERDOSAGE [, Enalapril Maleate]: A cross-reference, "(See WARNINGS, Anaphylactoid reactions during membrane exposure.)" has been added.

NDA 19-558 and 19-778:
CONTRAINDICATIONS: The phrase "and in patients with hereditary or idiopathic angioedema" has been added to the first sentence.

PRECAUTIONS, General [, Lisinopril]: A new subsection has been added: "Aortic Stenosis/Hypertrophic Cardiomyopathy: As with all vasodilators, lisinopril should be given with caution to patients with obstruction in the outflow tract of the left ventricle."

PRECAUTIONS, Drug Interactions [, Lisinopril]: A new subsection has been added: "Non-steroidal Anti-inflammatory Agents: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the coadministration of lisinopril may result in a further deterioration of renal function. These effects are usually reversible." The information formerly in the subsection "Indomethacin" now follows the above two sentences. The "Indomethacin" subheading has been deleted.

ADVERSE REACTIONS, [Lisinopril,] Special Senses: "taste disturbances" has been added.

OVERDOSAGE [, Lisinopril]: A cross-reference, "(See WARNINGS, Anaphylactoid reactions during membrane exposure.)" has been added.

NDA 18-998:
HOW SUPPLIED: Information on unit of use bottles of
. has been deleted due to the discontinuation of production and sale of these items.

NDA 19-558
ADVERSE REACTIONS, Respiratory System: "eosinophilic pneumonitis" has been added.

NDA 19-778:
ADVERSE REACTIONS, Lisinopril, Respiratory: "eosinophilic pneumonitis" has been added.

Recommendation: I will prepare an approval letter for these supplements for Dr. Lipicky's signature. These supplements fall under 21 CFR 314.70 (c) Supplements for changes that may be made before FDA approval.

/S/

Kathleen F. Bongiovanni

2-1-99

cc: 18-998/S-057
19-221/S-025
19-309/S-022
19-558/S-036
19-778/S-029
HFD-110 (all)
HFD-110/KBongiovanni
HFD-110/DRoeder
HFD-110/SBenton
HF-2/MedWatch
kb/2/1/99.

OCT 28 1998

RHPM Review of Labeling

NDA: 18-998/S-057 Vasotec (enalapril maleate) Tablets
19-221/S-025 Vaseretic (enalapril maleate/HCTZ) Tablets
19-309/S-022 Vasotec (enalaprilat) I.V.
19-558/S-036 Prinivil (lisinopril) Tablets
19-778/S-029 Prinzide (lisinopril/HCTZ) Tablets
20-507/S-001 Teczem (enalapril maleate/diltiazem maleate) Tablets

Dates of submissions: December 10, 1997, May 20, 1998, and July 10, 1998

Dates of receipt: December 12, 1997, May 22, 1998, and July 13, 1998

Applicant: Merck Research Laboratories

Background: On May 20, 1997, I called Larry Bell, M.D.'s office and, based on Dr. Ganley's May 14, 1997 MOR of a D report to NDA 18-998 dated April 16, 1997, asked that the word be deleted from the sentence

in

the WARNINGS, Neutropenia/Agranulocytosis subsection of the labeling for enalapril-containing products.

On September 19, 1997, we issued a supplement request letter to Merck, recommending that the ADVERSE REACTIONS section of the package inserts of ACE inhibitor products be revised to include eosinophilic pneumonitis.

Merck responded with these supplements, dated December 10, 1997. We issued an approvable letter on January 7, 1998.

At an internal meeting on April 4, 1998, to discuss whether some recent labeling revisions to ACE inhibitors should be requested of other members of the class, Drs. Lipicky, Fenichel, and Karkowsky wanted additional information about why Merck had requested one of the changes included in the supplements for which we had issued the January 7, 1998 approvable letter - the addition of "PRECAUTIONS, General, Aortic Stenosis/Hypertrophic Cardiomyopathy: As with all vasodilators, [enalapril or lisinopril] should be given with caution to patients with obstruction in the outflow tract of the left ventricle."

On April 6, 1998: I called Larry Bell at Merck and asked him to send in the support for the statement on Aortic Stenosis. Merck responded with submissions dated May 20, 1998, that include only package inserts for other products and journal articles..

On June 19, 1998: I called Jeff White to ask for more specific support for the inclusion of the statements in the enalapril/lisinopril labeling, or revised labeling. Merck responded with submissions dated July 10, 1998, that included the same journal articles that were included in the May 20, 1998 submissions, but the firm highlighted the language that supports their position.

Dr. Karkowsky reviewed the submissions (MOR dated September 23, 1998) and proposed the following wording:

> PRECAUTIONS, General, Aortic Stenosis/Hypertrophic Cardiomyopathy:
> "In patients with aortic stenosis, the potential benefit of treatment should be balanced against the theoretical risks of diminished cardiac output as well as compromised coronary and cerebral perfusion. Caution should be exercised in the use of ____, particularly in patients with critical or flow-limited aortic stenosis." Or
>
> "Caution should be exercised in the use of ____, particularly in patients with critical or flow-limited aortic stenosis."

Dr. Ganley recommended that we ask the firm to include the first of Dr. Karkowsky's proposals.

Dr. Lipicky reviewed Dr. Karkowsky's MOR on October 21, 1998, and wrote, "The data cited above deny the mechanism stated. I would not put the expanded statement in labelling." He said he would allow them to have the statement they originally proposed.

Review: I will draft a second approvable letter, asking for final printed labeling identical to the draft labeling included in the December 10, 1997 submission:

<u>NDA 18-998, 19-221, 19-309, and 20-507:</u>
WARNINGS, Neutropenia/Agranulocytosis: The word referring to the number of cases of agranulocytosis reported, has been deleted from the third sentence.

<u>NDA 18-998, 19-221, 19-309, 19-558, 19-778, and 20-507:</u>
ADVERSE REACTIONS, Respiratory: "eosinophilic pneumonitis" has been added.

CONTRAINDICATIONS: The phrase "and in patients with hereditary or idiopathic angioedema" has been added.

PRECAUTIONS, Drug Interactions: A new subsection has been added: "Non-steroidal Anti-inflammatory Agents: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of enalapril/lisinopril may result in a further deterioration of renal function. These effects are usually reversible."

OVERDOSAGE: A cross-reference, "(See WARNINGS, Anaphylactoid reactions during membrane exposure.)" has been added.

<u>NDA 19-558 and 19-778:</u>
ADVERSE REACTIONS, Special Senses: "taste disturbances" has been added.

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

/S/

Kathleen F. Bongiovanni

10-21-98

cc: 18-998/S-057
19-221/S-025
19-309/S-022
19-558/S-036
19-778/S-029
HFD-110 (all)
HFD-110/KBongiovanni
HFD-110/DRoeder
HFD-110/SBenton
HF-2/MedWatch

kb/10/21/98.

JAN -7 1998

RHPM Review of Labeling

NDA: 18-998/S-057 Vasotec (enalapril maleate) Tablets
19-221/S-025 Vaseretic (enalapril maleate/HCTZ) Tablets
19-309/S-022 Vasotec (enalaprilat) I.V.
19-558/S-036 Prinivil (lisinopril) Tablets
19-778/S-029 Prinzide (lisinopril/HCTZ) Tablets
20-507/S-001 Teczem (enalapril maleate/diltiazem maleate) Tablets

Date of submissions: December 10, 1997

Date of receipt: December 12, 1997

Applicant: Merck Research Laboratories

Background: On September 19, 1997, we issued a supplement request letter to Merck, recommending that the ADVERSE REACTIONS section of the package inserts of ACE inhibitor products be revised to include eosinophilic pneumonitis.

On May 20, 1997, I called Larry Bell, M.D.'s office and, based on Dr. Ganley's May 14, 1997 MOR of a D report to NDA 18-998 dated April 16, 1997, asked that the word be deleted from the sentence in the WARNINGS, Neutropenia/Agranulocytosis subsection of the labeling for enalapril-containing products.

Review: Merck has submitted draft labeling with the following revisions:

NDA 18-998, 19-221, 19-309, and 20-507:
WARNINGS, Neutropenia/Agranulocytosis: The word referring to the number of cases of agranulocytosis reported, has been deleted from the third sentence.

NDA 18-998, 19-221, 19-309, 19-558, 19-778, and 20-507:
ADVERSE REACTIONS, Respiratory: "eosinophilic pneumonitis" has been added.

CONTRAINDICATIONS: The phrase "and in patients with hereditary or idiopathic angioedema" has been added.

PRECAUTIONS, General: A new subsection has been added: "Aortic Stenosis/Hypertrophic Cardiomyopathy: As with all vasodilators, [enalapril or lisinopril] should be given with caution to patients with obstruction in the outflow tract of the left ventricle."

PRECAUTIONS, Drug Interactions: A new subsection has been added: "Non-steroidal Anti-inflammatory Agents: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of enalapril may result in a further deterioration of renal function. These effects are usually reversible.

OVERDOSAGE: A cross-reference, "(See WARNINGS, Anaphylactoid reactions during membrane

exposure.)" has been added.

NDA 19-558 and 19-778:
ADVERSE REACTIONS, Special Senses: "taste disturbances" has been added.

Recommendation: I will prepare an approvable letter for these supplements since the firm has chosen to submit draft, rather than final printed, labeling. They fall under 21 CFR 314.70 (c) Supplements for changes that may be made before FDA approval.

/S/

Kathleen F. Bongiovanni 12-22-97

cc: 18-998/S-057
19-221/S-025
19-309/S-022
19-558/S-036
19-778/S-029
HFD-110 (all)
HFD-110/KBongiovanni
HFD-110/DRoeder
HFD-110/SBenton
HF-2/MedWatch
kb/12/22/97.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20507/S001

CORRESPONDENCE

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Jeffery R. White, M.D.
Director
Regulatory Affairs

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January 21, 1999

Raymond J. Lipicky, M.D. - Director
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HFD-110, Room 16B-45
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5600 Fishers Lane
Rockville, Maryland 20857

ORIGINAL

MERCK
Research Laboratories

NDA SUPP AMEND
SLR-001
(AF)

NDA 20-507/S-001: TECZAM™ Tablets
(Enalapril Maleate/Diltiazim Maleate)
Final Printed Labeling

Dear Dr. Lipicky:

Reference is made to the Supplemental New Drug Application for 20-507/S-001 TECZAM™ Tablets dated December 10, 1997 and to the Agency's approvable letter dated October 28, 1998.

With this submission, we are providing 20 copies of the printed circular (Attachment 1). A mock-up of the circular, annotated for revisions is provided in Attachment 2.

The circular has been revised as outlined in the FDA Approvable Letter dated 28-October-98 under **CONTRAINDICATIONS; WARNINGS, General, Enalapril Maleate, Neutropenia/Agranulocytosis; PRECAUTIONS, General, Enalapril Maleate; PRECAUTIONS, Drug Interactions, Enalapril Maleate; ADVERSE REACTIONS, Enalapril Maleate, Respiratory;** and **OVERDOSAGE, Enalapril Maleate.**

Please direct questions or need for additional information to Jeffery R. White, M.D. (610/397-3180) or, in my absence, Larry P. Bell, M.D. (610/397-2310).

Sincerely yours,

Larry P Bell
by

Jeffery R. White, M.D.
Director
Regulatory Affairs

Certified P 967 671 233.

Q:SELIGA/GINNY/LETTERS/NDA20507

ORIGINAL

Jeffery R. White, M.D.
Director
Regulatory Affairs

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November 9, 1998

MERCK
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Office of Drug Evaluation I (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUPPL NEW CORRESP
(SNC to S-001)

NDA 20-507/S-001: TECZAM™ Tablets
(Enalapril Maleate/Diltiazim Maleate)

Dear Dr. Lipicky:

Reference is made to the Supplemental New Drug Application for 20-507/S-001 TECZAM™ Tablets dated December 10, 1997 and to the Agency's approvable letter dated October 28, 1998.

With this letter, we wish to notify you of our intent to amend this supplement.

Please direct questions or need for additional information to Jeffery R. White, M.D. (610/397-3180) or, in my absence, Larry P. Bell, M.D. (610/397-2310).

Sincerely yours,

Jeffery R. White, M.D.
Director
Regulatory Affairs

LPB

Certified P 967 683 890

Q:SELIGA/GINNY/LETTERS/NDA20507

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Larry P. Bell, M.D.
Senior Director
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July 10, 1998

MERCK Research Laboratories
CENTER DRUG
REC'D
JUL 13 1998
HFD-110
EVALUATION AND RESEARCH

Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products
HFD-110, Room 16B-45
Office of Drug Evaluation I (CDER)
Food and Drug Administration
Rockville, MD 20857

SUPPL AMEND
SLR-001
(BL)

Dear Dr. Lipicky:

NDA 20-507/S-001: TECZEM® (Enalapril Maleate/Diltiazem Malate ER Tablets)

Reference is made to the above reference Supplemental New Drug Application NDA 20-507 for Tablets TECZEM® submitted on December 10, 1997, to the Approvable Letter on January 8, 1998 and to the submission of supportive documentation on May 20, 1998. This documentation was requested by the Agency in support of the precaution statement regarding "Aortic Stenosis" under the **PRECAUTIONS** section of the packaging circular. Reference is also made to a telephone conversation on June 22, 1998 between Dr. Jeffrey White, (MRL) and Ms. Kathleen Bongiovanni (FDA) requesting clarification relating to the supportive documentation provided in the May 20, 1998 submission.

Specifically, the Agency requested that MRL provide an explanation of the physiologic basis for concern in the use of ACE Inhibitors is the setting of aortic stenosis and that we specify where to find the precise language in the submitted references that support our position.

By copy of this letter, we are providing the requested information. It should be noted that supportive documentation provided in the attached Tabs 1 and 2 is the exact documentation that was provided in the May 20, 1998 submission, however the documents have been highlighted to direct the Agency to precise language that supports our position.

Questions concerning this supplemental application should be directed to Larry P. Bell, M.D. (610-397-2310) or, in my absence, to Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely,

Jeffrey White for

Larry P. Bell, M.D.
Senior Director
Regulatory Affairs

Attachments
Federal Express #1
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Larry P. Bell, M.D.
Senior Director
Regulatory Affairs

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NDA SUPPL #S
SLR-001 (AL)

Merck & Co., Inc.
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May 20, 1998

MERCK
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Raymond J. Lipicky, M.D., Director
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Office of Drug Evaluation I (CDER)
Food and Drug Administration
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 2 2 1998
HFD-110

Dear Dr. Lipicky:

NDA 20-507/S-001: TABLETS TECZEM®

Reference is made to the above reference Supplemental New Drug Application NDA 20-507 for Tablets TECZEM® submitted on December 10, 1997 and to the Approvable Letter on January 8, 1998. Reference is also made to a telephone conversation on April 4, 1998 between to Dr. Larry Bell, (MRL) and Ms. Kathleen Bongiovanni (FDA) requesting additional supportive documentation in support of the precaution statement regarding "Aortic Stenosis" under the **PRECAUTIONS** section of the packaging circular.

By copy of this letter, we are providing the requested supportive documentation as follows:

- Tab 1 - Circulars for CAPOTEN® Tablets, NORVASC® Tablets, CARDENE® Capsules and ADALAT® Capsules
- Tab 2 - Supportive Journal Articles

Questions concerning this supplemental application should be directed to Larry P. Bell, M.D. (610-397-2310) or, in my absence, to Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely,

Larry P. Bell, M.D.
Senior Director
Regulatory Affairs

Attachments

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Larry P. Bell, M.D.
Senior Director
Regulatory Affairs

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December 10, 1997

MERCK
Research Laboratories

Raymond J. Lipicky, M.D., Director
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Office of Drug Evaluation I (CDER)
Food and Drug Administration
Rockville, MD 20857

NDA NO. 20-507 REF. NO. 021
NDA SUPPL FOR SLR

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 12 1997
HFD-110

Dear Dr. Lipicky:

NDA 20-507: TABLETS TECZEM® (Enalapril Maleate/Diltiazem ER)
Supplemental New Drug Application
Draft Labeling for Prior Approval

Reference is made to a request from September 19, 1997 letter from the Food and Administration (FDA) to Dr. Larry Bell, Merck Research Laboratories recommending that the ADVERSE REACTIONS section of the package inserts of ACE inhibitor products be revised to include eosinophilic pneumonitis. With this letter, Merck Research Laboratories (MRL) is submitting revisions to the circular for NDA 20-507, Tablets TECZEM® (enalapril maleate).

The circular for Tablets TECZEM® has been revised under **ADVERSE REACTIONS** to include "eosinophilic pneumonitis" in response to the FDA letter of September 19, 1997 and under **WARNINGS, Neutropenia/Agranulocytosis**, to delete the word in response to a verbal FDA request on May 20, 1997.

In addition, we have included the following revisions we plan to submit as Changes Being Effected at the next revised printing of the label:

- Revision of the statement to include a contraindication in patients with hereditary or idiopathic angioedema, based on published literature.

- Addition of a new subheader *"Aortic Stenosis/Hypertrophic Cardiomyopathy"* and statement regarding caution in administering enalapril to patients with obstruction in the outflow tract of the left ventricle, based on published literature.

- Addition of new subheader *"Non-steroidal Anti-inflammatory Agents"* and text regarding the co-administration of enalapril with non-steroidal anti-inflammatory drugs, based on published literature.

- Addition of a cross-reference to the PRECAUTIONS section regarding high-flux dialysis membranes, for completeness.

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All revisions are outlined in the attached Summary of Revisions and appear under the following sections of the circular: **CONTRAINDICATIONS; PRECAUTIONS, General; PRECAUTIONS, Drug Interactions;** and **OVERDOSAGE.**

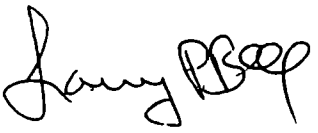
Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act and in accordance with *21 CFR 314.70(b)*, we submit, for your approval, a supplement to NDA 20-507. As indicated on the attached Form 356h, this supplemental application provides for changes in Item 4.c.i. of the approved New Drug Application for NDA 20-507, Tablets TECZEM®. In accordance with the Prescription Drug User Fee Act of 1992, as indicated on the attached Form 3397, no fee is required for this supplemental application.

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a (k) (1)], we hereby certify that, in connection with this application, Merck & Co. Inc. did not and will not use in any capacity the services of any person debarred under subsections 306 (a) or (b) of the Act.

We consider the filing of this Supplemental New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this supplemental application should be directed to Larry P. Bell, M.D. (610-397-2310) or, in my absence, to Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely,



Larry P. Bell, M.D.
Senior Director, Regulatory Affairs

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Attachments: Summary of Revisions
Annotated Circular

Certified No. P 914 177 720

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January 16, 1998

SUPPL NEW CORRESP
(SAME TO S-001)

MERCK
Research Laboratories

Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products
HFD-110, Room 16B-45
Office of Drug Evaluation I (CDER)
Food and Drug Administration
Rockville, MD 20857

Dear Dr. Lipicky:

NDA 18-998/S-057: VASOTEC® Tablets (Enalapril Maleate)
NDA 19-221/S-025: VASERETIC® Tablets (Enalapril Maleate/Hydrochlorothiazide)
NDA 19-309/S-022: VASOTEC® I.V. (Enalaprilat)
NDA 19-558/S-036: PRINIVIL® Tablets (Lisinopril)
NDA 19-778/S-029: PRINZIDE Tablets (Lisinopril/Hydrochlorothiazide)
NDA 20-507/S-001: TECZEM® Tablets (Enalapril Maleate/Diltiazem Maleate)
General Correspondence: Intent to File Amendment

Please refer to the above-referenced Supplemental New Drug Applications submitted by Merck Research Laboratories (MRL) on October 20, 1997 and to the Agency's approvable letter dated January 7, 1998.

In accordance with 21 CFR 314.110, the purpose of this letter is to notify the Agency of our intent to file an amendment to these supplemental applications.

Questions concerning this information should be directed to Larry P. Bell, M.D. (610-397-2310) or, in my absence, to Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely,

Larry P. Bell, M.D.
Senior Director, Regulatory Affairs

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Official Copies: File NDA 18-998, HFD-110 (2 copies)
File NDA 19-221, HFD-110 (2 Copies)
File NDA 19-309, HFD-110 (2 Copies)
File NDA 19-558, HFD-110 (2 Copies)
File NDA 19-778, HFD-110 (2 Copies)
File NDA 20-507, HFD-110 (2 Copies)

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