

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-909

APPROVAL LETTER

OCT 15 2001

Dr. Reddy's Laboratories Inc.
Attention: C. Jeanne Taborsky
U.S. Agent for: Dr. Reddy's Laboratories Limited
One Park Way
Upper Saddle River, NJ 07458

Dear Madam:

This is in reference to your abbreviated new drug application dated June 16, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Enalapril Maleate and Hydrochlorothiazide Tablets USP, 5 mg/12.5 mg and 10 mg/25 mg.

Reference is also made to your amendments dated September 20, 2000, and September 11, and September 28, 2001.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Enalapril Maleate and Hydrochlorothiazide Tablets USP, 5 mg/12.5 mg and 10 mg/25 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Vaseretic[®] Tablets, 5 mg/12.5 mg and 10 mg/25 mg, respectively, of Merck Research Laboratories, Division of Merck Co. Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy, which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,



Gary Buehler 10/15/01
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-909

APPROVED DRAFT LABELING

ENALAPRIL MALEATE AND HYDROCHLOROTHIAZIDE TABLETS, USP

Issued: September 2001

Rx Only

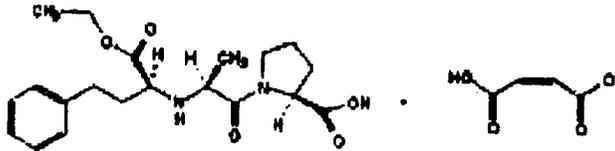
USE IN PREGNANCY

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, enalapril maleate and hydrochlorothiazide tablets should be discontinued as soon as possible. See WARNINGS, Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Enalapril maleate-hydrochlorothiazide combines an angiotensin converting enzyme inhibitor, enalapril maleate, and a diuretic, hydrochlorothiazide.

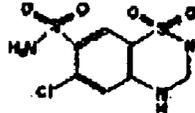
Enalapril maleate is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat. Enalapril maleate is chemically described as 1-[(S)-1-Carboxy-3-phenylpropyl]-L-alanyl]-L-proline 1'-ethyl ester, maleate (1:1). Its molecular formula is $C_{20}H_{28}N_2O_6 \cdot C_8H_8O_4$ and its structural formula is:



Enalapril maleate is a white to off-white crystalline powder with a molecular weight of 492.53. It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol.

Enalapril is a pro-drug; following oral administration, it is bioactivated by hydrolysis of the ethyl ester to enalaprilat, which is the active angiotensin converting enzyme inhibitor.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiazine-7-sulfonamide 1,1-dioxide. Its molecular formula is $C_7H_8ClN_2O_4S_2$ and its structural formula is:



It is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

Enalapril maleate and hydrochlorothiazide tablets are available in two tablet combinations: Enalapril maleate and hydrochlorothiazide tablets 5 mg/12.5 mg, containing 5 mg enalapril maleate and 12.5 mg hydrochlorothiazide and Enalapril maleate and hydrochlorothiazide tablets 10 mg/25 mg, containing 10 mg enalapril maleate and 25 mg hydrochlorothiazide. Inactive ingredients are: lactose monohydrate, pregelatinized starch, starch (corn starch), zinc stearate, and purified water.

CLINICAL PHARMACOLOGY

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

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

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

Enalapril Maleate

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

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

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

Pharmacokinetics and Metabolism: Following oral administration of enalapril maleate, peak serum concentrations of enalapril occur within about one hour. Based on urinary recovery, the extent of absorption of enalapril is approximately 60 percent. Enalapril absorption is not influenced by the presence of food in the gastrointestinal tract. Following absorption, enalapril is hydrolyzed to enalaprilat, which is a more potent angiotensin converting enzyme inhibitor than enalapril; enalaprilat is poorly absorbed when administered orally. Peak serum concentrations of enalaprilat occur three to four hours after an oral dose of enalapril maleate. Excretion of enalaprilat and enalapril is primarily renal. Approximately 94 percent of the dose is recovered in the urine and feces as enalaprilat or enalapril. The principal components in urine are enalaprilat, accounting for about 40 percent of the dose, and intact enalapril. There is no evidence of metabolites of enalapril, other than enalaprilat.

The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently representing a small fraction of the administered dose that has been bound to ACE. The amount bound does not increase with dose, indicating a saturable site of binding. The effective half-life for accumulation of enalaprilat following multiple doses of enalapril maleate is 11 hours.

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

Studies in dogs indicate that enalapril crosses the blood-brain barrier poorly, if at all; enalaprilat does not enter the brain. Multiple doses of enalapril maleate in rats do not result in accumulation in any tissues. Milk of lactating

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

Pharmacodynamics: Administration of enalapril maleate to patients with hypertension of severity ranging from mild to severe results in a reduction of both supine and standing blood pressure usually with no orthostatic component. Symptomatic postural hypotension is infrequent with enalapril alone but it can be anticipated in volume-depleted patients, such as patients treated with diuretics. In clinical trials with enalapril and hydrochlorothiazide administered concurrently, syncope occurred in 1.3 percent of patients. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

In most patients studied, after oral administration of a single dose of enalapril maleate, onset of antihypertensive activity was seen at one hour with peak reduction of blood pressure achieved by four to six hours.

At recommended doses, antihypertensive effects of enalapril maleate monotherapy have been maintained for at least 24 hours. In some patients the effects may diminish toward the end of the dosing interval; this was less frequently observed with concomitant administration of enalapril maleate and hydrochlorothiazide.

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

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

In hemodynamic studies in patients with essential hypertension, blood pressure reduction produced by enalapril was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. Following administration of enalapril maleate, there is an increase in renal blood flow; glomerular filtration rate is usually unchanged. The effects appear to be similar in patients with renovascular hypertension.

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

Hydrochlorothiazide

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure. Hydrochlorothiazide is a diuretic and antihypertensive. It affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. After oral use diuresis begins within two hours, peaks in about four hours and lasts about 8 to 12 hours. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

INDICATIONS AND USAGE

Enalapril maleate and hydrochlorothiazide tablets are indicated for the treatment of hypertension.

These fixed dose combinations are not indicated for initial treatment (see DOSAGE AND ADMINISTRATION).

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

In considering use of Enalapril maleate and hydrochlorothiazide tablets, 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

Enalapril maleate and hydrochlorothiazide tablets are contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

General

Enalapril Maleate

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

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

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

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 enalapril maleate and hydrochlorothiazide tablets) 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 enalapril maleate and hydrochlorothiazide tablets 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.

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.

Hydrochlorothiazide

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

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

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

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

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

Pregnancy

Enalapril Maleate-Hydrochlorothiazide

There was no teratogenicity in mice given up to 30 mg/kg/day or in rats given up to 90 mg/kg/day of enalapril in combination with 10 mg/kg/day of hydrochlorothiazide. These doses of enalapril are 4.3 and 28 times (mice and rats, respectively) the maximum recommended human daily dose (MRHDD) when compared on a body surface area basis (mg/m²); the dose of hydrochlorothiazide is 0.8 times (in mice) and 1.6 times (in rats) the MRHDD. At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses; 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

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

Enalapril Maleate

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

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

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

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

If oligohydramnios is observed, enalapril maleate and hydrochlorothiazide tablets 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.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.
Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions, Enalapril Maleate and Hydrochlorothiazide*).

Pregnancy

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There was no teratogenicity in mice given up to 30 mg/kg/day or in rats given up to 90 mg/kg/day of enalapril in combination with 10 mg/kg/day of hydrochlorothiazide. These doses of enalapril are 4.3 and 26 times (mice and rats, respectively) the maximum recommended human daily dose (MRHDD) when compared on a body surface area basis (mg/m²); the dose of hydrochlorothiazide is 0.8 times (in mice) and 1.8 times (in rats) the MRHDD. At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses; 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

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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 MRHDD.

Hydrochlorothiazide

Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg/kg/day, respectively, provided no evidence of harm to the fetus. These doses are more than 150 times the MRHDD on a body surface area basis. Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions that have occurred in adults.

PRECAUTIONS

General

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 hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See *Drug Interactions*.)

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in 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.

Hydrochlorothiazide

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine

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electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

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

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

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

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

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required.

Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

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

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

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

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

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

Information for Patients

Angioedema: Angioedema, including laryngeal edema, may occur 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 enalapril maleate and hydrochlorothiazide tablets 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 coadministration 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, nifedipine, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

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

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

Hydrochlorothiazide

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

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

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

Other antihypertensive drugs — additive effect or potentiation.

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

Corticosteroids, ACTH — intensified electrolyte depletion, particularly hypokalemia.

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

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

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

Non-steroidal Anti-inflammatory Drugs — In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when enalapril maleate and hydrochlorothiazide tablets and non-steroidal

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Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Enalapril Maleate

There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to 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* cytogenetic study using mouse bone marrow.

There were no adverse effects on reproductive performance of 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).

Hydrochlorothiazide

Two year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice at doses up to approximately 800 mg/kg/day (53 times the MRHDD when compared on a body surface area basis) or in male and female rats at doses up to approximately 100 mg/kg/day (18 times the MRHDD when compared on a body surface area basis). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

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

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation. In mice and rats these doses are 9 times and 0.7 times, respectively, the MRHDD when compared on a body surface area basis.

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, enalaprilat, and hydrochlorothiazide have been detected in human breast milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue enalapril maleate and hydrochlorothiazide tablets, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Enalapril maleate and hydrochlorothiazide tablets has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with enalapril maleate and hydrochlorothiazide tablets no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

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

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

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

Angioedema: Angioedema has been reported in patients receiving enalapril maleate and hydrochlorothiazide tablets, 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 enalapril maleate and hydrochlorothiazide tablets should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, Cough.

Clinical Laboratory Test Findings

Serum Electrolytes: See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with enalapril maleate and hydrochlorothiazide tablets. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with enalapril maleate and hydrochlorothiazide tablets but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

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

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

Enalapril Maleate — Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with enalapril maleate and hydrochlorothiazide tablets. However, since enalapril has been marketed, the following adverse reactions have been reported: *Body As A Whole*: Anaphylactoid reactions (see WARNINGS, *Anaphylactoid reactions during membrane exposure*); *Cardiovascular*: Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; hypotension; angina pectoris, Raynaud's phenomenon; *Digestive*: Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice) (see WARNINGS, *Hepatic Failure*), melena, anorexia, glossitis, stomatitis, dry mouth; *Hematologic*: Rare cases of neutropenia, thrombocytopenia and bone marrow depression. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril cannot be excluded. *Nervous System/Psychiatric*: Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia), dream abnormality; *Urogenital*: Renal failure, oliguria, renal dysfunction, (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), flank pain, gynecomastia; *Respiratory*: Pulmonary infiltrates, eosinophilic pneumonitis, bronchoepasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection; *Skin*: Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pemphigus, alopecia, flushing, photosensitivity; *Special Senses*: Blurred vision, taste alteration, anemia, conjunctivitis, dry eyes, tearing.

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

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

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

OVERDOSAGE

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

Enalapril Maleate — Single oral doses of enalapril above 1,000 mg/kg and $\geq 1,775$ mg/kg were associated with lethality in mice and rats, respectively. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. Enalapril 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*.)

Hydrochlorothiazide — Lethality was not observed after administration of an oral dose of 10 g/kg to mice and rats. The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

DOSAGE AND ADMINISTRATION

Enalapril and hydrochlorothiazide are effective treatments for hypertension. The usual dosage range of enalapril is 10 to 40 mg per day administered in a single or two divided doses; hydrochlorothiazide is effective in doses of 12.5 to 50 mg daily. The side effects (see WARNINGS) of enalapril are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former much more common than the latter. Therapy with any combination of enalapril and hydrochlorothiazide will be associated with both sets of dose-independent side effects but the addition of enalapril in clinical trials blunted the hypokalemia normally associated with hydrochlorothiazide. The combination of enalapril and hydrochlorothiazide is more effective than either drug alone in the treatment of hypertension.

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

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Dose Titration Guided by Clinical Effect: A patient whose blood pressure is not adequately controlled with either enalapril or hydrochlorothiazide monotherapy may be given enalapril maleate and hydrochlorothiazide tablets 5 mg/12.5 mg or enalapril maleate and hydrochlorothiazide tablets 10 mg/25 mg. Further increases of enalapril, hydrochlorothiazide or both depend on clinical response. The hydrochlorothiazide dose should generally not be increased until 2-3 weeks have elapsed. In general, patients do not require doses in excess of 20 mg of enalapril or 50 mg of hydrochlorothiazide. The daily dosage should not exceed four tablets of enalapril maleate and hydrochlorothiazide tablets 5 mg/12.5 mg or two tablets of enalapril maleate and hydrochlorothiazide tablets 10 mg/25 mg.

Replacement Therapy: The combination may be substituted for the titrated components.

Use in Renal Impairment: The usual regimens of therapy with enalapril maleate and hydrochlorothiazide tablets 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 μ mol/L). In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so enalapril maleate-hydrochlorothiazide is not recommended (see WARNINGS, *Anaphylactoid reactions during membrane exposure*).

Use in Elderly: Clinical studies of enalapril maleate and hydrochlorothiazide tablets did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

HOW SUPPLIED

Enalapril maleate and hydrochlorothiazide tablets 5 mg/12.5 mg are white, uncoated, round, compressed tablets, coded C133 on one side. Each tablet contains 5 mg of enalapril maleate and 12.5 mg of hydrochlorothiazide. They are supplied as follows:

NDC 49884-686-01 bottles of 100 (with desiccant).

NDC 49884-686-10 bottles of 1000 (with desiccant).

Enalapril maleate and hydrochlorothiazide tablets 10 mg/25 mg are white, uncoated, round, compressed tablets, coded C134 on one side. Each tablet contains 10 mg of enalapril maleate and 25 mg of hydrochlorothiazide. They are supplied as follows:

NDC 49884-687-01 bottles of 100 (with desiccant).

NDC 49884-687-10 bottles of 1000 (with desiccant).

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

Dispense in a well-closed container as defined in the USP, if product package is subdivided.

Manufactured by:
Dr. Reddy's Laboratories Limited
Bachepalli - 502 325 INDIA

Manufactured for:
Par Pharmaceutical, Inc.
Spring Valley, NY 10977 USA

Container Label: 100's count

110-913

PAR

NDC 49884-687-01

**ENALAPRIL MALEATE AND
HYDROCHLOROTHIAZIDE**

TABLETS, USP

10 mg/25 mg

Rx only

100 TABLETS

Each tablet contains:
Enalapril Maleate, USP 10 mg
Hydrochlorothiazide, USP 25 mg

USUAL ADULT DOSAGE:
See accompanying product literature.

**KEEP THIS AND ALL DRUGS OUT OF
REACH OF CHILDREN.**

Bottle contains desiccant.
Keep container tightly closed.
This is a bulk package and not intended
for dispensing.
Dispense in a well-closed container as
defined in the USP.

PROTECT FROM MOISTURE
Store below 30°C (86°F) and avoid
exposure to excessive heat above 40°C (104°F).

Control No.:
Exp. Date:
Tablet Imprint:
1001

APPROVED
OCT 15 2001

Manufactured in India by
Dr. Reddy's Laboratories Limited
Bachampally, Andhra Pradesh
500002, India

Par Pharmaceutical, Inc.
Spring Valley, NY 10977 USA



PAR

NDC 49884-687-01

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Bottle contains desiccant.
Keep container tightly closed.
This is a bulk package and not intended
for dispensing.
Dispense in a well-closed container as
defined in the USP.

PROTECT FROM MOISTURE
Store below 30°C (86°F) and avoid
exposure to excessive heat above 40°C (104°F).

Control No.:
Exp. Date:
Tablet Imprint:
1001

APPROVED
OCT 15 2001

Manufactured in India by
Dr. Reddy's Laboratories Limited
Bachampally, Andhra Pradesh
500002, India

Par Pharmaceutical, Inc.
Spring Valley, NY 10977 USA



- Black
- 315 Blue
- 428 Grey
- 185 Red

Container Label: 1000's count

PAR

NDC 49884-687-10

**ENALAPRIL MALEATE AND
HYDROCHLOROTHIAZIDE
TABLETS, USP**

10 mg/25 mg

Rx only

1000 TABLETS

Each tablet contains:
Enalapril Maleate, USP 10 mg
Hydrochlorothiazide, USP 25 mg

USUAL ADULT DOSAGE:
See accompanying product literature.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Bottle contains desiccant.
Keep container tightly closed.
This is a bulk package and not intended for dispensing.
Dispense in a well-sealed container as defined in the USP.

PROTECT FROM MOISTURE
Store below 30°C (86°F) and avoid excursions temperatures above 50°C (122°F).

Control No.:
Exp. Date:
Tablet #87
10001

APPROVED

OCT 15 2007

Manufactured in India by
Dr. Reddy's Laboratories Limited,
Bangalore - 562 388 INDIA

For
Par Pharmaceutical, Inc.,
Spring Valley, NY 10977 USA



- Black
- 315 Blue
- 428 Grey
- 185 Red

PAR

NDC 49884-687-10

**ENALAPRIL MALEATE AND
HYDROCHLOROTHIAZIDE
TABLETS, USP**

10 mg/25 mg

Rx only

1000 TABLETS

Each tablet contains:
Enalapril Maleate, USP 10 mg
Hydrochlorothiazide, USP 25 mg

USUAL ADULT DOSAGE:
See accompanying product literature.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Bottle contains desiccant.
Keep container tightly closed.
This is a bulk package and not intended for dispensing.
Dispense in a well-sealed container as defined in the USP.

PROTECT FROM MOISTURE
Store below 30°C (86°F) and avoid excursions temperatures above 50°C (122°F).

Control No.:
Exp. Date:
Tablet #87
10001

APPROVED

OCT 15 2007

Manufactured in India by
Dr. Reddy's Laboratories Limited,
Bangalore - 562 388 INDIA

For
Par Pharmaceutical, Inc.,
Spring Valley, NY 10977 USA



**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

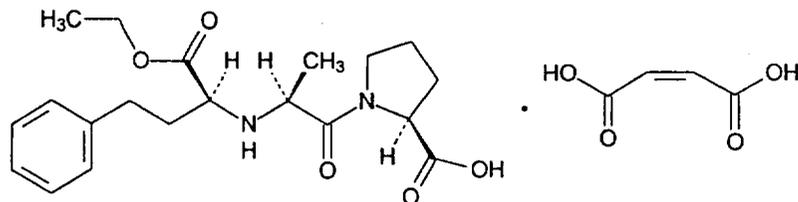
75-909

CHEMISTRY REVIEW(S)

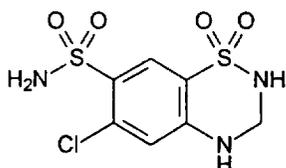
1. CHEMISTRY REVIEW NO.: 3
2. ANDA: 75-909
3. NAME AND ADDRESS OF APPLICANT:
Reddy-Cheminor, Inc.
Attention: Paul V. Campanelli
U.S. Agent for: Dr. Reddy's Laboratories Limited
66 South Maple Avenue
Ridgewood, NJ 07450
Telephone: (201)-444-4424
Facsimile: (201)-444-1456
4. LEGAL BASIS FOR SUBMISSION: See Chemistry Review #1
5. SUPPLEMENTS: N/A
6. PROPRIETARY NAME: N/A
7. NONPROPRIETARY NAME:
Enalapril Maleate and Hydrochlorothiazide Tablets USP
8. SUPPLEMENTS PROVIDE FOR: N/A
9. AMENDMENTS AND OTHER DATES:
Original Submission: June 16, 2000
Amendment: September 20, 2000
Amendment: January 16, 2001
Amendment: March 28, 2001
Amendment: September 11, 2001
Amendment: September 26, 2001
Amendment: September 28, 2001
10. PHARMACOLOGICAL CATEGORY: Treatment of Hypertension
11. OTC/R_x: R_x
12. RELATED IND/NDA/DMF(s): See DMF Checklist
13. DOSAGE FORM: Tablet
14. POTENCY: Enalapril Maleate/Hydrochlorothiazide at
5 mg/12.5 mg and 10 mg/25 mg strengths

15. CHEMICAL NAME AND STRUCTURE:

Enalapril Maleate (Antihypertensive): L-Proline, 1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-, (S)-, (Z)-2-butenedioate (1:1). $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$. MW = 492.53. CAS# 76095-16-4.



Hydrochlorothiazide (Diuretic): 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-1,1-dioxide. $C_7H_8ClN_3O_4S_2$. MW = 297.75. CAS# 58-93-5.



16. RECORDS AND REPORTS: N/A

17. COMMENTS: Cheminor Drugs Limited (original applicant) has merged with Dr. Reddy's Laboratories. As of 1/2/01 the applicant is known as Dr. Reddy's Laboratories Limited.

The address and all other information remain the same. Documents have been filed to change the Registration Number and Labeler code to that of Dr. Reddy's Laboratories Limited.

On September 26, 2001, the firm requested expedited review of the ANDA, based upon the deletion of an exclusivity provision from the Orange Book.

The Labeling Review is acceptable is draft.

18. CONCLUSIONS AND RECOMMENDATIONS: **Approvable**

19. REVIEWER: ARaw

DATE COMPLETED: 10/01/01

Page(s) 14

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

Chem Rev. 3

10/1/01

JUL 27 2001

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-909 APPLICANT: Dr. Reddy's Laboratories Limited

DRUG PRODUCT: Enalapril Maleate and Hydrochlorothiazide
Tablets USP, 5 mg/12.5 mg and 10 mg/25 mg

The deficiencies presented below represent FAX deficiencies.

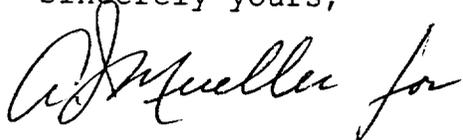
A. Chemistry Deficiencies:

1. Please submit an chromatogram at low attenuation for Enalapril Maleate USP (Batch RE0061) using your revised method (Related Substances). Please include a blank run and label all known and unknown impurities in your test sample.
2. Please provide a commitment that the maximum holding time for your drug product in the bulk container shall not be greater than 30 days. Otherwise we request that you provide room temperature stability data to justify a longer storage period.
3. In regard to your : impurity, we note that your accelerated and room temperature stability data do not indicate that this impurity is a viable degradant in your drug product formulation. Therefore your proposed drug product release and stability limits for this impurity should be no higher than the proposed limit for this impurity in the drug substance
4. Please revise your release and stability specifications for impurities in the drug product to specify "Total Impurities" rather than "Sum of Enalaprilat, Enalapril and other Related Compounds".
5. We note that your updated room temperature stability data reflect your original stability specifications. Please provide updated stability data, which reflect your revised stability specifications (individual limits for enalaprilat, enalapril and unknown individual impurities). If possible, please resubmit the accelerated stability data previously acquired, which reflect these revisions to your stability specifications.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

You have not yet responded to the labeling deficiencies communicated to you on December 14, 2000. The labeling for your drug product must be found acceptable in final print prior to approval.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "R. M. Patel for".

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

1.1
DEC 14 2000

39. Chemistry Comments to be Provided to the Applicant:

ANDA: 75-909 APPLICANT: Cheminor Drugs Limited

DRUG PRODUCT: Enalapril Maleate and Hydrochlorothiazide
Tablets USP, 5 mg/12.5 mg and 10 mg/25 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies

1. Regarding the active ingredient, Enalapril Maleate USP, we have following comments:

- a. Please tighten your specification for petroleum based upon observed values.
- b. Please incorporate the test for Related Substances into the retest schedule.
- c. Please revise your specifications for Related Impurities and incorporate a limit for the RSS isomeric impurity of Enalapril Maleate. Please specify limits that are based upon observed values.
- d. Please provide a methods validation report for Related Substances Solvents (GC) according to USP 24 General Chapter <1225> Validation of Compendial Methods or the CDER Guideline. Based upon the method's accuracy, please incorporate relative response factors, if known, into your calculation of known impurities.

2. Regarding the active ingredient, Hydrochlorothiazide USP, we have following comments:

- a. Please incorporate a test for melting point. Please specify a range based upon observed values.
- b. Please provide a method validation report for Related Substances . . . Based upon the method's accuracy, please incorporate a relative response factor, if known, into your calculation of impurity.

Page (s) 2

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

12/14/00

2. Labeling review is pending. You will be notified on the status of the labeling review under a separate cover.

Sincerely yours,


Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-909

Bioequivalence Review(s)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-909 APPLICANT: CHEMINOR DRUGS LTD.

DRUG PRODUCT: ENALAPRIL MALEATE /HYDROCHLOROTHIAZIDE TABLETS
5 mg/12.5 mg & 10 mg/25 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and has no further questions at this time.

The dissolution testing should be incorporated into your stability and quality control programs as specified in USP XXIV.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for 
Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Enalapril Maleate Hydrochlorothiazide
Tablets 5 mg/12.5 mg & 10 mg/25 mg
ANDA #: 75909
Reviewer: Patrick Nwakama
File Name: 75909SDW.600

Reddy-Cheminor, Ltd
66 South Maple Avenue
Ridgewood, NJ 07450
Submission Date:
June 16, 2000

September 20, 2000(Amendment)

REVIEW OF TWO *IN VIVO* BIOEQUIVALENCE STUDIES, DISSOLUTION DATA AND WAIVER REQUEST

The firm has submitted two *in vivo* bioequivalence (single-dose fasting and single-dose non-fasting) studies comparing its test product, Enalapril Maleate Hydrochlorothiazide Tablet, 10 mg/25 mg, to the reference listed drug, Merck's Vaseretic^R Tablets, 10 mg/25 mg. The firm has also submitted *in vitro* dissolution data and a waiver request.

Introduction

Enalapril is a prodrug that is not highly active and, therefore must be hydrolyzed by hepatic esterases to produce its active metabolite, enalaprilat. Enalapril is rapidly absorbed orally and has an oral bioavailability of about 60% (not reduced by food). Although, peak plasma levels are attained within 1 hour, enalaprilat concentrations do not peak until 3 - 4 hours. Enalapril has a half-life of 1.3 hours but enalaprilat has a plasma half-life of about 11 hours because of its strong binding to the angiotensin-converting enzyme (ACE). The drug is eliminated mostly via the kidney either in its parent or metabolite form. Enalapril is indicated for the treatment of hypertension and congestive heart failure. Hydrochlorothiazide is not metabolized and is excreted unchanged in the urine. Its half-life ranges from 6-15 hours and more than 60% of the drug is eliminated within 24 hours.

The bioavailability of the individual drug is not affected when given as a combination product. Therefore, the combination product is reported to be bioequivalent to concomitant administration of the individual agents.

The reference listed drug is Merck's Vaseretic^R Tablets, 10 mg/25 mg.

I. Single-dose Bioequivalence Study Under Fasting Conditions (Study #:

A. Study Information:

Protocol #:

IRB Approval: Yes

Consent Form Signed: Yes

Clinical Site: AAI Clinic, Chapel Hill, NC

Analytical Site:

Principal Investigator: Ralph Scallion, EE, MD

Study Dates: March 10 - 28, 2000

Analysis Dates: April 5 - May 11, 2000 (Enalapril and Enalaprilat)

March 29 - May 3, 2000 (HCTZ)

Study Design: Randomized, 2-way cross-over study with washout period of 14 days.

Randomization Scheme:

Sequence Number	Subject Numbers	Period 1	Period 2
1	3,4,5,6,7,9,10, 11, 12, 14,19, 24, 26, 28, 30, 31, 32,34, 36	A	B
2	1,2,8,13,15,16 17, 18,20,21, 22,23, 25,27, 29,33,35	B	A

A = Merck Vasertic[®]

B = Cheminor Enalapril-Hydrochlorothiazide

Treatments: A: Enalapril-Hydrochlorothiazide, (10mg/25mg) Tablets; Cheminor; Lot # E001B; Manufacturing Date: 10/99; Lot size: \bar{x} : 99.4%(enalapril), 99.0% (HCTZ); Content Uniformity: 101.2%(enalapril) 100.3%(hydrochlorothiazide)

B: Vaseretic[®], (10mg/25mg) Tablets; Merck; Lot # J4897; Expiry Date: 01/01; Assay: 98.3%(enalapril) 98.7%(HCTZ); Content Uniformity: 97.6%(enalapril), 99.2%(HCTZ)

Formulation of Test Drug: Table 1

Subjects: 36 non-smoking male subjects were enrolled per protocol.

Housing: From the evening prior to dosing until after 36 hour blood draw.

Dosing: After 10-hour fast, with 240 ml water. Standard meals given at 4 hours after dosing.

Sampling Times: Blood samples (2 × 7 mL) collected at 0 h (pre-dose), 0.167, 0.333, 0.667, 1, 1.5, 2.0, 2.5, 3, 4, 6, 9, 12, 16, 24, 36, 48, and 72 h

B. Study Results:

1. CLINICAL:

Drop-outs: None.

Adverse Events: A total of 9 medical adverse events were experienced by 7 subjects during the study. The adverse events include headache (4), lightheadedness (2), arm tingling (1), corneal abrasion (1) and fracture of the finger (1).

Protocol Deviations: There were 11 blood draw deviations involving 7 subjects. Blood draws were delayed mostly by \leq 3 minutes.

2. ANALYTICAL METHODOLOGY:

Method:

Internal Standards: de

Sensitivity (LOQ): 0.25 ng/mL (enalapril)
0.50 ng/mL (enalaprilat)
2.50 ng/mL (hydrochlorothiazide)

Specificity: No interfering peaks at retention times of enalapril, enalaprilat, hydrochlorothiazide and their internal standards.

Linearity: Standard Curve Range:
0.25 - 250.0 ng/mL (Enalapril)
0.50 - 250.0 ng/mL (Enalaprilat)
2.50 - 300.0 ng/mL (HCTZ)
Correlation Coefficients:
Enalapril \geq 0.98701
Enalaprilat \geq 0.98190
Hydrochlorothiazide \geq 0.99831

Quality Control Samples:
0.40, 20.0, and 200.00 ng/mL(enalapril)
0.80, 20.0, and 200.00 ng/mL(enalaprilat)
4.00, 40.0, and 200.0 ng/mL(HCTZ)

Regression: linear-weighted (1/concentration)

Accuracy: [Enalapril]
Standard: 97.2 - 103.4%
QC Samples: 99.7 - 107.5%

[Enalaprilat]
Standard: 91.7 - 107.1%
QC Samples: 98.1 - 104.5%

[Hydrochlorothiazide]
Standard: 96.1 - 102.5%
QC Samples: 99.7 - 101.3%

Precision: [Enalapril]
Standard: 4.0 - 9.5%
QC Samples: 6.2 - 10.5%

[Enalaprilat]
Standard: 3.1 - 7.1%
QC Samples: 7.9 - 10.6%

[Hydrochlorothiazide]

Standard: 1.1 - 4.8%

QC Samples: 2.2 - 6.6%

Reassays:

A total of 34 and 73 samples were reanalyzed for enalapril and enalaprilat, respectively (13 samples for each analyte due to inconsistencies in PK profile and the remaining 21 enalapril and 60 enalaprilat samples due to poor chromatograms. A total of 21 samples were reanalyzed for hydrochlorothiazide (13 samples were from subject #11). An interference close to HCTZ peak and not baseline separated was the reason for reanalysis in subject #11 and since the reanalysis confirmed the first measurement, the interference was concluded to be an inherent artifact of the samples from subject #11. Therefore, no values were reported for subject 11 from the 13 samples. For the remaining 8 samples for HCTZ and all the samples for enalapril and enalaprilat, the reassays were accepted as the final results.

The firm has provided the following pre-study method validation results for both fasting and non-fasting studies:

Linearity:

[Enalapril]

Standard Curve Range:

0.25 - 500.0 ng/mL

QC Sample:

0.300, 30.0, 300 ng/mL

Correlation Coefficient: ≥ 0.99778

[Enalaprilat]

Standard Curve Range:

0.25 - 500.0 ng/mL

QC Sample:

0.300, 30.0, 300 ng/mL

Correlation Coefficient: ≥ 0.99783

[Hydrochlorothiazide]

Standard Curve Range:

1.0 - 150.0 ng/mL

QC Sample:
3.0, 30.0, 120 ng/mL
Correlation Coefficient: ≥ 0.99975

Accuracy:

[Enalapril]
INTER-DAY
Standard: 94.2 - 115.9%
QC Samples: 96.5 - 102.9%

INTRA-DAY
QC Samples: 97.5 - 110.0%

[Enalaprilat]
INTER-DAY
Standard: 94.9 - 112.5%
QC Samples: 99.5 - 106.1%

INTRA-DAY
QC Samples: 97.3 - 111.3%

[Hydrochlorothiazide]
INTER-DAY
Standard: 99.2 - 102.8%
QC Samples: 96.9 - 99.5%

INTRA-DAY
QC Samples: 98.7 - 98.9%

Precision:

[Enalapril]
INTER-DAY
Standard: 1.8 - 10.7%
QC Samples: 9.2 - 12.5%

INTRA-DAY
QC Samples: 4.0 - 6.1%

[Enalaprilat]
INTER-DAY
Standard: 1.7 - 10.4%
QC Samples: 3.9 - 10.7%

INTRA-DAY
QC Samples: 1.8 - 6.8%

[Hydrochlorothiazide]

INTER-DAY

Standard: 0.61 - 5.4%
QC Samples: 1.57 - 3.58%

INTRA-DAY

QC Samples: 0.76 - 1.81%

Specificity: no interference from endogenous compounds noted in plasma blanks or pre-dose subject plasma samples.

Recovery:

[Enalapril]

0.30 ng/mL	78% (10.9 %CV)
30.0 ng/mL	50% (4.1 %CV)
300.0 ng/mL	52% (4.5 %CV)

Quinapril(IS) 71.4%

[Enalaprilat]

0.30 ng/mL	89% (14.5 %CV)
30.0 ng/mL	85% (4.0 %CV)
300.0 ng/mL	93% (7.6 %CV)

Quinaprilat (IS) 64.3%

[Hydrochlorothiazide]

20 ng/mL	86.5%
200 ng/mL	85.1%
2000 ng/mL	81.5%

Chlorothiazide(IS) 63.5%

Stability:

[ENALAPRIL and ENALAPRILAT]

- Stored Frozen at - 20°C: stable for 1185 days.
Note: Study samples stored for less than 52 days.
- Freeze/Thaw: Stable over 3 cycles.
- In-process: stable for 24 hours at room temp.
- Refrigerator (5 °C): for 5 days
- Autosampler: stable for 24 hours.

[HYDROCHLOROTHIAZIDE]

- a) Stored Frozen at - 20°C: stable for 372 days.
Note: Study samples stored for less than 44 days.
- b) Freeze/Thaw: Stable over 3 cycles.
- c) In-process: stable for 48 hours at room temp.
- d) Refrigerator (5 °C): for 48 hours
- e) Autosampler: stable for 24 hours.

Conclusion: Assay validation is acceptable.

3. PHARMACOKINETIC / STATISTICAL ANALYSES:

Enalapril:

Mean Plasma Concentrations: Table 2; Figure 1

Pharmacokinetic Parameters: Table 5

90% Confidence Intervals:	LAUC _{0-72h}	-	94.3 - 109.2%
	LAUC _{0-INF}	-	95.7 - 111.7%
	LC _{MAX}	-	97.1 - 121.6%

Test/Reference Ratio:	AUC _{0-72h}	1.00(0.92 - 0.95)
	AUC _{0-INF}	1.01(0.79 - 0.94)
	C _{MAX}	1.06(0.91 - 2.73)

AUC _{0-72h} /AUC _{0-INF} Ratio:	Test	0.98(0.98 - 1.00)
	Reference	0.99(0.85 - 0.99)

Enalaprilat:

Mean Plasma Concentrations: Table 3; Figure 2

Pharmacokinetic Parameters: Table 6

90% Confidence Intervals:	LAUC _{0-72h}	-	94.9 - 110.1%
	LAUC _{0-INF}	-	95.7 - 111.1%
	LC _{MAX}	-	93.1 - 122.6%

Test/Reference Ratio:	AUC _{0-72h}	1.02(0.91 - 1.23)
	AUC _{0-INF}	1.01(0.94 - 1.20)
	C _{MAX}	1.06(0.84 - 2.06)

AUC_{0-72h}/AUC_{0-INF} Ratio:	Test	0.92(0.91 - 0.92)
	Reference	0.91(0.88 - 0.95)
Hydrochlorothiazide:		
Mean Plasma Concentrations:	Table 4; Figure 3	
Pharmacokinetic Parameters:	Table 7	
90% Confidence Intervals:	LAUC _{0-72h}	- 97.3 - 105.1%
	LAUC _{0-INF}	- 98.3 - 106.7%
	LC _{MAX}	- 96.0 - 113.5%
Test/Reference Ratio:	AUC _{0-72h}	1.01(1.01 - 1.02)
	AUC _{0-INF}	1.01(1.05 - 1.08)
	C _{MAX}	1.03(0.93 - 1.07)
AUC_{0-72h}/AUC_{0-INF} Ratio:	Test	0.94(0.92 - 0.93)
	Reference	0.94(0.92 - 0.95)

Comments:

1. The maximum (mean) plasma concentrations for enalapril, enalaprilat and hydrochlorothiazide were attained at 1, 3 and 2 hours, respectively (Tables 2,3&4).
2. No subjects with zero-hour drug level, first scheduled post-dose time point as C_{max} or first measurable drug concentration as C_{max}. The reviewer recalculated the pharmacokinetic parameters and found them in complete agreement with those of the firm.
3. The reviewer's recalculated 90% confidence intervals for log-transformed AUC, AUC_{0-INF}, and C_{max} for enalapril, enalaprilat and hydrochlorothiazide corresponded with those of the firm and are all within the within acceptable limits.
4. The fasting study is complete.

II. Single-dose Bioavailability Study Under Non-Fasting Conditions (Protocol

A. Study Information:

Protocol #: _____
 IRB Approval: Yes
 Consent Form Signed: Yes
 Clinical Site: AAI Clinic, Chapel Hill, NC

Analytical Site:y
Principal Investigator: Ralph Scallion, EE, MD
Study Dates: March 3 - April 4, 2000
Analysis Dates: April 10 - May 9, 2000 (Enalapril and Enalaprilat)
 April 4 - April 28, 2000 (HCTZ)

Study Design: Randomized, 3-way cross-over design with washout period of 14 days.

Randomization Scheme:

Sequence Number	Subject Numbers	Phase I	Phase II	Phase III
1	6, 7,20,21	A	B	C
2	1,2,11,24	B	C	A
3	10,15,17,18	C	A	B
4	5,9,12,13	C	B	A
5	4,16,19,23	B	A	C
6	3,8,14,22	A	C	B

A = Cheminor's enalapril/Hydrochlorothiazide (test, non-fasting)

B = Vaseretic® (reference, non-fasting)

C = Cheminor's enalapril/Hydrochlorothiazide (test, fasting)

Treatments: A: Enalapril-Hydrochlorothiazide, (10mg/25mg) Tablets; Cheminor; Lot # E001B; Manufacturing Date: 10/99 (test, non-fasting)

B: Vaseretic®, (10mg/25mg) Tablets; Merck; Lot # H4897; Expiry Date: 01/01 (reference, non-fasting)

C: Enalapril-Hydrochlorothiazide, (10mg/25mg) Tablets; Cheminor; Lot # E001B; Manufacturing Date: 10/99 (test, fasting)

Formulation of Test Drug: Table 1

Subjects: 24 non-smoking male subjects were enrolled per protocol.

Housing: At least 10 hours prior dosing until 36 hours blood draw.

Dosing:

Treatments A & B:
Administered with 240mL water, 15 minutes after consuming a standard breakfast.

Treatment C:
Given with 240mL water after 10-hour fasting.

Sampling Times

Blood samples (2 × 7 mL) collected at 0 h (pre-dose), 0.167, 0.333, 0.667, 1, 1.5, 2.0, 2.5, 3, 4, 6, 9, 12, 16, 24, 36, 48, and 72 h

B. Study Results:

1. CLINICAL:

Drop-outs:

A total of 4 subjects dropped out. In period II, subjects #5 and #7 were dropped due to failure to return to clinic. Subjects #9 and #14 withdrew after completing period I due to personal reasons. Therefore, 20 subjects completed the study.

Adverse Events:

A total of 7 adverse events occurring in 5 subjects were reported. These include headache (2), lightheadedness (1), nausea (1), hematoma (1), fever (1) and sore throat (1). Hematoma, fever and sore throat were considered not to be treatment-related. All were mild or moderate in nature and not definitely drug-related. The events appeared to occur evenly in both the test and reference products and resolved without pharmacologic treatment.

Protocol Deviations:

There were 10 deviations in blood collection times involving 7 subjects. Blood sampling delays were mostly ≤ 1 minute with the exceptions of Subjects #23 and 15 who had 61- and 270- minute delays, respectively. None of the subjects violated inclusion /exclusion criteria or took concomitant medications during the study.

2. ANALYTICAL METHODOLOGY:

Method:

Internal Standards:

Sensitivity (LOQ): 0.25 ng/mL (enalapril)
0.50 ng/mL (enalaprilat)
2.50 ng/mL (hydrochlorothiazide)

Specificity: No interfering peaks at retention times of enalapril, enalaprilat, hydrochlorothiazide and their internal standards.

Linearity:

Standard Curve Range:

0.25 - 250.0 ng/mL (Enalapril)
0.50 - 250.0 ng/mL (Enalaprilat)
2.50 - 300.0 ng/mL (HCTZ)

Correlation Coefficients:

Enalapril \geq 0.99566
Enalaprilat \geq 0.99126
Hydrochlorothiazide \geq 0.99851

Quality Control Samples:

0.40, 20.0, and 200.00 ng/mL(enalapril)
0.80, 20.0, and 200.00 ng/mL(enalaprilat)
4.00, 40.0, and 200.0 ng/mL(HCTZ)

Regression: linear-weighted (1/concentration)

Accuracy:

[Enalapril]
Standard: 96.2 - 102.4%
QC Samples: 99.7 - 103.2%

[Enalaprilat]
Standard: 94.8 - 104.0%
QC Samples: 99.9 - 101.9%

[Hydrochlorothiazide]
Standard: 95.5 - 102.1%
QC Samples: 99.6 - 102.6%

Precision:

[Enalapril]
Standard: 1.8 - 4.8%
QC Samples: 4.5 - 10.7%

[Enalaprilat]

Standard: 2.1 - 5.7%

QC Samples: 3.5 - 4.9%

[Hydrochlorothiazide]

Standard: 1.4 - 6.5%

QC Samples: 4.8 - 5.9%

Reassays:

A total of 17 samples were reanalyzed for both enalapril and enalaprilat (5 and 7 samples for enalapril and enalaprilat, respectively, due to poor chromatograms; 6 and 3 samples for enalapril and enalaprilat, respectively, for irregular concentration value; 4 and 2 samples for enalapril and enalaprilat, respectively, for below LOQ; 1 sample for both enalapril and enalaprilat due to "lost sample", and 1 and 4 samples for enalapril and enalaprilat, respectively, because established criteria despite of acceptable value. A total of 26 samples were reanalyzed for hydrochlorothiazide (14 due to "chromatogram not evaluable", 10 due to "irregular concentration value", 1 for "above upper limit concentration value," and 1 because "lost sample"). Additional 18 samples from subject #10 were reinjected because of interference peak was not separated from HCTZ at first injection. The values of last repeats or the mean values of repeats that are similar in value were reported as final results.

Conclusion:

Assay is acceptable.

3. PHARMACOKINETIC / STATISTICAL ANALYSES:

Enalapril:

Mean Plasma Concentrations: Table 8; Figure 4

Pharmacokinetic Parameters: Table 11

Test-fed/Ref. Fed Ratio: AUC_{0-72h} 0.95(0.95 - 1.10)

AUC_{0-INF} 0.94(0.95 - 1.12)

C_{MAX} 1.09(0.68 - 1.09)

AUC_{0-72h}/AUC_{0-INF} Ratio: Test Fasting 0.98(0.99-1.00)

Test Non-fasting 0.99(0.98-0.99)

Ref. Non-fasting 0.98(0.98-0.99)

Enalaprilat:

Mean Plasma Concentrations: Table 9; Figure 5

Pharmacokinetic Parameters: Table 12

Test-fed/Ref. Fed Ratio:	AUC _{0-72h}	0.96(0.76 - 0.84)
	AUC _{0-INF}	0.97(0.79 - 0.80)
	C _{MAX}	0.93(0.60 - 1.11)
AUC _{0-72h} /AUC _{0-INF} Ratio:	Test Fasting	0.93(0.88-0.94)
	Test Non-fasting	0.93(0.90-0.93)
	Ref. Non-fasting	0.91(0.88-0.95)

Hydrochlorothiazide:

Mean Plasma Concentrations: Table 10; Figure 6

Pharmacokinetic Parameters: Table 13

Test-fed/Ref. Fed Ratio:	AUC _{0-72h}	0.92(0.89 - 0.90)
	AUC _{0-INF}	0.93(0.88 - 0.91)
	C _{MAX}	0.99(0.92 - 1.08)
AUC _{0-72h} /AUC _{0-INF} Ratio:	Test Fasting	0.94(0.91-0.96)
	Test Non-fasting	0.94(0.92-0.96)
	Ref. Non-fasting	0.95(0.97-0.98)

Comments:

1. The reviewer recalculated the pharmacokinetic parameters and ratios of means and found them in complete agreement with those of the firm.
2. No subjects with first scheduled post-dose time point as C_{max}, and no subjects with first measurable drug level as C_{max}. Subjects # 6 and #19 had zero-hour (predose) enalapril levels but were not dropped. The reviewer agrees with this decision since the levels were < 5% of the respective C_{max} values of the subjects.
3. Ratio of the means for AUC_{0-72h}, AUC_{0-INF}, and C_{max} between test (non-fasting) and reference (non-fasting) are within acceptable limits.
4. The non-fasting study is complete.

***In Vitro* Dissolution Testing and Waiver Request:**

The firm has conducted dissolution testing on its 5 mg/12.5 mg and 10 mg/25 mg tablets of both the test and reference products, using the current USP method and is requesting waivers of the in-vivo bioequivalence study requirements for its 5 mg/12.5 mg tablet per 21 CFR 320.22(d)(2), based on an acceptable in-vivo bioequivalence study on the 10 mg/25 mg strength, similarly proportional formulations as listed in Table 1. The comparative dissolution data and testing conditions are presented in Table 14.

Comments:

1. The test and reference products used in the dissolution testing and biostudies were from same lots.
2. The following f_2 comparisons were performed:

	Test 5mg/12.5mg	Test 10mg /25 mg	Ref. 5mg/ 12.5mg	Ref. 10mg /25 mg
Test 5mg/12.5mg	- / -	66 / 67	54/50	62 / 48
Test 10mg/25 mg	66 / 67	- / -	71 / 51	82 / 57
Ref. 5mg/12.5mg	54/50	71/51	- / -	77 / 55
Ref. 10mg/25 mg	62 / 48	82 / 57	77 / 55	- / -

Recommendations:

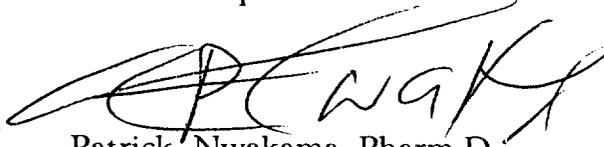
- I. The *in vivo* bioequivalence study conducted under fasting conditions by Cheminor, on its Enalapril Maleate Hydrochlorothiazide tablets, 10 mg/25 mg, lot #E001B, comparing it to the reference product, Vaseretic^R tablets, 10 mg/25mg, lot # J4897, by Merck & Co., is acceptable to the Division of Bioequivalence. The study demonstrates that Cheminor's Enalapril Maleate Hydrochlorothiazide tablets, 10 mg/25 mg, is bioequivalent to the reference product, Vaseretic^R tablets, 10 mg/25mg, manufactured by Merck & Co.
- II. The *in vivo* bioavailability study conducted under non-fasting conditions by Cheminor, Inc. on its Enalapril Maleate Hydrochlorothiazide tablets, 10 mg/25 mg, lot #E001B, comparing it to the reference product, Vaseretic^R tablets, 10 mg/25 mg, lot # J4897, by Merck & Co., is acceptable to the Division of Bioequivalence. The study demonstrates that Cheminor's Enalapril Maleate Hydrochlorothiazide tablets, 10 mg/25 mg, is bioequivalent to the reference product, Vaseretic^R tablets, 10 mg/25mg, manufactured by Merck & Co.

III. The *in vitro* dissolution testing submitted by the firm on its Enalapril Maleate-Hydrochlorothiazide (5 mg/12.5 mg and 10 mg/ 25 mg) tablets is acceptable. The formulation for 5 mg/12.5 mg, test tablets is proportionally similar to the 10 mg/25 mg strength of the test product which underwent bioequivalence testing. The waiver of the *in vivo* bioequivalence study requirements for 5 mg /12.5 mg of the test product can be granted under 21 CFR 320.22(d)(2). The 5 mg/12.5 mg test tablets are therefore deemed bioequivalent to the 5 mg/12.5 mg tablets of Vaseretic® manufactured by Merck & Co.

IV. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution should be conducted in 900 mL Water using USP Apparatus II(Paddle) at 50 rpm. The test product should meet the following specifications:

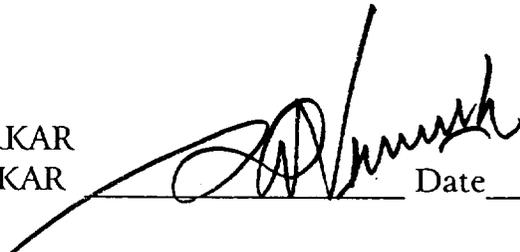
Enalapril -	in 30 minutes
Hydrochlorothiazide -	in 30 minutes

V. From bioequivalence point of view, the firm has met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing and the application is acceptable.

 9/20/2000

Patrick Nwakama, Pharm.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR

 Date 9/21/2000

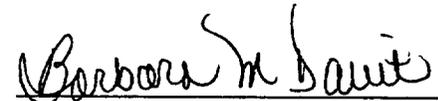
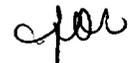
Concur:  Date 9/29/00
 Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

TABLE 2

**FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY
ARITHMETIC MEAN ENALAPRIL PLASMA LEVELS (ng/mL) Vs TIME (n= 36)**

Time	Test Treatment A		Reference Treatment B		Ratio (A/B)
		(CV %)		(CV%)	
0	0.00		0.00		.
0.17	1.13	162.29	1.1073	116.62	1.02
0.33	16.20	91.82	15.00	104.12	1.08
0.67	75.81	36.29	68.79	46.35	1.10
1.00	83.12	26.26	77.27	36.52	1.07
1.50	54.74	37.47	54.65	37.06	1.00
2.00	33.50	40.13	33.76	40.39	0.99
2.50	20.57	39.68	21.07	41.50	0.98
3.00	12.35	37.79	12.77	38.33	0.97
4.00	5.77	37.17	6.09	42.72	0.95
6.00	1.96	40.21	2.18	61.63	0.90
9.00	0.65	55.67	0.95	78.71	0.68
12.00	0.26	106.14	0.42	101.49	0.62
16.00	0.05	287.85	0.15	185.55	0.33
24.00	0.00	-	0.04	376.74	0.00
36.00	0.00	-	0.00	0.00	0.00
48.00	0.00	-	0.00	0.00	0.00
72.00	0.00	-	0.00	0.00	0.00

TABLE 3

FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY ARITHMETIC MEAN ENALAPRILAT PLASMA LEVELS (ng/mL) Vs TIME (n = 36)

Time	Test Treatment A		Reference Treatment B		Ratio (A/B)
		(CV %)		(CV%)	
0	0.00	(CV %)	0.00	(CV%)	.
0.17	0.03	600.00	0.09	460.29	0.33
0.33	0.12	310.93	0.18	251.91	0.67
0.67	2.10	115.72	1.70	70.34	1.23
1.00	7.63	121.24	6.24	110.00	1.22
1.50	20.46	76.03	21.35	85.44	0.96
2.00	35.63	53.91	34.11	58.50	1.04
2.50	45.10	43.66	42.56	51.53	1.06
3.00	49.33	43.13	46.71	43.34	1.06
4.00	48.90	38.23	45.07	36.61	1.08
6.00	33.82	32.38	33.90	34.01	1.00
9.00	20.27	30.71	19.96	28.71	1.02
12.00	11.12	28.68	11.18	33.15	0.99
16.00	5.41	32.03	5.71	33.73	0.95
24.00	2.81	31.33	2.88	35.25	0.97
36.00	1.52	22.74	1.53	28.78	0.99
48.00	1.16	26.72	1.13	31.34	1.03
72.00	0.71	49.55	0.70	48.06	1.01

TABLE 4

**FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY ARITHMETIC MEAN
HYDROCHLOROTHIAZIDE PLASMA LEVELS (ng/mL) Vs TIME
(n = 36)**

Time	Test Treatment A		Reference Treatment B		Ratio (A/B)
		(CV %)		(CV%)	
0	0.00	(CV %)	0.00	(CV%)	.
0.17	0.27	421.92	0.00	-	-
0.33	5.53	186.34	3.81	132.90	1.45
0.67	53.94	72.43	48.53	76.47	1.11
1.00	114.24	48.36	102.61	56.73	1.11
1.50	143.50	32.78	131.41	38.15	1.09
2.00	145.69	26.80	138.69	31.43	1.05
2.50	135.50	22.86	138.10	28.12	0.98
3.00	122.69	21.48	125.34	23.96	0.98
4.00	99.63	20.42	101.48	21.55	0.98
6.00	61.05	23.30	61.85	24.21	0.99
9.00	38.64	22.02	40.28	28.09	0.96
12.00	25.13	22.57	25.42	23.93	0.99
16.00	17.01	25.08	17.07	24.41	0.99
24.00	11.02	29.35	10.72	25.11	1.03
36.00	5.17	47.93	4.70	37.45	1.10
48.00	1.71	116.51	1.63	116.78	1.05
72.00	0.15	412.55	0.18	412.23	0.83

TABLE 5

MEAN (%CV) ENALAPRIL PHARMACOKINETIC PARAMETERS FOLLOWING 10 MG/25 MG (1 X 10 MG/25 MG) DOSE OF ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE TABLETS UNDER FASTING CONDITIONS (n = 36)				
Parameter	Arithmetic Mean A = TEST Vaseretic®	Arithmetic Mean B = Vaseretic®	LSMEANS Ratio (A/B)*	90% Confidence Interval**
AUCT (ng x hr/mL)	143.5 (37.0)	142.5(41.8)	1.01	94.3% - 109.2%
AUCI (ng x hr/mL)	145.7(38.4)	143.8 (41.2)	1.03	95.7% - 111.7%
C _{MAX} (ng/mL)	89.1(22.6)	84.2(27.4)	1.09	97.1% - 121.6%
KEL (hr ⁻¹)	0.39 (0.16)	0.33 (0.16)	-----	-----
THALF (hr)	2.08 (0.85)	2.65 (1.88)	-----	-----
T _{MAX} (hr)	0.87 (0.20)	0.93 (0.29)	-----	-----

TABLE 6

MEAN (%CV) ENALAPRILAT PHARMACOKINETIC PARAMETERS FOLLOWING 10 MG/25 MG (1 X 10 MG/25 MG) DOSE OF ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE TABLETS UNDER FASTING CONDITIONS (n = 41)				
Parameter	Arithmetic Mean A = TEST	Arithmetic Mean B = Vaseretic®	LSMEANS Ratio (A/B)*	90% Confidence Interval**
AUCT (ng x hr/mL)	455.9 (106.11)	447.8 (113.4)	1.02	94.9% - 110.1%
AUCI (ng x hr/mL)	497.4 (105.2)	492.7 (115.2)	1.03	95.7% - 111.1%
C _{MAX} (ng/mL)	52.9 (21.1)	50.1 (21.3)	1.07	93.1% - 122.6%
KEL (hr ⁻¹)	0.02 (0.01)	0.03 (0.01)	-----	-----
THALF (hr)	32.6 (12.8)	31.7 (11.4)	-----	-----
T _{MAX} (hr)	3.50 (0.86)	3.31 (0.81)	-----	-----

*Ratio (A/B) = e [LSMEAN of Ln A - LSMEAN of Ln B]

**Used natural Log Transformed Parameter

TABLE 7

MEAN (%CV) HYDROCHLOROTHIAZIDE PHARMACOKINETIC PARAMETERS FOLLOWING 10 MG/25 MG (1 X 10 MG/25 MG) DOSE OF ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE TABLETS UNDER FASTING CONDITIONS (n = 36)				
Parameter	Arithmetic Mean A = Vaseretic®	Arithmetic Mean B = TEST	LSMEANS Ratio (A/B)*	90% Confidence Interval**
AUCT (ng x hr/mL)	1150.7 (236.6)	1141.92 (251.8)	1.01	97.3% - 105.1%
AUCI (ng x hr/mL)	1127.9 (250.4)	1213.8 (265.3)	1.02	98.3% - 106.7%
C _{MAX} (ng/mL)	162.3 (39.9)	157.14(43.5)	1.04	96.0% - 113.5%
KEL (hr ⁻¹)	0.06 (0.01)	0.06 (0.01)	-----	-----
THALF (hr)	13.3 (9.1)	11.54 (3.47)	-----	-----
T _{MAX} (hr)	1.86(0.69)	2.1(0.75)	-----	-----

*Ratio (A/B) = e [LSMEAN of LNA - LSMEAN of LNB]

**Used natural Log Transformed Parameter

TABLE 8

**ARITHMETIC MEAN ENALAPRIL PLASMA LEVELS [ng/mL] Vs TIME IN NON-FASTING STUDY
(n = 20)**

Time (Hours)	Non-Fasting Test Treatment A Mean (CV%)	Non-Fasting Reference Treatment B Mean (CV%)	Fasting Test Treatment C Mean (CV%)	Ratio (A/C)	Ratio (A/B)
0	0.04 (435.89%)	0.01 (447.21%)	0.00	-	4.00
0.17	0.33 (207.53%)	0.13 (273.31%)	1.35 (192.16%)	0.24	2.54
0.33	4.04 (189.49%)	1.94 (119.21%)	19.08 (89.74%)	0.21	2.08
0.67	21.81 (78.16%)	14.26 (84.48%)	63.80 (53.50%)	0.34	1.53
1.00	38.85 (57.73%)	29.72 (69.88%)	65.39 (43.11%)	0.59	1.31
1.5	35.30 (47.37%)	37.19 (43.64%)	43.41 (33.75%)	0.81	0.95
2.0	24.39 (52.49%)	31.43 (42.19%)	25.91 (34.39%)	0.94	0.78
2.5	17.73 (75.33%)	21.45 (44.40%)	17.13 (47.44%)	1.03	0.83
3.0	11.87 (87.18%)	14.47 (61.97%)	10.15 (61.65%)	1.17	0.82
4.0	5.20 (79.05%)	6.64 (63.08%)	4.78 (55.46%)	1.09	0.78
6.0	1.19 (47.76%)	1.43 (40.07%)	1.44 (68.51%)	0.83	0.83
9.0	0.34 (61.82%)	0.43 (47.98%)	0.40 (70.70%)	0.85	0.79
12.0	0.09 (179.50%)	0.14 (134.66%)	0.12 (144.84%)	0.75	0.64
16.0	0.02 (447.21%)	0.03 (307.87%)	0.01 (447.21%)	2.00	0.66
24.0	0.00	0.00	0.00	-	-
36.0	0.00	0.00	0.00	-	-
48.0	0.00	0.02 (447.21%)	0.00	-	-
72.0	0.00	0.00	0.02 (447.21%)	0.00	-

TABLE 9

**ARITHMETIC MEAN ENALAPRILAT PLASMA LEVELS [ng/mL] VS TIME IN NON-FASTING STUDY
(n = 20)**

Time (Hours)	Non-Fasting Test Treatment A Mean (CV%)	Non-Fasting Reference Treatment B Mean (CV%)	Fasting Test Treatment C Mean (CV%)	Ratio (A/C)	Ratio (A/B)
0	0.00	0.00	0.00	-	-
0.17	0.00	0.00	0.00	-	-
0.33	0.00	0.00	0.00	-	-
0.67	0.20 (191.07%)	0.06 (308.90%)	1.02 (81.76%)	0.20	3.33
1.00	1.03 (136.95%)	0.58 (119.24%)	4.80 (96.62%)	0.21	1.77
1.5	4.45 (166.22%)	2.59 (120.10%)	17.69 (74.02%)	0.25	1.72
2.0	10.09 (110.79%)	6.51 (103.01%)	29.94 (49.69%)	0.34	1.55
2.5	15.05 (80.14%)	12.41 (73.35%)	37.45 (40.98%)	0.40	1.21
3.0	20.08 (64.37%)	18.83 (50.73%)	41.76 (36.15%)	0.48	1.21
4.0	25.43 (42.07%)	27.40 (42.27%)	43.71 (26.99%)	0.58	0.93
6.0	21.88 (35.78%)	23.61 (39.32%)	30.32 (25.14%)	0.72	0.93
9.0	14.51 (36.52%)	16.32 (44.84%)	19.46 (28.93%)	0.75	0.89
12.0	9.22 (39.10%)	9.61 (39.03%)	11.04 (36.49%)	0.84	0.96
16.0	4.83 (48.09%)	5.24 (46.37%)	5.69 (49.49%)	0.85	0.92
24.0	2.50 (42.04%)	2.57 (35.83%)	2.61 (39.83%)	0.96	0.97
36.0	1.37 (27.28%)	1.33 (28.15%)	1.38 (30.52%)	0.99	1.03
48.0	1.02 (33.98%)	1.00 (35.42%)	0.97 (34.41%)	1.05	1.02
72.0	0.71 (32.96%)	0.68 (33.13%)	0.64 (41.75%)	1.11	1.04

TABLE 10

**ARITHMETIC MEAN HYDROCHLOROTHIAZIDE PLASMA LEVELS (ng/mL) VS
TIME IN NON-FASTING STUDY
(n = 20)**

Time (Hours)	Non-Fasting Test Treatment A Mean (CV%)	Non-Fasting Reference Treatment B Mean (CV%)	Fasting Test Treatment C Mean (CV%)	Ratio (A/C)	Ratio (A/B)
0	0.00	0.00	0.00	0.00	0.00
0.17	0.00	0.00	0.57 (447.21%)	-	0.00
0.33	5.46 (301.44%)	0.48 (320.33%)	8.79 (159.49%)	0.62	11.37
0.67	29.59 (128.74%)	13.93 (110.14%)	58.36 (77.85%)	0.51	2.12
1.00	64.02 (65.28%)	48.83 (91.82%)	118.42 (52.98%)	0.54	1.31
1.5	102.76 (36.57%)	86.59 (67.90%)	158.86 (46.44%)	0.65	1.19
2.0	117.62 (29.77%)	111.02 (44.32%)	154.53 (33.13%)	0.76	1.06
2.5	115.59 (24.23%)	120.03 (31.39%)	146.01 (23.84%)	0.79	0.96
3.0	111.91 (30.18%)	116.22 (20.91%)	129.74 (23.50%)	0.86	0.96
4.0	95.30 (34.59%)	105.01(20.97%)	105.42 (20.89%)	0.90	0.91
6.0	58.29 (32.40%)	69.13 (26.01%)	63.58 (27.17%)	0.92	0.89
9.0	36.10 (30.03%)	40.73 (23.57%)	40.22 (23.68)	0.90	0.89
12.0	25.06 (31.58%)	27.13 (22.83%)	27.55 (22.87%)	0.91	0.92
16.0	16.13 (29.88%)	17.83 (24.86%)	18.56 (24.82%)	0.87	0.90
24.0	10.08 (31.02%)	11.31 (30.41%)	11.78 (27.28%)	0.86	0.89
36.0	4.41 54.28%)	4.73 (51.21%)	5.11 (50.91%)	0.86	0.93
48.0	1.63 (115.20%)	1.58 (114.94%)	2.05 (106.29%)	0.79	1.03
72.0	0.00	0.00	0.13 (447.21%)	-	0.00

TABLE 11

MEAN ENALAPRIL PHARMACOKINETIC PARAMETERS FOLLOWING A SINGLE ORAL 10 MG/25 MG (1 X 10 MG/25 MG) DOSE IN A FOOD STUDY (n = 20)				
Parameter	Arithmetic Mean A = TEST (Fed)	Arithmetic Mean B = REF (Fed)	Arithmetic Mean C = TEST (Fasting)	LSMEANS* Ratio (A/B)
AUCT (ng x hr/mL)	83.7 (25.4)	88.5 (25.4)	116.2 (41.0)	0.95
AUCI (ng x hr/mL)	84.6 (25.6)	89.9 (25.9)	118.7 (41.5)	0.94
C _{MAX} (ng/mL)	50.5(15.6)	45.4 (12.9)	72.7 (30.0)	1.09
KEL (hr ⁻¹)	0.54 (0.23)	0.48 (0.26)	0.52 (0.23)	-----
THALF (hr)	1.70 (1.25)	1.90 (1.07)	1.62 (0.74)	-----
TMAX (hr)	1.23 (0.43)	1.52 (0.62)	0.83 (0.22)	-----

* Ratio (A/B) = e^[LSMEAN of Ln A - LSMEAN of Ln B]

TABLE 12

MEAN ENALAPRILAT PHARMACOKINETIC PARAMETERS FOLLOWING A SINGLE ORAL DOSE 10 MG/25 MG DOSE IN A FOOD STUDY (n = 20)				
Parameter	Arithmetic Mean A = TEST (Fed)	Arithmetic Mean B = REF (Fed)	Arithmetic Mean C = TEST (Fasting)	LSMEANS* Ratio (A/B)
AUCT (ng x hr/mL)	295.9 (85.3)	307.1 (99.9)	162 (42.2)	0.96
AUCI (ng x hr/mL)	335.2 (89.2)	337.2 (100.8)	169 (41.8)	0.97
C _{MAX} (ng/mL)	26.7 (11.6)	28.2(11.7)	101 (38.2)	0.93
KEL (hr ⁻¹)	0.02 (0.01)	0.02 (0.01)	0.60 (50.6)	-----
THALF (hr)	36.2 (11.2)	32.5 (8.1)	1.55 (62.0)	-----
TMAX (hr)	4.2 (1.2)	4.6 (0.94)	1.01 (34.3)	-----

* Ratio (A/B) = e^[LSMEAN of Ln A - LSMEAN of Ln B]

TABLE 13

MEAN HYDROCHLOROTHIAZIDE PHARMACOKINETIC PARAMETERS FOLLOWING A SINGLE ORAL DOSE 10 MG/25 MG DOSE IN A FOOD STUDY (n = 20)				
Parameter	Arithmetic Mean A = TEST (Fed)	Arithmetic Mean B = REF (Fed)	Arithmetic Mean C = TEST (Fasting)	LSMEANS* Ratio (A/B)
AUCT (ng x hr/mL)	1020.2 (274.05)	1090.1 (233.9)	1220.7 (262.2)	0.92
AUCI (ng x hr/mL)	1084.0 (274.2)	1148.9 (237.3)	1292.9 (276.7)	0.93
C_{MAX} (ng/mL)	137.1 (29.2)	137.7 (33.1)	181.5 (60.2)	0.99
K_{EL} (hr⁻¹)	0.07 (0.02)	0.07 (0.02)	0.06 (0.02)	-----
T_{HALF} (hr)	11.2 (2.7)	10.53 (2.5)	11.3 (3.06)	-----
T_{MAX} (hr)	1.93 (0.67)	2.42 (0.78)	2.22 (1.25)	-----

* Ratio (A/B) = e^[LSMEAN of Ln A - LSMEAN of Ln B]

TABLE 14

IN-VITRO DISSOLUTION TESTING

Drug: Enalapril Maleate and Hydrochlorothiazide Tablets Dose Strength(s): 5 mg/12.5 mg and 10 mg/25 mg ANDA #: 75-909 Firm: Cheminor Drugs Ltd. Submission Date: June 16, 2000 File Name: 75-909SDW.600						
I. Conditions for Dissolution/Release Testing: USP METHOD						
USP XXIV Apparatus: Type 2 (Paddles) RPM: 50 No. Units Tested: 12 Reference Drug: Vaseretic®				Media: Water at 37°C Volume: 900 mL Tolerance: _____ in 30 min(enalapril) Tolerance: _____ in 30 min(Hydrochlorothiazide) Assay Method: _____		
II. Results of In Vitro Dissolution/Release Testing:[ENALAPRIL COMPONENT]						
Sampling Times (min)	Test Product: Enalapril Maleate /HCTZ Tablets Lot No.: E001A Strength: 5 mg/12.5 mg			Reference Product: Vaseretic® Tablets Lot No.: J4944 Strength: 5 mg/12.5 mg		
	Mean %	Range	CV%	Mean %	Range	CV%
10	79.0		17.0	95.0		2.9
20	95.0		6.2	97.0		1.4
30	98.0		3.4	98.0		1.1
45	99.0		1.9	99.0		1.2
Sampling Times (min)	Test Product: Enalapril Maleate /HCTZ Tablets Lot No.: E001B Strength: 10 mg/25 mg			Reference Product: Vaseretic® Tablets Lot No.: J4897 Strength: 10 mg/25 mg		
	Mean %	Range	CV%	Mean %	Range	CV%
10	88.0		15.2	90.0		5.1
20	97.0		6.9	97.0		1.5
30	99.0		3.2	97.0		1.3
45	100.0		1.3	97.0		0.9

II. Results of In Vitro Dissolution/Release Testing:[HYDROCHLOROTHIAZIDE]

Sampling Times (min)	Test Product: Enalapril Maleate/ <u>HCTZ</u> Tablets Lot No.: E001A Strength: 5 mg/ <u>12.5 mg</u>			Reference Product: Vaseretic® Tablets Lot No.: J4944 Strength: 5 mg/12.5 mg		
	Mean %	Range	CV%	Mean %	Range	CV%
10	57		16.9	70		6.2
20	89		9.5	85		3.4
30	97		6.0	88		2.7
45	100		4.6	89		2.5
Sampling Times (min)	Test Product: Enalapril Maleate / <u>HCTZ</u> Tablets Lot No.: E001B Strength: 10 mg/ <u>25 mg</u>			Reference Product: Vaseretic® Tablets Lot No.: J4897 Strength: 10 mg /25 mg		
	Mean %	Range	CV%	Mean %	Range	CV%
10	65		12.8	78		4.9
20	92		9.2	93		2.7
30	99		6.3	96		2.0
45	102		4.1	97		1.7

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-909

APPLICANT: CHEMINOR DRUGS LTD.

DRUG PRODUCT: ENALAPRIL MALEATE /HYDROCHLOROTHIAZIDE TABLETS
5 mg/12.5 mg & 10 mg/25 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and has no further questions at this time.

The dissolution testing should be incorporated into your stability and quality control programs as specified in USP XXIV.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for 
Dale P. Conner, Pharm. D.
Director

Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-909

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY

ANDA: 75-909

DRUG PRODUCT: Enalapril Maleate/Hydrochlorothiazide Tablets USP

FIRM: Dr. Reddy's Laboratories Limited

DOSAGE FORM: Oral Tablets

STRENGTH: 5 mg/12.5 mg and 10 mg/25 mg

cGMP STATEMENT/EER UPDATE STATUS: Acceptable (EGASM, 8/11/00)

BIO STUDY: Acceptable (P. Nwakama, 9/29/00)

The recommended dissolution specifications and conditions are as follows:

900 mL of Water, at 37 °C using USP Apparatus 2 (Paddle) at 50 rpm.

Enalapril Maleate -) in 30 minutes
 Hydrochlorothiazide - in 30 minutes

VALIDATION: N/A

STABILITY: The container/closure system used for the stability study (100-unit and 1000-unit packaging configurations) is equivalent to the system proposed for commercial use. All reported data are within specifications as listed. A 24-month expiration date is proposed.

Stability tests and specifications are as follows:

	Specifications
Physical Description	
Dissolution	
Assay	
Related Compounds	
LOD	

LABELING: Acceptable in Draft (J. Barlow, 9/27/01)

STERILIZATION VALIDATION: (IF APPLICABLE): N/A

SIZE OF BIO Batch:

Reddy-Cheminor manufactured two ANDA batches, one for each strength. The batch size and lot numbers are as follows:

<u>Strength</u>	<u>Lot Number</u>	<u>Batch size</u>	<u>Purpose</u>
5 mg/12.5 mg	E001A		stability
10 mg/25 mg	E001B		bioequivalence/stability

SIZE OF STABILITY BATCHES: See above

PROPOSED PRODUCTION BATCHES:

The batch sizes for the proposed production batches are as follows:

<u>Strength</u>	<u>Proposed Production Batch size</u>
5 mg/12.5 mg	
10 mg/25 mg	

Review Chemist: Andre Raw
Andre Raw, Ph.D.

DATE: 10/1/01

Team Leader: Albert Mueller
Albert Mueller, Ph.D.

DATE: 10/1/01

V:

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number:	75-909
Date of Submission:	June 16, 2000
Applicant's Name:	Cheminor Drugs Limited (manufactured for Par Pharmaceuticals)
Established Name:	Enalapril Maleate and Hydrochlorothiazide Tablets USP, 5 mg/12.5 mg & 10 mg/25 mg.

Labeling Deficiencies:

1. **CONTAINER** – Bottles of 100 and 1000 tablets
Please assure that the established name and expression of strength are the **most prominent print** on the label.

2. **PACKAGE INSERT**
 - a. **General Comments**
Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert .

 - b. **Title:**
We encourage you to include "USP" in the established name of your drug product in this section.

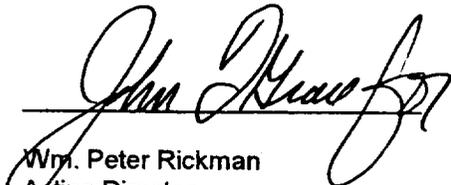
 - c. **Description**
Third paragraph, first sentence –

...with a molecular weight of 492.53. [replace "with" with "weight" and replace "492.52" with "492.53"]

Please revise your labels and labeling, as instructed above, and submit in final print, or draft if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.


Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75-909

CORRESPONDENCE



DR. REDDY'S

DR. REDDY'S LABORATORIES, INC.

ONE PARK WAY

UPPER SADDLE RIVER, NJ 07458

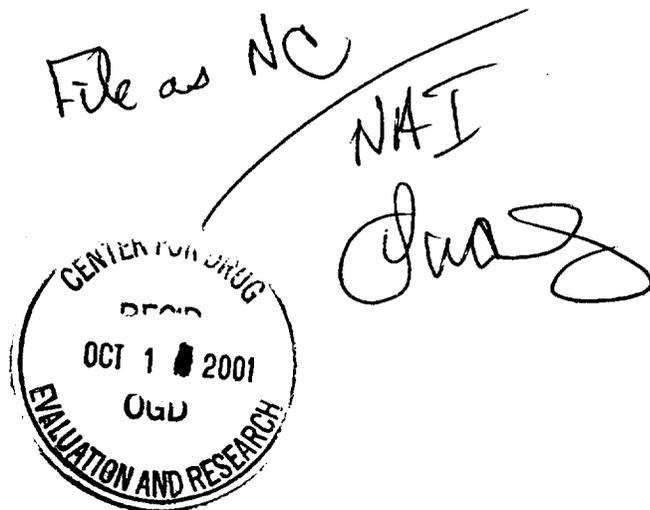
TELEPHONE (201) 760-2880

FAX (201) 760-0401

September 26, 2001

Via Courier & Fax – 301 594-0108

Mr. Tim Ames, Project Manager
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773



RE: REQUEST FOR EXPEDITED REVIEW
Enalapril Maleate and HCTZ Tablets USP, 5 mg/12.5 mg and 10 mg/25 mg.
Dr. Reddy's Laboratories, Ltd./ANDA 75-909

Dear Mr. Ames:

This request for expedited review is being submitted by the US Agent, Dr. Reddy's Laboratories, Inc. on behalf of Dr. Reddy's Laboratories Limited, Bachepalli, 502 325 India.

Further to my September 26th, teleconference with Mr. Gregory Davis-Branch Chief, we would like to make the agency aware of several inconsistencies with respect to the Agency's electronic "Orange Book" regarding the above referenced Drug Product.

On September 18, 2001, the Agency granted final approval status to several generic manufacturers of Enalapril Maleate and Hydrochlorothiazide based upon the expiration of US Patent 4,472,380. However, we would like to bring to your attention the 21st Edition of the *Approved Drug Products with Therapeutic Equivalence Evaluations* reflects a pediatric extension has been granted to Enalapril Maleate; Vasoretic, thus extending the exclusivity period to March 18, 2002 (Exhibit 1). Further, the most recent electronic update, *Cumulative Update No. 6*; indicates no deletions have been made to the published pediatric extension for Enalapril Maleate; Vasoretic (Exhibit 2).

In addition to these official publications, the Agency's website entitled *CDER New and Generic Drug Approvals* reflect its position that final approval shall be awarded upon the expiry of pediatric exclusivity ending on March 18, 2002, as reflected in several Tentative Approval Letters (Exhibit 3).

Page 2
September 26, 2001
Mr. Tim Ames, Office of Generic Drugs

Based upon this published literature, Dr. Reddy's Laboratories, Ltd. has justly assumed the granting of a full 6-months pediatric exclusivity period. Further, Dr. Reddy's Laboratories Ltd. had planned to maximize Drug Product expiration dating by strategically scheduling its validation batches and commercialization based upon the Agency's original posted position indicating a March 18, 2002 expiration of pediatric exclusivity. As a result of the Agency granting final approval prior to this dated, it would appear as though the Agency erroneously listed 6-months of pediatric exclusivity to Enalapril Maleate; Vasercetic (the '380 patent).

In consideration of the above commercial impact, Dr. Reddy's Laboratories, Inc. hereby requests an expedited review to its amendment submitted September 11, 2001 and for final approval to ANDA 75-909.

Should you have any questions to the request, please contact me at (201) 760-2880.

Very truly yours,

DR. REDDY'S LABORATORIES, INC.



Paul V. Campanelli
Vice President, Formulations Business

cc. Mr. Gregory Davis, Office of Generic Drugs

Enclosures



ONE PARKWAY
LITTLE LAMBDA ROAD, NORTH
TELEPHONE: (201) 750-2880
FAX: (201) 750-2401

HAND DELIVERED

September 28, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/FA

**Reference: ANDA 75-909 Enalapril Maleate and Hydrochlorothiazide USP,
5-12.5 mg and 10-25 mg**

Telephone Amendment

Dear Sir/ Madam:

This amendment is being submitted by the US Agent, Dr. Reddy's Laboratories, Inc. on behalf of Dr. Reddy's Laboratories Limited, Bachepalli, 502 325 India. Reference is made to the original submission dated June 16, 2000, the amendment submitted on March 28, 2001 and agency letters dated December 14, 2000, July 27, 2001 and September 11, 2001 and September 28, 2001. Reference is also made to the correspondence from Mr. Paul Campanelli dated September 27, 2001 relating to Pediatric Exclusivity being lifted.

The agency request:

*Please reduce the limits for the dimer present in the Hydrochlorothiazide from
match the release limits.*

As requested the limits have been reduced. The Firm commits to provide revised copies of the specifications sheet to the agency.





Pursuant to *Code of Federal Regulations* Title 21 §314.440 (a) (4), a Field Copy of this application is being submitted to the Office of Generic Drugs. The Firm hereby certifies that it is a true copy of the technical section as described in *Code of Federal Regulations* Title 21 §314.50 (d) (1).

Please communicate any remaining questions or issues to C. Jeanne Taborsky, and they will be addressed and a response submitted immediately. This concludes our submission. Please feel free to contact me if you have any questions, tele (410) 309-3145, Fax (410) 309-6145.

Sincerely yours,

A handwritten signature in cursive script that reads "C. Jeanne Taborsky".

C. Jeanne Taborsky
Regulatory Affairs





DR. REDDY'S

Dr. Reddy's Laboratories, Inc.

ONE PARK WAY
UPPER SADDLE RIVER, NJ 07458
TELEPHONE: (201) 760-2880
FAX: (201) 760-0401

HAND DELIVERED

September 28, 2001

ORIG AMENDMENT

N/AA

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Reference: **ANDA 75-909 Enalapril Maleate and Hydrochlorothiazide USP,
5-12.5 mg and 10-25 mg**

Gratuitous Labeling Amendment EXPEDITED

Dear Sir/ Madam:

This amendment is being submitted by the US Agent, Dr. Reddy's Laboratories, Inc. on behalf of Dr. Reddy's Laboratories Limited, Bachepalli, 502 325 India. Reference is made to the original submission dated June 16, 2000, the amendment submitted on March 28, 2001 and agency letters dated December 14, 2000, July 27, 2001 and September 11, 2001.

Reference is also made to the correspondence from Mr. Paul Campanelli dated September 27, 2001 relating to Pediatric Exclusivity being lifted. Please be advised that the computer generated insert is of lesser quality than the actual insert. The US Agent commits to provide copies of the actual printed insert on receipt, next week.

The Firm is herein providing copies of computer generated final print labeling, and requesting immediate review and approval, should all chemistry issues be found to be satisfactory. Please communicate any remaining questions or issues to C. Jeanne Taborsky, and they will be addressed and a response submitted immediately. This concludes our submission. Please feel free to contact me if you have any questions, tele (410) 309-3145, Fax (410) 309-6145.

Sincerely yours,

C. Jeanne Taborsky
Regulatory Affairs



FA noted, -
to CMC Renewal for
review.
JRS
9/14/01



DR. REDDY'S

Dr. Reddy's Laboratories, Inc.

ONE PARK WAY
UPPER SADDLE RIVER, NJ 07458
TELEPHONE: (201) 760-2880
FAX: (201) 760-0401

VIA FEDERAL EXPRESS
September 11, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/FA

OTIC AMENDMENT

Reference: **ANDA 75-909 Enalapril Maleate and Hydrochlorothiazide USP,
5-12.5 mg and 10-25 mg**

RESPONSE TO MINOR NA LETTER

Dear Sir/ Madam:

This response is being submitted by the US Agent, Dr. Reddy's Laboratories, Inc. on behalf of Dr. Reddy's Laboratories Limited, Bachepalli, 502 325 India. Reference is made to the original submission dated June 16, 2000, the amendment submitted on March 28, 2001 and agency letters dated December 14, 2000 and July 27, 2001. The following information is the Firm's response to the agency CMC and Labeling questions:

FDA Comment:

A. *Chemistry Deficiencies:*

- 1.



Page (s) 1

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Commercial/Confidential
Information and are not
releasable.

9/11/01



DR. REDDY'S

Dr. Reddy's Laboratories, Inc.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

You have not yet responded to the labeling deficiencies communicated to you on December 14, 2001. The labeling for your drug product must be found acceptable in final print prior to approval.

We note and acknowledge agency's comment. The response to the labeling deficiency is submitted below.

Labeling Deficiencies dated December 14, 2000

1. Container – Bottles of 100 and 1000 tablets

Please ensure that the established name and expression of strength are the prominent print on the label.

As per the agency's recommendation the size of established name and strength are increased to improve the prominence on the label. A comparison is provided in Section IV and the draft labels are provided in Section V Labeling.

2. Package Insert

a. General comments

Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert

As requested by the agency, the USAN name has been treated as the common name in the labeling text (i.e. lower case), except for the title where upper case is used.

b. Title:

We encourage you to include "USP" in the established name of your drug product in this section.

In the side panel, under the heading 'Each tablet contains' "USP" is added after Enalapril Maleate and Hydrochlorothiazide.



DR. REDDY'S

Dr. Reddy's Laboratories, Inc.

c. *Description*

Third Paragraph first sentence –

With a molecular weight of 492.53 (replace "with" with "weight" and replaces 492.52" with 492.53")

As per agency's recommendation under "Description", paragraph third, "with" is "weight" and "492.52" is changed to "492.53".

This concludes our response to the Minor NA Letter. Please feel free to contact me if you have any questions, tele (410) 309-3145, Fax (410) 309-6145.

Sincerely yours,

C. Jeanne Taborsky
Regulatory Affairs



DR. REDDY'S

Dr. Reddy's Laboratories, Inc.

ONE PARK WAY

UPPER SADDLE RIVER, NJ 07458

TELEPHONE: (201) 760-2880

FAX: (201) 760-6491

HAND DELIVERED

September 28, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N/FA

**Reference: ANDA 75-909 Enalapril Maleate and Hydrochlorothiazide USP,
5-12.5 mg and 10-25 mg**

Telephone Amendment

Dear Sir/ Madam:

This amendment is being submitted by the US Agent, Dr. Reddy's Laboratories, Inc. on behalf of Dr. Reddy's Laboratories Limited, Bachepalli, 502 325 India. Reference is made to the original submission dated June 16, 2000, the amendment submitted on March 28, 2001 and agency letters dated December 14, 2000, July 27, 2001 and September 11, 2001 and September 28, 2001. Reference is also made to the correspondence from Mr. Paul Campanelli dated September 27, 2001 relating to Pediatric Exclusivity being lifted.

The agency request:

*Please reduce the limits for the dimer present in the Hydrochlorothiazide from
, match the release limits.*

As requested the limits have been reduced. The Firm commits to provide revised copies of the specifications sheet to the agency.





DR. REDDY'S

Dr. Reddy's Laboratories, Inc.

Pursuant to *Code of Federal Regulations* Title 21 §314.440 (a) (4), a Field Copy of this application is being submitted to the Office of Generic Drugs. The Firm hereby certifies that it is a true copy of the technical section as described in *Code of Federal Regulations* Title 21 §314.50 (d) (1).

Please communicate any remaining questions or issues to C. Jeanne Taborsky, and they will be addressed and a response submitted immediately. This concludes our submission. Please feel free to contact me if you have any questions, tele (410) 309-3145, Fax (410) 309-6145.

Sincerely yours,

C. Jeanne Taborsky
Regulatory Affairs



66 South Maple Avenue,
Ridgewood, NJ 07450
Phone: 201-444-4424
Fax: 201-444-1456

VIA FEDERAL EXPRESS
March 28, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
AC

Reference: **ANDA 75-909 Enalapril Maleate and Hydrochlorothiazide USP,
5-12.5 mg and 10-25 mg
RESPONSE TO MAJOR NA LETTER**



Dear Sir/ Madam:

Reference is made to the agency letter dated December 14, 2000. This response is being submitted by the US Agent, Reddy-Cheminor, Inc. on behalf of Dr. Reddy's Laboratories Limited, Bachepalli, 502 325 India. The following information is the agency CMC questions and the Firm's corresponding responses.

1. Regarding the active ingredient, Enalapril Maleate USP, we have the following Comments:

a. *Please tighten your specifications for, based upon observed values.*

The Specification of Organic Volatile Impurities and Residual Solvent have been revised to tighten the limits based on observed values. The revised specifications, and Analysis Report as per the revised specifications are provided in **Section VIII**.

b. *Please incorporate the test for Related Substances into the retest schedule.*

As recommended by the agency, the test for Related Substance is incorporated in Retest Schedule. The revised retest schedule is provided in **Section VIII**.

c. *Please revise your specifications for Related Impurities and incorporate a limit for the RSS isomeric impurity of Enalapril Maleate. Please specify limits that are bases upon observed values.*

The specifications are revised to incorporate a limit for RSS isomeric impurity. The revised specification for Related Impurities is well below the limits given in the monograph of Enalapril Maleate, USP in the USP 24, Supplement 3 (Page No. 3024). The existing test method for Related Substance is not resolving RSS isomeric impurity. Hence, USP 24, Supplement 3 test method is adopted with minor changes and the method is validated. The method validation of Related Substance is performed by API manufacturer (Dr. Reddy's Laboratories Limited - Bulk Drug Division) and the same method is transferred to Dr. Reddy's Laboratories Limited - Generic Division (Formerly Cheminor Drugs Limited - Pharma Division). The revised Specification and Analysis Report as per the revised specification are provided in **Section VIII** and the revised Test Procedures, Method Validation Report and Method Transfer Report are provided in **Section XV**.

- d. *Please provide a methods validation report for Related Substances (HPLC) and OVI/Residual Solvents (GC) according to the USP 24 General Chapter <1225> Validation of Compendial Methods of the CDER Guideline. Based upon the method's accuracy, please incorporate relative response factors, if known, into your calculation of known impurities.*

The method validation for Related Substance and Residual Solvents are performed according to USP 24 General Chapter <1225>. The method validation report for Related Substance is provided in **Section XV**, the method validation for Residual solvents was performed by API manufacturer (Dr. Reddy's Laboratories Limited - Bulk Drug Division) and the same method is transferred to Dr. Reddy's Laboratories Limited - Generic Division. The Method Transfer Report for Residual Solvents was already submitted in ANDA (Please refer to page no. 5205 - 5207). The method validation report for Residual Solvents is provided in **Section XV**. The Test Procedure is revised to incorporate relative response factor in the calculation of known impurities. The revised test procedure is provided in **Section XV**.

2. Regarding the active ingredient, Hydrochlorothiazide USP, we have the following comments:

- a. *Please incorporate a test for melting point, please specify a range based upon observed values.*

The specifications are revised to incorporate Melting range based on the observed values. The revised specifications and Analysis Report are provided in **Section VIII**.

- b. *Please provide a method validation report for Related Substance . Based upon the method's accuracy, please incorporate a relative response factor, if known, into your calculation of dimer impurity.*

~~Keeping the FDA comment (Point No. 2c) in view, the test method for estimation of _____ is changed. The _____ impurity standard is isolated and the method validation for estimation of _____ impurity is performed. The relative response factor is established and the test procedure is revised to incorporate, the relative response factor in the calculation of~~

Page (s) 4

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Information and are not

releasable.

3/28/07

We acknowledge the receipt of labeling deficiency and the response will be sent to labeling review branch separately, as labeling amendment.

We appreciate your assistance in this matter. Please feel free to contact me if you have any questions, tele (201) 444-4424, Fax (210) 444-1456.

Sincerely yours,

A handwritten signature in cursive script that reads "Paul Campanelli".

Paul Campanelli
Vice President

ONE PARK WAY
UPPER SADDLE RIVER, NJ 07458
TELEPHONE (201) 760-2880
FAX (201) 760-0401

AUG 21 2001

SENT VIA FEDERAL EXPRESS

NEW CORRESP
NC

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NA3 10/15/01
Zak's letter

**Reference: ANDA #75-909 Enalapril Maleate and Hydrochlorothiazide Tablets
USP 5/12.5 mg and 10/25 mg
Correspondence**

Dear Sir/ Madam:

Dr. Reddy's Laboratories, Inc. US Agent for Dr. Reddy's Laboratories Limited, Bachepalli 502 325, INDIA, is herein submitting a revised Letter of Authorization for US Agent with updated information.

Please be advised that the name and address of the US agent has changed.

Pursuant to *Code of Federal Regulations* Title 21 §314.440 (a) (4), a third copy of this communication is being provided. This is the required field copy and we certify that it is a true copy of the technical section as described in *Code of Federal Regulations* Title 21 §314.50 (d) (1).

This concludes our submission. Please contact C. Jeanne Taborsky at (410) 309-3145 or Paul V. Campanelli, Vice President Formulations Business, Reddy-Cheminor, Inc. at (201) 760-2880 ext 203, if you have any questions concerning this submission.

Sincerely yours,

C. Jeanne Taborsky
C. Jeanne Taborsky
Regulatory Affairs Consultant



66 South Maple Avenue,
Ridgewood, NJ 07450

Phone: 201-444-4424
Fax: 201-444-1456

NEW CORRESP

NC

January 16, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**Reference: ANDA 75-909 Enalapril Maleate and Hydrochlorothiazide Tablets USP,
5/12.5 and 10/25 mg
Correspondence**

This correspondence is being provided by the US Agent on behalf of Cheminor Drugs Limited (Pharma Division), Via IDA Bollaram, Bachepalli - 502 325, INDIA. On January 2, 2001, the Andhra Pradesh High Court ruled on the merger of Cheminor Drugs Limited and Dr. Reddy's Laboratories. As of that date, Cheminor Drugs Limited is known as Dr. Reddy's Laboratories Limited.

The address and all other information remain the same. Documents have been filed to change the Registration Number and labeler code to that of Dr. Reddy's Laboratories Limited.

Pursuant to Code of Federal Regulations Title 21 § 314.440 (a) (4), a Field Copy of this correspondence is being submitted to the Office of Generic Drugs. The Firm hereby certifies that it is a true copy of the technical section as described in 21 CFR 314.50 (d) (1).

Thank you for your assistance in this matter. Please feel free to contact us if necessary.

Sincerely yours,


C. Jeanne Taborsky
Regulatory Affairs Consultant



1/1 Duplicate

REDDY-CHEMINOR, INC. **R-C**

66 South Maple Avenue,
Ridgewood, NJ 07450

Phone: 201-444-4424

Fax: 201-444-1456

NEW CORRESP

NC

January 16, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Acknowledged.
B. notify HFD-92
FBI/DOH 1/19/01

**Reference: ANDA 75-909 Enalapril Maleate and Hydrochlorothiazide Tablets USP,
5/12.5 and 10/25 mg
Correspondence**

This correspondence is being provided by the US Agent on behalf of Cheminor Drugs Limited (Pharma Division), Via IDA Bollaram, Bachepalli - 502 325, INDIA. On January 2, 2001, the Andhra Pradesh High Court ruled on the merger of Cheminor Drugs Limited and Dr. Reddy's Laboratories. As of that date, Cheminor Drugs Limited is known as Dr. Reddy's Laboratories Limited.

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Thank you for your assistance in this matter. Please feel free to contact us if necessary.

Sincerely yours,

C. Jeanne Taborsky
C. Jeanne Taborsky
Regulatory Affairs Consultant



66 South Maple Avenue
Ridgewood, New Jersey 07450
Telephone (201) 444-4424
Telefax (201) 444-1456

September 20, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT

N/AB

Reference: Telephone Amendment/Cheminor Drugs Limited
Enalapril Maleate Tablets HCTZ/ANDA 75-909

Dear Sir or Madam:

On September 7, 2000, Reddy-Cheminor, Inc., (US Agent for Cheminor Drugs Ltd.) was contacted by Jennifer Fan and Patrick Nwakama from the Office of Generic Drugs regarding the above referenced ANDA 75-909.

Upon completion of the teleconference, the Sponsor was issued Telephone Amendment status for the following cited bioequivalence deficiencies:

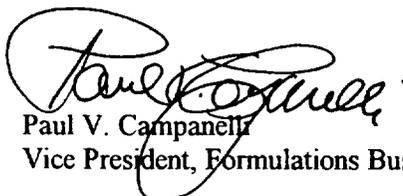
- Preliminary review of ANDA 75-909 was discussed. Issue: Reviewer can not locate percent recovery for the internal standards for
• Reddy-Cheminor is required to provide data within 10 business days in order to maintain telephone amendment status.

Reddy-Cheminor herewith provides the following information via facsimile and hardcopy original:

- Determination of Hydrochlorothiazide in human Plasma by
- Determination of Enalapril and Enalaprilat in Human Plasma by

Please contact the undersigned at (201) 444-4424 or by fax at (201) 444-1456 should you have any questions regarding this submission.

Very truly yours,
REDDY-CHEMINOR, INC.


Paul V. Campanelli
Vice President, Formulations Business

Attachments



ANDA 75-909

Reddy-Cheminor, Inc.,
U.S. Agent for: Cheminor Drugs Limited
Attention: Paul V. Campanelli
66 South Maple Avenue
Ridgewood, NJ 07450
|||||

AUG -9 2000

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Enalapril Maleate and Hydrochlorothiazide Tablets
USP, 5 mg;12.5 mg and 10 mg;25 mg

DATE OF APPLICATION: June 16, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 23, 2000

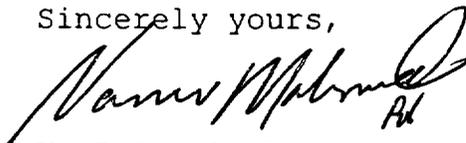
We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Bonnie McNeal
Project Manager
(301) 827-5848

Sincerely yours,



Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



66 South Maple Avenue
Ridgewood, New Jersey 07450
Telephone (201) 444-4424
Telefax (201) 444-1456

June 16, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Reference : **Enalapril Maleate and Hydrochlorothiazide Tablets, USP**
 5-12.5 mg and 10-25 mg.
 Abbreviated New Drug Application

Dear Sir/ Madam:

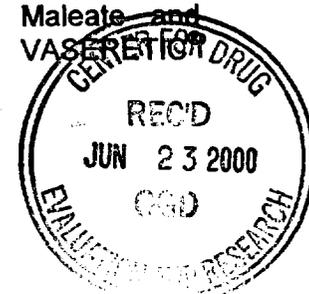
Cheminor Drugs Limited herewith submits an abbreviated new drug application (ANDA) for Enalapril Maleate and Hydrochlorothiazide Tablets, USP 5-12.5 mg and 10-25 mg pursuant to Section 505 (j) of the Federal Food, Drug, and Cosmetic Act.

This ANDA refers to the listed drug, VASERETIC® (Enalapril Maleate – Hydrochlorothiazide) Tablets, 5-12.5 mg and 10-25 mg which is manufactured by MERCK & Co., the holder of the approved application, and which is listed in the 1999 Approved Drug Products with Therapeutic Equivalence Evaluations, 19th Edition. U.S Patent No. 4,374,829 will expire on February 22, 2000 and patent number 4,472,380 will expire on September 18, 2001. Cheminor Drugs Limited is not seeking to market the product until after the patents expire.

Enalapril Maleate and Hydrochlorothiazide Tablets, USP 5-12.5 mg and 10-25 mg will be manufactured, tested and packed by at Cheminor Drugs Limited, Pharma Division, Bachepally, Post Bag No.: 15, Kukatpally P.O., Hyderabad – 500 072, INDIA in accordance with 21 CFR § parts 210 and 211.

Enalapril Maleate, USP manufactured by Dr. Reddy's Laboratories Limited, Plot No. 116, I.D.A. Bollaram, Narsapur (Tq), Medak (Dt.), Andhra Pradesh, INDIA, (DMF No. 13836), and Hydrochlorothiazide, USP manufactured by

The required bioavailability / bioequivalence studies were conducted on Enalapril Maleate and Hydrochlorothiazide Tablets, USP 10-25 mg and VASERETIC® (Enalapril Maleate – Hydrochlorothiazide) Tablets, 10-25 mg by AAI, 6101 Quadrangle Drive, Chapel Hill, NC 27514. These studies indicate that Enalapril Maleate and Hydrochlorothiazide Tablets, USP 10-25 mg are bioequivalent to VASERETIC® (Enalapril Maleate – Hydrochlorothiazide) Tablets, 10-25 mg.



REDDY-CHEMINOR, INC.

June 16, 2000

Food and Drug Administration
Enalapril Maleate and Hydrochlorothiazide Tablets, USP 5-12.5 mg and 10-25 mg.
Abbreviated New Drug Application

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The *in-vitro* dissolution profiles for Enalapril Maleate and Hydrochlorothiazide Tablets, USP 5-12.5 mg and 10-25 mg are comparable to those of VASERETIC® (Enalapril Maleate – Hydrochlorothiazide) Tablets, 5-12.5 mg and 10-25 mg.

Enalapril Maleate and Hydrochlorothiazide Tablets, USP 5-12.5 mg and 10-25 mg are stable and a two year expiration dating is requested. The two year expiration dating for this product is supported by one, two and three months accelerated stability data (40°C / 75% relative humidity) in the smallest and largest package size of the container / closure system proposed for marketing. The stability studies were conducted under a stability protocol that is in conformance with the current FDA stability guidelines.

The dosage form, route of administration, active ingredient, potency and labeling (except DESCRIPTION and HOW SUPPLIED Sections) for Enalapril Maleate and Hydrochlorothiazide Tablets, USP 5-12.5 mg and 10-25 mg are the same as those for VASERETIC® (Enalapril Maleate–Hydrochlorothiazide) Tablets, 5-12.5 mg and 10-25 mg.

This ANDA is submitted in ten (10) volumes :

Volume I	:	Sections I through Section VI
Volume II	:	Section VI (continued)
through	:	
Volume VII	:	Section VI (continued) through Section VII
Volume VIII	:	Section VIII through Section XI
Volume IX	:	Section XII through Section XIV
Volume X	:	Section XV through Section XXII

Par Pharmaceutical, Inc. will be the distributor for this product. The proposed labeling has been prepared using the Par logo. A letter authorizing Reddy-Cheminor, Inc., to act as the U.S agent for this ANDA, is provided in Section XX. Included in this submission is an extra copy of our cover letter. Please acknowledge by date stamping this letter upon receipt and forwarding this copy to us in the self-addressed stamped envelope provided for your convenience.

REDDY-CHEMINOR, INC.

June 16, 2000

Food and Drug Administration
Enalapril Maleate and Hydrochlorothiazide Tablets, USP 5-12.5 mg and 10-25 mg
Abbreviated New Drug Application

Page 3

Pursuant to 21 CFR 314.440 (a) (4), a third copy of this application is also enclosed. This is the required field copy and we certify that it is a true copy of the technical section as described in 21 CFR 314.50 (d) (1).

Sincerely,

A handwritten signature in black ink, appearing to read "Paul V. Campanelli". The signature is written in a cursive style with a horizontal line underneath.

Paul V Campanelli
Vice President
Formulations Business