

## Enalapril

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**Abstract:** Enalapril is an angiotensin converting enzyme (ACE) inhibitor, known as the dicarboxylate-containing ACE inhibitors, and is normally used in the treatment of hypertension and chronic heart failure. The enalapril structure formula is  $C_{20}H_{28}N_2O_5$ , molecular weight is 376.447, half life is 11 hours and excreted by renal. Enalapril maleate (Vasotec) is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat. The chemical name of enalapril maleate is (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (Z)-2-butenedioate salt (1:1). The enalapril maleate structure formula is  $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$  and molecular weight is 492.53. Enalapril maleate is unlike the prototype angiotensin-converting enzyme inhibitor captopril in that a standard meal does not appear to influence absorption of this new drug.

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### 1. Introduction

Enalapril is an angiotensin converting enzyme (ACE) inhibitor, known as the dicarboxylate-containing ACE inhibitors, and is normally used in the treatment of hypertension and chronic heart failure. It is developed and patented by Merck & Co., Inc (Whitehouse Station, NJ, USA) under the trade names Renitec and Vasotec. The primary effect of enalapril, as with all ACE inhibitors, is to lower blood pressure. Enalaprilat itself, however, was not without its problems. The consequence of the structural modifications was that it proved to have unfavourable ionisation characteristics to allow sufficient potency for oral administration. Thus enalaprilat was only suitable for intravenous administration. This was overcome by the researchers at Merck by the esterification of enalaprilat with ethanol to produce enalapril. Although there are several fixed-combination drugs, the combination lercanidipine plus enalapril appears to be one of the most promising therapies in the treatment of hypertension (Barrios, Escobar et al. 2008). The dihydropyridine calcium channel blocker lercanidipine and the ACE inhibitor enalapril are frequently used in the treatment of hypertensive patients (Menne and Haller 2008). Long-term administration of enalapril results in partial restoration of disturbed at diabetes mellitus reactions and also to reduction of oxygen cost of smooth muscles and myocardial work (Prisyazhna, Kotsiuruba et al. 2007). Combined therapy or dose-titration are acceptable second-line therapeutic options after a first treatment failure (Marin-Iranzo, de la Sierra-Iserte et al. 2005). The clinical studies suggest a potential antiarrhythmic role of angiotensin-converting enzyme inhibitors in preventing atrial fibrillation. Intravenous

enalapril does not avoid the occurrence of pacing-induced acute electrical atrial remodeling, modify its time course, or impede the induction of atrial fibrillation (Moreno, Villacastin et al. 2004).

Enalapril is a prodrug that is converted by deesterification to converting enzyme inhibitor, enalaprilat, with effects similar to those of captopril. Enalapril itself is available only for intravenous use, primarily for hypertensive emergencies. Vasotec is in a group of drugs called ACE inhibitors. ACE stands for angiotensin converting enzyme. Vasotec is used to treat high blood pressure (hypertension), congestive heart failure, kidney problems caused by diabetes, and to improve survival after a heart attack. Vasotec may also be used for purposes other than those listed in this medication guide. Do not use this medication without telling your doctor if you are pregnant or planning a pregnancy. Vasotec could cause birth defects in the baby if you take the medication during pregnancy. Use an effective form of birth control. Stop using this medication and tell your doctor right away if you become pregnant during treatment. Vomiting, diarrhea, or heavy sweating can cause you to become dehydrated. This can lead to very low blood pressure, electrolyte disorders, or kidney failure while you are taking Vasotec. Drink plenty of water each day while you are taking this medication (<http://www.drugs.com/vasotec.html>).

### 2. Characterization and structure of enalapril

The characterization and structure of enalapril are following (Figure 1):

Formula:  $C_{20}H_{28}N_2O_5$

MW: 376.447

Half life: 11 hours

Excretion: renal

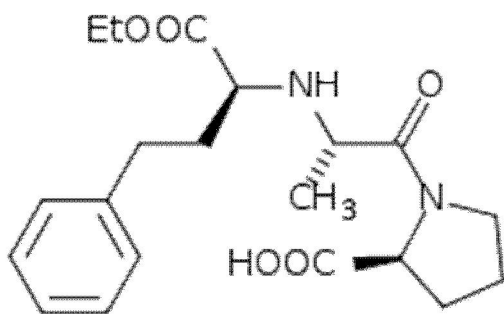


Figure 1. Chemical structure of enalapril

Enalapril maleate (Vasotec) is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat. The chemical name of enalapril maleate is (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (Z)-2-butenedioate salt (1:1).

The cis- and trans-isomers of enalapril and enalaprilat can be resolved by HPLC and by capillary electrophoresis. The isomeric content of enalapril is perturbed by the ionization of both its carboxyl and amine groups, while the isomeric content of enalaprilat is only perturbed by the ionization of its amine group. Increasing the hydrophobicity of the

analyte solvent, as reflected in its molar polarization, increases the Z (cis) content of enalapril and markedly decreases the kinetics for isomerization. Far UV circular dichroic measurements suggest that the increase in Z (cis) content of enalapril is due to protonation of its carboxylate group. Taken together, the in-vitro properties of enalapril and enalaprilat suggest that the in-vivo transformation of the prodrug enalapril to the inhibitor enalaprilat and its delivery to angiotensin-converting enzyme should not be significantly limited by cis/trans-isomerization (Ledger and Stellwagen 2005).

### 3. Characterization and structure of enalapril maleate

The characterization and structure of enalapril maleate are following (Figure 2):

Formula:  $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$

MW: 492.53

Product: white to off-white, crystalline powder

Resolve: sparingly soluble in water, soluble in ethanol, and freely soluble in methanol.

Administration: a pro-drug, oral administration

Biology: bioactivated by hydrolysis of the ethyl ester to enalaprilat

Medical: active angiotensin converting enzyme inhibitor.

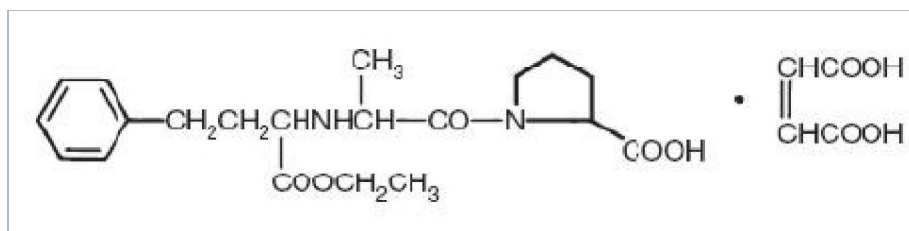


Figure 2. Chemical structure of enalapril maleate (Vasotec)

In the study by the group of Gu et al, a rapid, sensitive, and highly selective liquid chromatography-tandem mass spectrometry method was developed and validated for simultaneous determination of enalapril and its major active metabolite enalaprilat in human plasma. The analytes were extracted from plasma samples by liquid-liquid extraction, separated on a Zorbax Extend-C(18) column, and detected by tandem mass spectrometry with a Turbo IonSpray ionization interface. The method has a lower limit of quantification (LLOQ) of 0.1 ng/ml for both enalapril and enalaprilat. The chromatographic run time was approximately 3.5 min. The standard calibration curves for both enalapril and enalaprilat were linear in the concentration ranges of 0.10-100.0 ng/ml in human plasma. The intra- and inter-run precisions,

expressed as the relative standard deviation (R.S.D.), were less than 7.7 and 7.8%, determined from QC samples for enalapril and enalaprilat, and accuracy was within +/-3.9 and +/-2.7% in terms of relative error, respectively. The method was successfully applied for the evaluation of the pharmacokinetics of enalapril and enalaprilat in 20 volunteers after an oral dose of 10 mg enalapril maleate (Gu, Chen et al. 2004).

In 2009, Sosnowska et al investigated the stability of enalapril maleate in oral formulations prepared from commercially available tablets. Extemporaneously compounded, 0.1 mg/mL and 1.0 mg/mL, oral suspensions of enalapril maleate in sugar-containing and sugar-free vehicles were stored in the absence of light at 4°C and 25°C for 30 days.

Enalapril maleate stability was quantified after 7, 14, 21, and 30 days using HPLC method. Viscosities and pH of prepared suspensions were measured on each study day and no appreciable changes from the initial pH and initial viscosities occurred in any of the samples both at 25°C and 4°C. It was shown that all the formulations retain minimum 98% of the initial enalapril maleate concentration after 30 days of storage at 25°C and 4°C and they may provide an option in situations where the marketed suspension is unavailable (Sosnowska, Winnicka et al. 2009).

#### 4. Enalaprilat

Enalaprilat, the first dicarboxylate-containing ACE inhibitor, was developed to overcome the limitations of captopril. In the structure of enalaprilat, the sulfhydryl-moiety is replaced by a carboxylate-moiety, but additional modifications are required in its structure-based design to achieve a similar potency to captopril. The consequence of the structural modifications is that it has unfavourable ionisation characteristics to allow sufficient potency for oral administration in tablets. Enalaprilat is only suitable for intravenous administration. This is overcome by the esterification of enalaprilat with ethanol to produce enalapril. As a prodrug, enalapril is metabolised *in vivo* to the active form enalaprilat by various esterases. Peak plasma enalaprilat concentrations occur 2 to 4 hours after oral enalapril administration. Elimination thereafter is biphasic, with an initial phase which reflects renal filtration (elimination half-life 2 to 6 hours) and a subsequent prolonged phase (elimination half-life 36 hours), the latter representing equilibration of drug from tissue distribution sites. The prolonged phase does not contribute to drug accumulation on repeated administration but is thought to be of pharmacological significance in mediating drug effects. Renal impairment (particularly creatinine clearance <20 ml/min) results in significant accumulation of enalaprilat and necessitates dosage reduction. Accumulation is probably the cause of reduced elimination in healthy elderly individuals and in patients with concomitant diabetes, hypertension and heart failure. The beneficial effect of enalapril is not related to effects on lysosomal membrane (Martinelli, Santos et al. 2007).

Enalaprilat eyedrops lower intraocular pressure in rabbits. The decline in intraocular pressure is proportional to the concentration of dissolved enalaprilat in low-viscosity aqueous eyedrop formulations (Loftsson, Thorisdottir et al. 2009).

Enalapril maleate is supplied as 2.5 mg, 5 mg, 10 mg, and 20 mg tablets for oral administration. In addition to the active ingredient enalapril maleate, each tablet contains the following inactive ingredients:

lactose, magnesium stearate, sodium bicarbonate, and starch. The 10 mg and 20 mg tablets also contain iron oxides. Blood pressure control remains poorly achieved in the general population, particularly in high- or very-high-risk hypertensive patients (Tocci, Palano et al. 2009).

#### 5. Vasotec (enalapril maleate)

Vasotec (enalapril maleate) is the maleate salt of enalapril, the ethyl ester of a long-acting ACE inhibitor, enalaprilat. Enalapril maleate is chemically described as (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (Z)-2-butenedioate salt (1:1). Its empirical formula is  $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$ , and its structural formula is shown by Figure 2.

Vasotec is indicated for the treatment of hypertension, symptomatic congestive heart failure, usually in combination with diuretics and digitalis. Vasotec is effective alone or in combination with other antihypertensive agents, especially thiazide-type diuretics. The blood pressure lowering effects of Vasotec and thiazides are approximately additive. And, Vasotec improves symptoms, increases survival, and decreases the frequency of hospitalization. In clinically stable asymptomatic patients with left ventricular dysfunction, Vasotec decreases the rate of development of overt heart failure and decreases the incidence of hospitalization for heart failure. In using Vasotec consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that Vasotec does not have a similar risk. In considering use of Vasotec, it should be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks.

#### 6. Administration and dosage

##### (1) Hypertension

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of Vasotec. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with Vasotec to reduce the likelihood of hypotension. If the patient's blood pressure is not controlled with Vasotec alone, diuretic therapy may be resumed. If the diuretic cannot be discontinued an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood

pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice daily administration should be considered. If blood pressure is not controlled with Vasotec alone, a diuretic may be added. Concomitant administration of Vasotec with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium. For hypertension patient, start dosage of enalapril is enalapril 5 mg/person/day (enalapril 0.08 mg/kg human/day). Dosage should be adjusted according to blood pressure response. The usual dosage range is enalapril 10 to 40 mg/person/day (enalapril 0.16-0.64 mg/kg human/day). The rat is about 0.3 kg each and the food for rat is about 10 g/rat/day. For rat research, dosage will be: enalapril 0.64 mg/kg rat/day = enalapril 0.2 mg/rat/day = enalapril 0.02 mg/g food.

Adverse experiences occurring in greater than 1% of patients with hypertension treated with Vasotec in controlled clinical trials are shown below. In patients treated with Vasotec, the maximum

duration of therapy was three years; in placebo treated patients the maximum duration of therapy was 12 weeks. The usual recommended starting dose is 0.08 mg/kg (up to 5 mg) once daily. Dosage should be adjusted according to blood pressure response. Vasotec is not recommended in neonates and in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m<sup>2</sup>.

In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure.

### (2) Dosage adjustment in hypertensive patients with renal impairment

For patients with creatinine clearance ≤30 mL/min (serum creatinine ≥3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily (Table 1).

Table 1. Dosage of enalapril

Renal Status	Creatinine-Clearance mL/min	Initial Enalapril Dose mg/day
Normal Renal Function	creatinine clearance >80 mL/min	5 mg
Mild Impairment	80 ≤ creatinine clearance < 30 mL/min	5 mg
Moderate to Severe Impairment	creatinine clearance ≤30 mL/min	2.5 mg
Dialysis Patients	—	2.5 mg on dialysis days

In April 2007, a fixed-dose combination of the two drugs was approved in Germany for the treatment of patients not responding to monotherapy. Two doses will be available with 10 mg lercanidipine each and 10 or 20 mg enalapril. The medication should be taken once daily, optimally =15 minutes before a meal and the consumption of grapefruit juice should be avoided. The fixed-dose combination of the two drugs has a stronger blood pressure-lowering effect than monotherapy with 20 mg enalapril or 10 mg lercanidipine. The combination is well tolerated and few patients stopped the treatment because of side effects. As expected, the most common side effects reported are cough, peripheral edema, flushing, dizziness and vertigo, occurring in 1-5% of patients. This new fixed-dose combination is a useful adjunct to the present treatment and should increase compliance and help reduce hypertension-related costs (Menne and Haller 2008). In patients with heart failure who have hyponatremia (serum sodium <130

mEq/L) or with serum creatinine >1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. The maximum daily dose is 40 mg.

### (3) Heart failure

Vasotec is indicated for the treatment of symptomatic heart failure, usually in combination with diuretics and digitalis. In the placebo-controlled studies that demonstrated improved survival, patients were titrated as tolerated up to 40 mg, administered in two divided doses. The recommended initial dose is 2.5 mg. The recommended dosing range is 2.5 to 20 mg given twice a day. Doses should be titrated upward, as tolerated, over a period of a few days or weeks. The maximum daily dose administered in clinical trials was 40 mg in divided doses. After the initial dose of Vasotec, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. If possible, the dose of any concomitant diuretic should be reduced which may

diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of Vasotec does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

Adverse experiences occurring in greater than 1% of patients with heart failure treated with Vasotec are shown below. The incidences represent the experiences from both controlled and uncontrolled clinical trials. In the placebo treated patients, the incidences reported are from the controlled trials. The percentage of patients with severe heart failure (NYHA Class IV) was 29% and 43% for patients treated with Vasotec and placebo, respectively. Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5 to 1.0% of patients with hypertension or heart failure in clinical trials are listed below and, within each category, are in order of decreasing severity.

#### **(4) Ventricular dysfunction**

In the trial that demonstrated efficacy, patients were started on 2.5 mg twice daily and were titrated as tolerated to the targeted daily dose of 20 mg. After the initial dose of Vasotec, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. If possible, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of Vasotec does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

To compare the effect of the dual endothelin A/B receptor antagonist enrasentan with enalapril on left ventricular (LV) remodeling, Prasad et al did studies in 2006. In this study, multicentre, randomised, double blind, parallel group study of 72 asymptomatic patients with LV dysfunction. Patients received enrasentan (60-90 mg/day) or enalapril (10-20 mg/day). The primary end point was the change in LV end diastolic volume index (EDVI) after six months' treatment. LV EDVI increased with enrasentan but decreased with enalapril. Enrasentan increased resting cardiac index compared with enalapril, as well as LV mass index. Other variables were comparable between groups. Enalapril lowered brain natriuretic peptide more than enrasentan. Noradrenaline increased more with enrasentan than with enalapril. Enrasentan was associated with more serious adverse events compared with enalapril; the rate of progression of heart failure did not differ. In asymptomatic patients with LV dysfunction, LV EDVI increased over six months with enrasentan compared with enalapril treatment, with adverse

neurohormonal effects. This suggests that enrasentan at a dose of 60-90 mg/day over six months causes adverse ventricular remodeling despite an increase in the resting cardiac index (Prasad, Dargie et al. 2006).

#### **(5) Preparation of suspension**

Combination of enalapril 10 mg with nitrendipine 20 mg combines an ACE inhibitor with a calcium channel antagonist (CCA) and is indicated for the treatment of patients with mild-to-moderate hypertension whose blood pressure (BP) is inadequately controlled with enalapril or nitrendipine monotherapy. By the studies of Siddiqui and Plosker, in randomised, double-blind clinical trials, enalapril/nitrendipine 10/20 mg/day was significantly more effective than its individual components in reducing diastolic BP (DBP) in patients with mild-to-moderate hypertension inadequately controlled with enalapril 10 mg/day or nitrendipine 20 mg/day. The fixed-dose combination was similar in efficacy at reducing DBP to amlodipine 10 mg/day in patients who failed to achieve BP control with amlodipine 5 mg/day, and to losartan/hydrochlorothiazide 50/12.5 mg/day in patients who received the combinations as first-line therapy. Enalapril/nitrendipine 10/20 mg produced a consistent antihypertensive effect that persisted for the entire 24-hour dosage interval as shown by ambulatory BP monitoring. Enalapril/nitrendipine 10/20 mg was well tolerated in clinical trials where it was administered to patients with mild-to-moderate hypertension for up to 12 weeks. The adverse events were those expected of ACE inhibitors and CCAs and included cough, headache and flushing. Evidence from clinical trials, including a pooled analysis, suggests that the incidence of oedema may be significantly lower with the fixed-dose combination than with CCA monotherapy. In conclusion, enalapril/nitrendipine 10/20 mg is a well tolerated fixed-dose combination of two established antihypertensive agents administered once daily that effectively lowers BP throughout the 24-hour dosage interval (Siddiqui and Plosker 2004).

#### **7. Side effects of Vasotec**

Vasotec has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. Vasotec has been found to be generally well tolerated in controlled clinical trials involving 2987 patients. For the most part, adverse experiences were mild and transient in nature. In clinical trials, discontinuation of therapy due to clinical adverse experiences was required in 3.3% of patients with hypertension and in 5.7% of patients with heart failure. The frequency of adverse experiences was not related to total daily dosage within the usual dosage ranges. In patients with

hypertension the overall percentage of patients treated with Vasotec reporting adverse experiences was comparable to placebo.

ACE inhibitors, as well as aminocephalosporins with peptide-like structures, are transported by the intestinal peptide carrier. The uniqueness of enalapril regarding its mode of interaction with the peptide carrier(s) which has been of increasing interest regarding its role in the intestinal absorption of peptide-type drugs (Yuasa, Fleisher et al. 1994).

While enalapril and captopril produce similar efficacy, enalapril is better tolerated and appears not to be associated with occurrence of captopril-type side-effects, particularly the skin rash, taste loss, leukopenia and proteinuria. Enalapril and other converting enzyme inhibitors may be associated with renal insufficiency when given to patients with bilateral renovascular hypertension (McFate Smith, Davies et al. 1984).

### **(1) Cardiovascular**

Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients; pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; palpitation, Raynaud's phenomenon.

Zhang et al reported the investigating the preventive and therapeutic effects of enalapril maleate (Enalaprilat) (E) on myocardial damage in early stage after burns in 2007. In their project, a total of 60 rats were subjected to 30% TBSA III degree scald injury, and randomly divided into scald group (with conventional fluid transfusion after scald) and ENA group (with intraperitoneal injection of 1 mg/kg Enalaprilat after scald). Normal control consisted of 6 rats. Plasma levels of cTnI and CK-MB were determined in all the groups at 1, 3, 6, 12, 24 post-scald hours (PSH) by enzyme linked immunosorbent assay. The pathological changes in myocardium were observed at the same time-points. The serum level of cTnI and CK-MB in scald group were significantly higher than that of normal controls at each time-point ( $P < 0.01$ ). The serum level of cTnI and CK-MB in ENA group were ( $1.32 \pm 0.12$  microg/L to  $2.47 \pm 0.22$  microg/L) and ( $438 \pm 68$  U/L to  $5569 \pm 322$  U/L), respectively, which were obviously lower than those in B group ( $6.42 \pm 0.96$  microg/L to  $15.10 \pm 3.69$  microg/L) and ( $2556 \pm 74$  U/L to  $8047 \pm 574$  U/L,  $P < 0.05$  or  $P < 0.01$ ) at different time-points. Compared with normal controls, cloudy swelling, stromal blood vessel dilatation and congestion inflammatory cell infiltration were observed in scald group, but these pathological changes were less marked in ENA group.

Severe myocardial damage in rat occurred early after burns. Enalaprilat injection can markedly alleviate myocardial damage (Zhang, Huang et al. 2007).

### **(2) Digestive**

Ileus, pancreatitis, hepatic failure, hepatitis, melena, anorexia, dyspepsia, constipation, glossitis, stomatitis, dry mouth.

Hepatic fibrosis is a common feature in different types of chronic liver injury. Enalapril is significantly more effective than captopril in improvement of hepatic fibrosis. Also, enalapril has a significant antioxidative effect in comparison with captopril. The antifibrotic effect of enalapril may be mostly related to the inhibition of ACE (Karimian, Mohammadi-Karakani et al. 2008).

### **(3) Nervous/Psychiatric**

Depression, confusion, ataxia, somnolence, insomnia, nervousness, peripheral neuropathy, dream abnormality.

### **(4) Respiratory**

Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection, pulmonary infiltrates, eosinophilic pneumonitis.

### **(5) Skin**

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

### **(6) Urogenital**

Renal failure, oliguria, renal dysfunction, flank pain, gynecomastia, impotence.

### **(7) Angioedema**

Angioedema has been reported in patients receiving Vasotec, 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 Vasotec should be discontinued and appropriate therapy instituted immediately.

### **(8) Hematologic**

Rare cases of neutropenia, thrombocytopenia and bone marrow depression.

### **(9) Musculoskeletal**

Muscle cramps.

### **(10) Pediatric Patients**

The adverse experience profile for pediatric patients appears to be similar to that seen in adult patients.

### **(11) Clinical Laboratory Test Findings on Serum Electrolytes**

Hyperkalemia, hyponatremia.

### **(12) Special Senses**

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

**(13) 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.

**8. Clinical lab information of Vasotec****(1) Creatinine, blood urea nitrogen**

In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with Vasotec alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of Vasotec and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

**(2) Hematology**

Small decreases in hemoglobin and hematocrit occur frequently in either hypertension or congestive heart failure patients treated with Vasotec but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril cannot be excluded.

**(3) Liver function tests**

Elevations of liver enzymes and/or serum bilirubin have occurred.

**(4) 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 close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour.

**(5) Agents Causing Renin Release**

The antihypertensive effect of Vasotec is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

**(6) Non-steroidal Anti-inflammatory Agents**

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of enalapril may result in a further deterioration of renal function. These effects are usually reversible. In a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving Vasotec. In this study there was no evidence of a blunting of the antihypertensive action of Vasotec. However, reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

**(7) Other Cardiovascular Agents**

Vasotec has been used concomitantly with beta adrenergic-blocking agents, methyl dopa, nitrates, calcium-blocking agents, hydralazine, prazosin and digoxin without evidence of clinically significant adverse interactions.

**(8) Agents Increasing Serum Potassium**

Vasotec attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium sparing agents should generally not be used in patients with heart failure receiving Vasotec.

**(9) 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 Vasotec 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.

**(10) Gold**

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including Vasotec.

**(11) 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 may be subject to a variety of adverse reactions, some of them serious.

**(12) Head and Neck Angioedema**

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including Vasotec. This may occur at any time during treatment. In such cases Vasotec 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.

**(13) Intestinal Angioedema**

Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain; in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor.

**(14) 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 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.

**(15) Blood Pressure**

Excessive hypotension is rare in uncomplicated hypertensive patients treated with Vasotec alone. Patients with heart failure given Vasotec commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic

hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic, reduce the diuretic dose or increase salt intake cautiously before initiating therapy with Vasotec in patients at risk for excessive hypotension who are able to tolerate such adjustments. In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of Vasotec, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of Vasotec or concomitant diuretic may be necessary.

**(16) 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.

**(17) Hepatic Failure**

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis, and 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.

#### **(18) 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. In a published retrospective epidemiological study, infants whose mothers had taken an ACE inhibitor during their first trimester of pregnancy appeared to have an increased risk of major congenital malformations compared with infants whose mothers had not undergone first trimester exposure to ACE inhibitor drugs. The number of cases of birth defects is small and the findings of this study have not yet been repeated. 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 Vasotec as soon as possible. Rarely, 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, Vasotec should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or

substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure. No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a body surface area basis, the doses used were 57 times and 12 times, respectively, the maximum recommended human daily dose (MRHDD).

### **9. Precautions**

#### **(1) 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.

#### **(2) Impaired Renal Function**

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including Vasotec, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% 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 Vasotec has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Vasotec may be required.

#### **(3) Hyperkalemia**

Elevated serum potassium was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients but was not a cause for discontinuation. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt

substitutes, which should be used cautiously, if at all, with Vasotec.

#### **(4) Cough**

Cough is an adverse event associated with the angiotensin-converting enzyme (AA inhibitor) drugs. ACE inhibitor-induced cough is believed to be related to the accumulation of bradykinin, substance P, and prostaglandins resulting from the inhibition of ACE. 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. Angiotensin-receptor blockers (AARBs) do not have any effect on ACE and theoretically might not cause cough. Therefore, a proposed option in patients suffering with ACE inhibitor-induced cough is to try an ARB. Patients who developed cough while receiving losartan treatment, which resolved after substitution with the ACE inhibitor enalapril (Dashti-Khavidaki, Faghihi et al. 2008). The most frequent adverse effect limiting all ACE inhibitor therapy in clinical practice is cough. This favourable profile of efficacy and tolerability, and the substantial weight of clinical experience, explain the increasing acceptance of enalapril as a major antihypertensive treatment and supports its use as logical first-line therapeutic option (Todd and Goa 1992).

#### **(5) 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.

#### **(6) Carcinogenesis, Mutagenesis, Impairment of Fertility**

There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to male and female rats at doses up to 90 mg/kg/day or for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively. These doses are 26 times (in rats and female mice) and 13 times (in male mice) the maximum recommended human daily dose (MRHDD) when compared on a body surface area basis. Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow. There were no adverse effects on

reproductive performance of male and female rats treated with up to 90 mg/kg/day of enalapril.

#### **(7) Pregnancy**

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

ACE inhibitors are commonly used drugs in the management of adult hypertension. However their use in pregnant women can have serious effects on the fetus. There was report to show the case of fatal neonatal renal failure associated with maternal intake of enalapril during third trimester. In the case of the report, the index case was born to a mother with PIH which was treated with enalapril (5 mg) once a day for 21 days prior to delivery in addition to other anti-hypertensives. Temporally, use of enalapril was associated with the onset of oligohydramnios. The neonate presented with intrauterine growth retardation, hydrops and oliguric renal failure, which did not respond to furosemide, peritoneal dialysis and exchange transfusion. Autopsy showed macroscopically and microscopically normal kidneys. The conclusion was that the use of ACE inhibitors during pregnancy should be avoided (Murki, Kumar et al. 2005).

#### **(8) Pediatric**

Antihypertensive effects of Vasotec have been established in hypertensive pediatric patients age 1 month to 16 years. Use of Vasotec in these age groups is supported by evidence from adequate and well-controlled studies of Vasotec in pediatric and adult patients as well as by published literature in pediatric patients. Vasotec is not recommended in neonates and in pediatric patients with glomerular filtration rate  $<30$  mL/min/1.73 m<sup>2</sup>, as no data are available.

In 2004, Proesmans et al published the paper to report ten pediatric patients with Alport syndrome received enalapril for 5 years. There were nine boys. Eight patients have the X-linked form of the disease and two the autosomal recessive form. The median age at the start of treatment was 10.25 years. Only one patient was hypertensive. The starting dose of enalapril was 0.05 mg/kg; the target dose was 0.5 mg/kg per day. The median dose given effectively was 0.24, 0.37, 0.45, 0.43, and 0.49 mg/kg per day at years of study 1, 2, 3, 4, and 5, respectively. The median urinary protein/creatinine ratio was 1.58 g/g (range 0.49-4.60) before treatment. This decreased to 0.98, 1.09, 1.35, 1.11, and 1.38 g/g after 1, 2, 3, 4, and 5 years, respectively. The median creatinine clearance at baseline was 100 ml/min per 1.73 m<sup>2</sup> and after 5 years 92 ml/min per 1.73 m<sup>2</sup>. Three patients did not

reach the target dose of enalapril because of orthostatic hypotension. One of them was the only patient to develop chronic renal failure within 5 years. The present study indicates that enalapril reduces urinary protein excretion and preserves glomerular filtration in Alport patients as a group. However, there was individual variation, as in most studies of patients with proteinuric nephropathies given inhibitors of ACE (Proesmans and Van Dyck 2004).

### **(9) Overdose**

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. Enalaprilat may be removed from general circulation by hemodialysis and has been removed from neonatal circulation by peritoneal dialysis. In 2006, Hasin et al described a case of severe heart failure due to the combined effect of verapamil and enalapril overdose in a patient treated regularly with metoprolol. The patient was dependent for 2 days on glucagon and dopamine infusion but remained oliguric, with deteriorating renal function. Marked improvement in all hemodynamic parameters was noted a short time after initiation of treatment with low-dose insulin infusion (1-2 units/h), which allowed the prompt withdrawal of glucagon and dopamine (Hasin, Leibowitz et al. 2006).

### **(10) Contraindications**

Vasotec is contraindicated in patients who are hypersensitive to 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. The clinical evolution was favorable under the treatment with an infusion of isotonic saline solutions, mild alkalinizing solutions, low-dose regular insulin and antibiotics. It is likely that metformin and enalapril, regularly taken by nephropathic patient, could have played an iatrogenic role, even if the doses were low (Franzetti, Paolo et al. 1997).

## **10. Clinical pharmacology**

### **(1) Mechanism**

Enalapril, after hydrolysis to enalaprilat, inhibits ACE in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of enalapril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma

angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. Although the latter decrease is small, it results in small increases of serum potassium. In hypertensive patients treated with Vasotec alone for up to 48 weeks, mean increases in serum potassium of approximately 0.2 mEq/L were observed. In patients treated with Vasotec plus a thiazide diuretic, there was essentially no change in serum potassium. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of Vasotec remains to be elucidated. While the mechanism through which Vasotec lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, Vasotec is antihypertensive even in patients with low-renin hypertension. Although Vasotec was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to enalapril monotherapy than non-black patients.

### **(2) Pharmacokinetics and metabolism**

Following oral administration of Vasotec, peak serum concentrations of enalapril occur within about one hour. Based on urinary recovery, the extent of absorption of enalapril is approximately 60%. 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 Vasotec is primarily renal. Approximately 94% 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% 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  $\leq 30$  mL/min or less. With glomerular filtration rate  $\leq$

30 mL/min, peak and trough enalaprilat levels increase, time to peak concentration increases and time to steady state may be delayed. The effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency. Enalaprilat is dialyzable at the rate of 62 mL/min. Studies in dogs indicate that enalapril crosses the blood-brain barrier poorly, if at all; enalaprilat does not enter the brain. Multiple doses of enalapril maleate in rats do not result in accumulation in any tissues. Milk of lactating rats contains radioactivity following administration of  $^{14}\text{C}$ -enalapril maleate. Radioactivity was found to cross the placenta following administration of labeled drug to pregnant hamsters.

### (3) Pharmacodynamics and clinical effects

Administration of Vasotec to patients with hypertension of severity ranging from mild to severe results in a reduction of both supine and standing blood pressure usually with no orthostatic component. Symptomatic postural hypotension is therefore infrequent, although it might be anticipated in volume-depleted patients. In most patients studied, after oral administration of a single dose of enalapril, onset of antihypertensive activity was seen at one hour with peak reduction of blood pressure achieved by four to six hours. At recommended doses, antihypertensive effects have been maintained for at least 24 hours. In some patients the effects may diminish toward the end of the dosing interval. In some patients achievement of optimal blood pressure reduction may require several weeks of therapy. The antihypertensive effects of Vasotec have continued during long term therapy. Abrupt withdrawal of Vasotec has not been associated with a rapid increase in blood pressure. In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. Following administration of Vasotec, there is an increase in renal blood flow; glomerular filtration rate is usually unchanged. The effects appear to be similar in patients with renovascular hypertension. When given together with thiazide-type diuretics, the blood pressure lowering effects of Vasotec are approximately additive. In a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving Vasotec. In this study there was no evidence of a blunting of the antihypertensive action of Vasotec. In trials in patients treated with digitalis and diuretics, treatment with enalapril resulted in decreased systemic vascular resistance, blood pressure, pulmonary capillary wedge pressure and heart size, and increased cardiac output and exercise tolerance. Heart rate was unchanged or slightly

reduced, and mean ejection fraction was unchanged or increased. There was a beneficial effect on severity of heart failure as measured by the New York Heart Association (NYHA) classification and on symptoms of dyspnea and fatigue. Hemodynamic effects were observed after the first dose, and appeared to be maintained in uncontrolled studies lasting as long as four months. Effects on exercise tolerance, heart size, and severity and symptoms of heart failure were observed in placebo-controlled studies lasting from eight weeks to over one year.

### (4) Mortality trials

In a multicenter, placebo-controlled clinical trial, 2,569 patients with all degrees of symptomatic heart failure and ejection fraction  $\leq 35\%$  were randomized to placebo or enalapril and followed for up to 55 months. Use of enalapril was associated with an 11% reduction in all-cause mortality and a 30% reduction in hospitalization for heart failure. Diseases that excluded patients from enrollment in the study included severe stable angina ( $>2$  attacks/day), hemodynamically significant valvular or outflow tract obstruction, renal failure (creatinine  $>2.5$  mg/dL), cerebral vascular disease, advanced pulmonary disease, malignancies, active myocarditis and constrictive pericarditis. The mortality benefit associated with enalapril does not appear to depend upon digitalis being present. A second multicenter trial used the SOLVD protocol for study of asymptomatic or minimally symptomatic patients. SOLVD-Prevention patients, who had left ventricular ejection fraction  $\leq 35\%$  and no history of symptomatic heart failure, were randomized to placebo ( $n=2117$ ) or enalapril ( $n=2111$ ) and followed for up to 5 years. The majority of patients in the SOLVD-Prevention trial had a history of ischemic heart disease. A history of myocardial infarction was present in 80% of patients, current angina pectoris in 34%, and a history of hypertension in 37%. No statistically significant mortality effect was demonstrated in this population. Enalapril-treated subjects had 32% fewer first hospitalizations for heart failure, and 32% fewer total heart failure hospitalizations. Compared to placebo, 32% fewer patients receiving enalapril developed symptoms of overt heart failure. Hospitalizations for cardiovascular reasons were also reduced. There was an insignificant reduction in hospitalizations for any cause in the enalapril treatment group (for enalapril vs. placebo, respectively, 1166 vs. 1201 first hospitalizations, 2649 vs. 2840 total hospitalizations), although the study was not powered to look for such an effect. The SOLVD-Prevention trial was not designed to determine whether treatment of asymptomatic patients with low ejection fraction would be superior, with respect to preventing hospitalization, to closer follow-up and use of

enalapril at the earliest sign of heart failure. However, under the conditions of follow-up in the SOLVD-Prevention trial (every 4 months at the study clinic; personal physician as needed), 68% of patients on placebo who were hospitalized for heart failure had no prior symptoms recorded which would have signaled initiation of treatment. The SOLVD-Prevention trial was also not designed to show whether enalapril modified the progression of underlying heart disease. In another multicenter, placebo-controlled trial limited to patients with NYHA Class IV congestive heart failure and radiographic evidence of cardiomegaly, use of enalapril was associated with improved survival. The results are shown in the following table.

#### **(5) Clinical pharmacology in pediatric patients**

A multiple dose pharmacokinetic study was conducted in 40 hypertensive male and female pediatric patients aged 2 months to  $\leq 16$  years following daily oral administration of 0.07 to 0.14 mg/kg enalapril maleate. At steady state, the mean effective half-life for accumulation of enalaprilat was 14 hours and the mean urinary recovery of total enalapril and enalaprilat in 24 hours was 68% of the administered dose. Conversion of enalapril to enalaprilat was in the range of 63-76%. The overall results of this study indicate that the pharmacokinetics of enalapril in hypertensive children aged 2 months to  $\leq 16$  years are consistent across the studied age groups and consistent with pharmacokinetic historic data in healthy adults. In a clinical study involving 110 hypertensive pediatric patients 6 to 16 years of age, patients who weighed  $< 50$  kg received either 0.625, 2.5 or 20 mg of enalapril daily and patients who weighed  $\geq 50$  kg received either 1.25, 5, or 40 mg of enalapril daily. Enalapril administration once daily lowered trough blood pressure in a dose-dependent manner. The dose-dependent antihypertensive efficacy of enalapril was consistent across all subgroups (age, Tanner stage, gender, race). However, the lowest doses studied, 0.625 mg and 1.25 mg, corresponding to an average of 0.02 mg/kg once daily, did not appear to offer consistent antihypertensive efficacy. In this study, Vasotec was generally well tolerated. In the above pediatric studies, enalapril maleate was given as tablets of Vasotec and for those children and infants who were unable to swallow tablets or who required a lower dose than is available in tablet form, enalapril was administered in a suspension formulation.

#### **(6) Patient information**

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. 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. Patients should be told not to use salt substitutes containing potassium without consulting their physician. Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia. Female patients of childbearing age should be told about the consequences of exposure to ACE inhibitors. These patients should be asked to report pregnancies to their physicians as soon as possible.

#### **11. Discussion**

Diabetic nephropathy is characterised by hypertension and persistent proteinuria. If ineffectively controlled, a progressive decline in renal function can result in end-stage renal disease. Patients with diabetic nephropathy are also at greatly increased risk of cardiovascular disease. ACE inhibitors display additional renoprotective effects beyond systemic blood pressure lowering, perhaps due to reduction in intraglomerular pressure by inhibition of angiotensin II activity. In type 2 diabetics, ACE inhibitors have variable effects, with some studies showing a reduction in microalbuminuria, prevention of the progression to macroalbuminuria and maintenance of renal function. Randomised studies have demonstrated that angiotensin II receptor blockers (ARBs), as well as controlling systemic blood pressure, delay progression of proteinuria in patients with diabetic nephropathy. Telmisartan has a number of features that may make it particularly suitable for the treatment of diabetic nephropathy. In addition to its long duration of action and almost exclusive faecal excretion, its high lipophilicity should assist in tissue penetration. The Diabetics Exposed to Telmisartan And enalapril (DETAIL) study was designed to compare the long-term renal outcome of treatment with telmisartan 40.80 mg versus enalapril 10.20 mg (with titration to the higher dose after 4 weeks) in patients with type 2 diabetes, mild-to-moderate hypertension and albuminuria. The primary endpoint is the change in glomerular filtration rate after 5 years' randomised treatment. Secondary endpoints are annual changes in glomerular filtration rate, serum

creatinine and urinary albumin excretion, as well as incidences of end-stage renal disease, cardiovascular events, all-cause mortality and adverse events (Barnett 2005). Enalapril maleate is unlike the prototype angiotensin-converting enzyme inhibitor captopril in that a standard meal does not appear to influence absorption of this new drug (Swanson, Vlasses et al. 1984). As the origin of an organism's life, stem cells have the potential to develop into many different types of cells in life bodies (Ma, et al, 2012). The research related to enalapril to stem cell is important.

Enalaprilat was developed partly to overcome these limitations of captopril. The consequence of the structural modifications was it proved to have unfavourable ionisation characteristics to allow sufficient potency for oral administration (in tablets). It was only suitable for intravenous administration. This was overcome by the researchers at Merck by the esterification of enalaprilat with ethanol to produce enalapril. As a prodrug, enalapril is metabolised *in vivo* to the active form enalaprilat by carboxylesterase. Peak plasma enalaprilat concentrations occur two to four hours after oral administration. Elimination thereafter is biphasic, with an initial phase which reflects renal filtration and a subsequent prolonged phase the latter representing equilibration of drug from tissue distribution sites. The prolonged phase does not contribute to drug accumulation on repeated administration, but is thought to be of pharmacological significance in mediating drug effects. Accumulation is probably the cause of reduced elimination in healthy elderly individuals and in patients with concomitant diabetes, hypertension, and heart failure. Normally, angiotensin I is converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II constricts blood vessels, increasing blood pressure. By inhibiting ACE, enalapril decreases levels of angiotensin II leading to less vasoconstriction and decreased blood pressure (Wikipedia, 2015).

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