Respiratory, thoracic and mediastinal disorders:
Very common: cough
Common: dyspnea
Uncommon: rhinorrhea, sore throat and hoarseness, bronchospasm/asthma
Rare: pulmonary infiltrates, rhinitis, allergic alveolitis/eosinophilic pneumonia

Gastrointestinal disorders:
Very common: nausea,
Common: diarrhoea, abdominal pain, taste alteration
Uncommon: ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, gastric irritations, dry mouth, peptic ulcer
Rare: stomatitis/aphthous ulcerations, glossitis
Very rare: intestinal angioedema

Hepatobiliary disorders:
Rare: hepatic failure, hepatitis – either hepatocellular or cholestatic, hepatitis including necrosis, cholestasis (including jaundice)

Skin and subcutaneous tissue disorders:
Common: rash, hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported
Uncommon: diaphoresis, pruritus, urticaria, alopecia
Rare: erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, pemphigus, erythroderma

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

Renal and urinary disorders:
Uncommon: renal dysfunction, renal failure, proteinuria
Rare: oliguria

Reproductive system and breast disorders:
Uncommon: impotence
Rare: gynecomastia

General disorders and administration site conditions:
Very common: asthenia
Common: fatigue
Uncommon: muscle cramps, flushing, tinnitus, malaise, fever

Investigations:
Common: hyperkalemia, increases in serum creatinine
Uncommon: increases in blood urea, hyponatremia
Rare: elevations of liver enzymes, elevations of serum bilirubin

Other adverse events reported with enalapril are presented below
– Pulmonary embolism and infarction; bronchitis, upper respiratory infection
– Ataxia, anosmia
– Flank pain, urinary tract infection
– Herpes zoster
– Dry eyes, tearing, conjunctivitis
– Peripheral neuropathy
– Melena

USE IN SPECIAL POPULATIONS

• Pregnancy
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see **WARNINGS AND PRECAUTIONS**). The use of ACE inhibitors is contra-indicated during the second and third trimester of pregnancy (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

INCREASED RISK OF BIRTH DEFECTS, FETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitors therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

ACE inhibitors therapy exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

• Lactation
Enalapril and enalaprilat are secreted in very low concentrations in breast milk (see **PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES**). Although these concentrations seem to be clinically irrelevant the use of enalapril in breast-feeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience. In case of an older infant the use of enalapril in breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

Use of enalapril is not recommended during breast feeding (see **WARNINGS AND PRECAUTIONS**).

• Pediatrics
Enalapril has not been studied in children

• Geriatrics
The dose should be in line with the renal function of the elderly patient.

OVERDOSE

Limited data are available for overdosage in humans. The most prominent features of overdosage reported to date are marked hypotension, beginning some six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system, and stupor. Symptoms associated with overdosage of ACE inhibitors may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. Serum enalaprilat levels 100- and 200-fold higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of enalapril, respectively.

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating enalapril maleate (e.g., emesis, gastric lavage, administration of absorbents, and sodium sulphate). Enalaprilat may be removed from the general circulation by haemodialysis. Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

STORAGE

Store below 30°C, protected from moisture.

PACKING

INVORIL TABLETS 5 mg
Alu/Alu strips of 10's; Box of 3x10's, 10x10's.
Blister strip of 10x10's, 3x10's

INVORIL TABLETS 10 mg
Alu/Alu strips of 10's; Box of 10x10's.
Blister strip of 10x10's, 3x10's

INVORIL TABLETS 20 mg
Alu/Alu strips Box of 3x10's, 10x10's.
Blister strip of 10x10's, 3x10's

Date of Revision: March 2023

Product Registration Holder for Malaysia /
Manufactured by :
RANBAXY (MALAYSIA) SDN. BHD.
Lot 23, Bakar Arang Industrial Estate,
08000 Sungai Petani, Kedah, Malaysia.

5239603

For the use of a Registered Medical Practitioner only

PRESCRIBING INFORMATION
INVORIL TABLETS

(Enalapril Maleate Tablets 5 mg/ 10 mg/ 20 mg)

COMPOSITION

INVORIL TABLETS 5 mg
Each tablet contains
Enalapril Maleate USP 5 mg.

INVORIL TABLETS 10 mg
Each tablet contains
Enalapril Maleate USP 10 mg

INVORIL TABLETS 20 mg
Each tablet contains
Enalapril Maleate USP 20 mg

Excipients: Colloidal Anhydrous Silica, Croscarmellose Sodium, Zinc Stearate, Purified Talc, Microcrystaline Cellulose, Lactose, Maleic acid, Sunset Yellow Lake, Ferric Oxide (Yellow)

PRODUCT DESCRIPTION

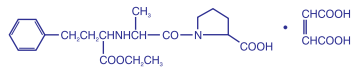
INVORIL TABLETS 5 mg
White, barrel shaped uncoated tablets embossed with '5' on one side and scored on other side.

INVORIL TABLETS 10 mg
Peach, barrel shaped uncoated tablets embossed with '10' on one side and scored on other side.

INVORIL TABLETS 20 mg
Light yellow, barrel shaped uncoated tablets embossed with '20' on one side and scored on other side.

DESCRIPTION

INVORIL TABLETS contain enalapril maleate. Enalapril maleate is chemically described as (S)-1-[-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, ()-2-butenedioate salt (1:1). Its empirical formula is $CHNO•CHO$, and its structural formula is:



STRUCTURAL FORMULA
ENALAPRIL MALEATE

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

• Pharmacodynamics
Enalapril, after hydrolysis to enalaprilat, inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of enalapril in hypertension 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 decrease aldosterone secretion. Although the latter decrease is small, it results in small increases of serum potassium. In hypertensive patients treated with enalapril alone for up to 48 weeks, mean increases in serum potassium of approximately 0.2 mEq/L were reported. In patients treated with enalapril 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 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 monotherapy than non-black patients.

• Pharmacokinetics
Oral enalapril is rapidly absorbed, with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril tablet is approximately 60%. The absorption of oral enalapril is not influenced by the presence of food in the gastrointestinal tract.

Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur about 4 hours after an oral dose of enalapril tablet. The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril is 11 hours. In subjects with normal renal function, steady-state serum concentrations of enalaprilat were reached after 4 days of treatment.

Over the range of concentrations which are therapeutically relevant, enalaprilat binding to human plasma proteins does not exceed 60%. Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril. Excretion of enalaprilat is primarily renal. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril (about 20%).

Pharmacokinetic in Special Population
Renal impairment
The exposure of enalapril and enalaprilat is increased in patients with renal insufficiency. In patients with mild to moderate renal insufficiency (creatinine clearance 40-60 ml/min) steady state AUC of enalaprilat was approximately two-fold higher than in patients with normal renal function after administration of 5 mg once daily. In severe renal impairment (creatinine clearance ≤ 30 ml/min), AUC was increased approximately 8-fold. The effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency and time to steady state is delayed. Enalaprilat may be removed from the general circulation by hemodialysis. The dialysis clearance is 62 ml/min.

Lactation
It has been reported that after a single 20 mg oral dose in postpartum women the average peak enalapril milk level was 1.7 µg/L (range 0.54 to 5.9 µg/L) at 4 to 6 hours after the dose. The average peak enalaprilat level was 1.7 µg/L (range 1.2 to 2.3 µg/L); peaks occurred at various times over the 24-hour period. Using the peak milk level data, the estimated maximum intake of an exclusively breastfed infant would be about 0.16% of the maternal weight-adjusted dosage.

A woman who had been taking oral enalapril 10 mg daily for 11 months had peak enalapril milk levels of 2 µg/L 4 hours after a dose and peak enalaprilat levels of 0.75 µg/L about 9 hours after the dose. The total amount of enalapril and enalaprilat measured in milk during the 24 hour period was 1.44 µg/L and 0.63 µg/L of milk respectively.

Enalaprilat milk levels were undetectable (<0.2 µg/L) 4 hours after a single dose of enalapril 5 mg in 1 mother and 10 mg in 2 mothers; enalapril levels were not determined.

INDICATIONS

Treatment of:
- All Grades of Essential Hypertension.
- Renovascular Hypertension.
- All Degrees of Heart Failure.

In patients with symptomatic heart failure, enalapril is also indicated to:
– Improve survival
– Retard the progression of heart failure
– Reduce hospitalization for heart failure

- Prevention of Symptomatic Heart Failure.

In asymptomatic patients with left ventricular dysfunction, enalapril is indicated to:
– Retard the development of symptomatic heart failure
– Reduce hospitalization for heart failure

- Prevention of Coronary Ischaemic Events in Patients with Left Ventricular Dysfunction.

Enalapril is indicated to:
– Reduce the incidence of myocardial infarction
– Reduce hospitalisation for unstable angina pectoris

DOSE AND METHOD OF ADMINISTRATION

Since absorption of enalapril tablets is not affected by food, the tablets may be administered before, during, or after meals.

Essential Hypertension
The initial dose is 10-20 mg once daily, depending on the degree of hypertension. In mild hypertension the recommended initial dose is 10 mg daily. For other degrees of hypertension the initial dose is 20 mg daily. The usual maintenance dose is 20 mg once daily. The dosage should be adjusted according to the needs of the patient to a maximum of 40 mg daily.

Renovascular Hypertension
Since blood pressure and renal function in such patients may be particularly sensitive to ACE inhibition, therapy should be initiated with a lower starting dose (5 mg or less). The dosage should then be adjusted according to the needs of the patient. Most patients may be expected to respond to 20 mg once daily. For patients with hypertension who have been treated recently with diuretics, caution is recommended (see next paragraph).

Concomitant Diuretic Therapy in Hypertension
Symptomatic hypotension may occur following the initial dose of enalapril; this is more likely in patients who are being treated currently with diuretics. Caution is recommended, therefore, since these patients may be volume- or salt-depleted. The diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with enalapril. If this is not possible, the initial dose of enalapril should be low (5 mg or less) to determine the initial effect on the blood pressure. Dosage should then be adjusted according to the needs of the patient.

Dosage in Renal Insufficiency
Generally, the intervals between the administration of enalapril should be prolonged and/or the dosage reduced.

Renal Status	Creatinine Clearance mL/min	Initial Dose mg/day
Mild Impairment	< 80 > 30 mL/min	5 mg - 10 mg
Moderate Impairment	≤ 30 > 10 mL/min	2.5 - 5 mg
Severe Impairment. Normally, these patients will be on dialysis#	≤ 10 mL/min	2.5 mg on dialysis days##

See **WARNINGS AND PRECAUTIONS - Haemodialysis Patients**
Enalaprilat is dialysable. Dosage on non-dialysis days should be adjusted depending on blood pressure response.

Heart Failure/Asymptomatic Left Ventricular Dysfunction
The initial dose of enalapril in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2.5 mg, and it should be administered under close medical supervision to determine the initial effect on the blood pressure. Enalapril may be used in the management of symptomatic heart failure usually with diuretics and, where appropriate, digitalis. In the absence of, or after effective management of, symptomatic hypotension following initiation of therapy with enalapril in heart failure, the dose should be increased gradually to the usual maintenance dose of 20 mg, given in a single dose or two divided doses, as tolerated by the patient. This dose titration may be performed over a 2 to 4 week period, or more rapidly if indicated by the presence of residual signs and symptoms of heart failure. In patients with symptomatic heart failure this dosage regimen was effective in reducing mortality.

Blood pressure and renal function should be monitored closely both before and after starting treatment with enalapril because hypotension and (more rarely) consequent renal failure have been reported. In patients treated with diuretics the dose should be reduced, if possible, before beginning treatment with enalapril. The appearance of hypotension after the initial dose of enalapril does not imply that hypotension will recur during chronic therapy with enalapril and does not preclude continued use of the medicine. Serum potassium also should be monitored.

CONTRAINDICATIONS
– Hypersensitivity to enalapril, to any of the excipients of this formulation or any other ACE inhibitor
– History of angioedema associated with previous ACE inhibitor therapy
– Hereditary or idiopathic angioedema
– Second and third trimesters of pregnancy (see **WARNINGS AND PRECAUTIONS** and **USE IN SPECIAL POPULATIONS**).

WARNINGS AND PRECAUTIONS
Symptomatic Hypotension
Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients. In hypertensive patients receiving enalapril, symptomatic hypotension is more likely to occur if the patient has been volume - depleted, e.g., by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting (see **DRUG INTERACTIONS** and **SIDE EFFECTS/ADVERSE REACTIONS**). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been reported. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of enalapril and/or diuretic is adjusted. 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, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with enalapril. This effect is anticipated, and usually is not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose and/or discontinuation of the diuretic and/or enalapril may be necessary.

Aortic or Mitral Valve Stenosis/Hypertrophic Cardiomyopathy
As with all vasodilators, ACE inhibitors should be given with caution in patients with left ventricular valvular and outflow tract obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Renal Function Impairment
In cases of renal impairment (creatinine clearance <80 ml/min) the initial enalapril dosage should be adjusted according to the patient's creatinine clearance (see **DOSE AND METHOD OF ADMINISTRATION**) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients.

Renal failure has been reported in association with enalapril and has been mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. If recognised promptly and treated appropriately, renal failure when associated with therapy with enalapril is usually reversible.

Some hypertensive patients, with no apparent pre-existing renal disease have developed increases in blood urea and creatinine when enalapril has been given concurrently with a diuretic. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required. This situation should raise the possibility of underlying renal artery stenosis (see **Renovascular hypertension** below).

Renovascular hypertension
There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors.

Loss of renal function may occur with only mild changes in serum creatinine. In these patients, therapy should be initiated under close medical supervision with low doses, careful titration, and monitoring of renal function.

Kidney Transplantation
There is no experience regarding the administration of enalapril in patients with a recent kidney transplantation. Treatment with enalapril is therefore not recommended.

Hepatic failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis 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.

Neutropenia/Agranulocytosis
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Enalapril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If enalapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Hypersensitivity/Angioneurotic oedema
Angioneurotic oedema 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 should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous epinephrine solution 1:1000 (0.3 ml to 0.5 ml) and/or measures to ensure a patent airway, should be administered promptly.

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks.

Intestinal Angioedema
Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); 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 (see **CONTRAINDICATIONS**).

Anaphylactoid Reactions during Hymenoptera Desensitisation
Rarely, patients receiving ACE inhibitors during desensitisation with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each desensitisation.

Anaphylactoid Reactions during LDL Apheresis
Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL)-apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis.

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

Hypoglycaemia
Diabetic patients treated with oral antidiabetic agents or insulin starting an ACE inhibitor, should be told to closely monitor for hypoglycaemia, especially during the first month of combined use (see **DRUG INTERACTIONS**).

Cough
Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, enalapril blocks 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.

Hyperkalaemia
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including enalapril. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (>70 years) diabetes mellitus, inter-current events in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. If concomitant use of enalapril and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see **DRUG INTERACTIONS**).

Lithium
The combination of lithium and enalapril is generally not recommended (see **DRUG INTERACTIONS**).

Pregnancy and lactation
ACE inhibitors have been shown to be strongly fetotoxic in animal studies. Recently available data indicate that ACE inhibitors can cause foetal and neonatal morbidity and mortality when administered to pregnant woman. The use of these agents during pregnancy is not recommended.

INCREASED RISK OF BIRTH DEFECTS, FETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see **CONTRAINDICATIONS** and **USE IN SPECIAL POPULATIONS**).

Use of enalapril is not recommended during breast feeding (see **USE IN SPECIAL POPULATIONS**).

Ethnic differences
As with other angiotensin converting enzyme inhibitors, enalapril is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Lactose
This product contains lactose and therefore should not be used by patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

DRUG INTERACTIONS
Potassium sparing diuretics or potassium supplements
ACE inhibitors attenuate diuretic induced potassium loss. Potassium sparing diuretics (e.g. spironolactone, eplerenone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium (see **WARNINGS AND PRECAUTIONS**).

Diuretics (thiazide or loop diuretics)
Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with enalapril (see **WARNINGS AND PRECAUTIONS**). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of enalapril.

Other antihypertensive agents
Concomitant use of these agents may increase the hypotensive effects of enalapril. Concomitant use with nitroglycerine and other nitrates, or other vasodilators, may further reduce blood pressure.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors. Use of enalapril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see **WARNINGS AND PRECAUTIONS**).

Tricyclic antidepressants/Antipsychotics/Anaesthetics/Narcotics
Concomitant use of certain anesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see **WARNINGS AND PRECAUTIONS**).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 (COX-2) Inhibitors
NSAIDs including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs. Therefore, the antihypertensive effect of angiotensin II receptor antagonists or ACE inhibitors may be attenuated by NSAIDs including selective COX-2 inhibitors.
The co-administration of NSAIDs (including COX-2 inhibitors) and angiotensin II receptor antagonists or ACE inhibitors exert an additive effect on the increase in serum potassium, and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function (such as the elderly or patients who are volume-depleted, including those on diuretic therapy).Therefore, the combination should be administered with caution in patients with compromised renal function. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy and periodically thereafter.

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 enalapril.

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment (See **WARNINGS AND PRECAUTIONS** and **SIDE EFFECTS/ADVERSE REACTIONS**).

Alcohol
Alcohol enhances the hypotensive effect of ACE inhibitors.

Acetyl salicylic acid, Thrombolytics and β-blockers
Enalapril can be safely administered concomitantly with acetyl salicylic acid (at cardiologic doses), thrombolytics and β-blockers.

SIDE EFFECTS/ADVERSE REACTIONS
Undesirable effects reported for enalapril include:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:
Uncommon: anaemia (including aplastic and hemolytic)

Rare: neutropenia, decreases in hemoglobin, decreases in hematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, pancytopenia, lymphadenopathy, autoimmune diseases

Endocrine disorders:
Not known: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Metabolism and nutrition disorders:
Uncommon: hypoglycaemia

Nervous system and psychiatric disorders:
Common: headache, depression
Uncommon: confusion, somnolence, insomnia, nervousness, paresthaesia, vertigo
Rare: dream abnormality, sleep disorders

Eye disorders:
Very common: blurred vision

Cardiac and vascular disorders:
Very common: dizziness
Common: hypotension (including orthostatic hypotension), syncope, chest pain, rhythm disturbances, angina pectoris, tachycardia
Uncommon: orthostatic hypotension, palpitations, myocardial infarction or cerebrovascular accident (Incidence rates were comparable to those in the placebo and active control), possibly secondary to excessive hypotension in high risk patients.
Rare: Raynaud's phenomenon