PRODUCT MONOGRAPH

Pr ENALAPRIL

enalapril tablets

2.5, 5, 10 and 20 mg

Each tablet is made with 2.5, 5, 10 or 20 mg of enalapril maleate that appears as 2, 4, 8 or 16 mg of enalapril sodium in the tablets.

Angiotensin Converting Enzyme Inhibitor

Manufactured by:
Cobalt Pharmaceuticals Inc.
6500 Kitimat Road
Mississauga, Ontario
Canada, L5N 2B8

Date of Preparation:
February 4, 2010

Control No. 136264

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enalapril tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Tablet* / 2.5 mg, 5 mg, 10 mg and 20 mg	Lactose monohydrate, pregelatinized maize starch, maize starch *For a complete listing see Dosage Forms, Composition and Packaging section.*

* The splitting of ENALAPRIL tablets is not advised. Each tablet is made with 2.5, 5, 10 or 20 mg of enalapril maleate that appears as 2, 4, 8 or 16 mg of enalapril sodium in the tablets.

INDICATIONS AND CLINICAL USE

ENALAPRIL (enalapril) is indicated for:
- essential or renovascular hypertension
- treatment of symptomatic congestive heart failure

Hypertension
ENALAPRIL is indicated in the treatment of essential or renovascular hypertension. It is usually administered in association with other drugs, particularly thiazide diuretics.

In using enalapril consideration should be given to the risk of angioedema (see WARNINGS AND PRECAUTIONS).

Geriatrics (>65 years of age): See DOSAGE AND ADMINISTRATION.

Pediatrics (<16 years of age): Enalapril may be used in children (see DOSAGE AND ADMINISTRATION).

Congestive Heart Failure
Enalapril is indicated in the treatment of symptomatic congestive heart failure usually in combination with diuretics and/or digitalis. In these patients, enalapril improves symptoms, increases survival, and decreases the frequency of hospitalization (see CLINICAL TRIALS for details and limitations of survival trials). Treatment with enalapril should be initiated under close medical supervision.

In clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction ≤ 35%), enalapril decreases the rate of development of overt heart failure and decreases the incidence of hospitalization for heart failure (see CLINICAL TRIALS for details and limitations

of survival trials).

CONTRAINDICATIONS

ENALAPRIL (enalapril) is contraindicated in:

- Patients who are hypersensitive to these products or to any ingredient in their formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Patients with a history of angioneurotic edema relating to previous treatment with an angiotensin converting enzyme inhibitor.
- Patients with hereditary or idiopathic angioedema.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- When used in pregnancy, angiotensin converting enzyme (ACE) inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected, ENALAPRIL should be discontinued as soon as possible.

General

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with enalapril. This may occur at any time during treatment and may be life threatening.

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

If angioedema occurs, 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 this may be life threatening and treatment with antihistamines and corticosteroids may not be sufficient.

In patients who experience angioedema, future administration is contraindicated (see CONTRAINDICATIONS).

The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black than in non-black patients.

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 Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Anaphylactoid Reactions during Desensitization: There have been isolated reports of patients experiencing sustained life-threatening anaphylactoid reactions while receiving ACE inhibitors during desensitizing treatment with hymenoptera (bees, wasp) venom. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for at least 24 hours, but they have reappeared upon inadvertent rechallenge.

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.

Cardiovascular

Hypotension: Symptomatic hypotension has occurred after administration of enalapril, usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision, usually in a hospital. 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 (see ADVERSE REACTIONS).

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

Valvular Stenosis: There is concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Ear/Nose/Throat

Cough: A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of enalapril, has been reported.

Such possibility should be considered as part of the differential diagnosis of the cough.

Endocrine and Metabolism

Hypoglycemia: Rare cases of hypoglycaemia in diabetic patients on oral antidiabetic agents or insulin have been reported. 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. In addition, hypoglycaemia appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment (see ADVERSE REACTIONS).

Hematologic

Neutropenia/ Agranulocytosis: Agranulocytosis and bone marrow depression have been caused by angiotensin converting enzyme inhibitors. Several cases of agranulocytosis and neutropenia have been reported in which a causal relationship to enalapril cannot be excluded. Current experience with the drug shows the incidence to be rare. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and renal disease.

Hepatic/Biliary/Pancreatic

Patients with Impaired Liver Function: Hepatitis, jaundice (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with enalapril in patients with or without pre-existing liver abnormalities (see ADVERSE REACTIONS). In most cases the changes were reversed on discontinuation of the drug.

Should the patient receiving enalapril experience any unexplained symptoms (see CONSUMER INFORMATION), particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary investigation be carried out. Discontinuation of enalapril should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. Enalapril should be used with particular caution in patients with pre-existing liver abnormalities. In such patients baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply.

Nitritoid Reactions – Gold: Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and symptomatic hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including enalapril (see DRUG INTERACTIONS).

Peri-Operative Considerations

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia 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.

Renal

Renal Impairment: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.

Use of enalapril should include appropriate assessment of renal function.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials with enalapril. 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. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes. The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function should be given only for documented hypokalemia and with caution and frequent monitoring of serum potassium since they may lead to a significant increase in serum potassium. Hyperkalemia 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, Agents Increasing Serum Potassium).

Special Populations

Pregnant Women: ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, enalapril should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function, associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development.

Prematurity, and patent ductus arteriosus and other structural cardiac malformations, as well as neurologic malformations, have also been reported following exposure in the first trimester of pregnancy.

Infants with a history 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 a means of reversing hypotension and/or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit.

Enalapril has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit and may, theoretically, be removed by exchange transfusion, although there is no experience with the latter procedure.

Animal Data
Maternal and fetal toxicity occurred in some rabbits given enalapril at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose). Enalapril was not teratogenic in rabbits.

There was no fetotoxicity or teratogenicity in rats treated with enalapril at doses up to 200 mg/kg/day (333 times the maximum human dose). Fetotoxicity expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril, but did not occur when these animals were supplemented with saline. The drug crosses the placental barrier in rats and hamsters.

Nursing Women: Enalapril and enalaprilat are secreted in human milk in trace amounts. Use of ACE inhibitors (ENALAPRIL) is not recommended during breast-feeding.

Pediatrics (<16 years of age): The safety and antihypertensive effect have been studied short-term (one month) in patients aged 6 to 16 years (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Enalapril is not recommended in neonates and in children with glomerular filtration rate <30 mL/min/1.73 m^2, as no data are available.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
In controlled clinical trials involving 2314 hypertensive patients and 363 patients with congestive heart failure, the most severe adverse reactions were: angioedema (0.2%), hypotension (2.3%) and renal failure (5 cases).

In hypertensive patients, hypotension occurred in 0.9% and syncope in 0.5%, with a discontinuation rate of 0.1 %.

In congestive heart failure patients, hypotension occurred in 4.4% and syncope in 0.8%, with a discontinuation rate of 2.5%.

The most frequent clinical adverse reactions in controlled clinical trials were: headache (4.8%), dizziness (4.6%) and fatigue (2.8%). Discontinuation of therapy was required in 6.0% of the 2677 patients.

Clinical Trial Adverse Drug Reactions-Hypertension

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Adverse experiences occurring in greater than one percent of patients with hypertension treated with enalapril in controlled clinical trials are shown below. In patients treated with enalapril, the maximum duration of therapy was three years; in placebo treated patients the maximum duration of therapy was 12 weeks.

Table 1 - Hypertension

	Enalapril n=2314	Placebo n=230
Body as a Whole		
Fatigue	3.0	2.6
Orthostatic Effects	1.2	0.0
Asthenia	1.1	0.9
Digestive		
Diarrhea	1.4	1.7
Nausea	1.4	1.7
Nervous/psychiatric		
Headache	5.2	9.1
Dizziness	4.3	4.3
Respiratory		
Cough	1.3	0.9
Skin		
Rash	1.4	0.4

Less Common Clinical Trial Adverse Drug Reactions (<1%) – Hypertension

Cardiovascular: Hypotension, chest pain, palpitations, acute myocardial infarction

Digestive: Vomiting, dysphagia, abdominal pain

Hematologic: Anemia, leukopenia

Hypersensitivity: Angioedema

Musculoskeletal: Muscle cramps

Nervous System/ Psychiatric: Insomnia, nervousness, somnolence, paresthesia

Respiratory: Dyspnea

Skin: Pruritus, hyperhidrosis

Special Senses: Taste disturbance

Urogenital: Renal failure, proteinuria, oliguria, impotence

Clinical Trial Adverse Drug Reactions-Heart Failure

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Adverse experiences occurring in greater than one percent of patients with heart failure treated with enalapril are shown below. The incidences represent the experiences from both controlled and uncontrolled clinical trials (maximum duration of therapy was approximately one year). In the placebo treated patients, the incidences reported are from the controlled trials (maximum duration of therapy is 12 weeks). The percentage of patients with severe heart failure [New York Heart Association (NYHA) Class IV] was 29 percent and 43 percent for patients treated with enalapril and placebo, respectively.

Table 2 – Congestive Heart Failure		
	Enalapril n=673	Placebo n=339
Body as a Whole		
Orthostatic Effects	2.2	0.3
Syncope	2.2	0.9
Chest Pain	2.1	2.1
Fatigue	1.8	1.8
Abdominal Pain	1.6	2.1
Asthenia	1.6	0.3
Cardiovascular		
Hypotension	6.7	0.6
Orthostatic Hypotension	1.6	0.3
Angina Pectoris	1.5	1.8
Myocardial Infarction	1.2	1.8
Digestive		
Diarrhea	2.1	1.2
Nausea	1.3	0.6
Vomiting	1.3	0.9
Nervous/psychiatric		
Dizziness	7.9	0.6
Headache	1.8	0.9
Vertigo	1.6	1.2
Respiratory		
Cough	2.2	0.6
Bronchitis	1.3	0.9
Dyspnea	1.3	0.4
Pneumonia	1.0	2.4
Skin		
Rash	1.3	2.4
Urogenital		
Urinary Tract Infection	1.3	2.4

Less Common Clinical Trial Adverse Drug Reactions (<1%) – Heart Failure
Cardiovascular: Palpitations

Musculoskeletal: Muscle cramps

Nervous System/ Psychiatric: Insomnia

Skin: Pruritus

Special Senses: Taste disturbance

Urogenital: Renal failure, impotence

Abnormal Hematologic and Clinical Chemistry Findings
Hyperkalemia: (see WARNINGS AND PRECAUTIONS, Renal)

Creatinine, Blood Urea Nitrogen (BUN): Increases in serum creatinine and BUN were reported in about 20% of patients with renovascular hypertension and in about 0.2% of patients with essential hypertension treated with enalapril alone.

In patients with congestive heart failure, who were also receiving diuretics and/or digitalis, increases in BUN and serum creatinine, usually reversible upon discontinuation of enalapril and/or concomitant therapy, were observed in about 9.7% of patients.

Hemoglobin and Hematocrit: Decreases in hemoglobin and hematocrit (mean approximately 0.34 g% and 1.0 vol%, respectively) occurred frequently in either hypertensive or congestive heart failure patients treated with enalapril, but were rarely of clinical importance. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Hepatic: Elevations of liver enzymes and/or serum bilirubin have occurred (see WARNINGS AND PRECAUTIONS).

Pediatric Patients: In a four-week placebo-controlled clinical trial, 110 hypertensive pediatric patients (6-16 years of age) received medication for 14 days including 51 patients for a four-week period. The adverse experience profile was no different from that seen in adult patients.

Post-Market Adverse Drug Reactions
Adverse Reactions Reported in Uncontrolled Trials and/or Marketing Experience:
Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5 to 1.0 percent of patients with hypertension or heart failure in clinical trials are listed below and, within each category, are in order of decreasing severity.

Body as a Whole
Anaphylactoid reactions (see WARNINGS AND PRECAUTIONS).

Cardiovascular
Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS AND PRECAUTIONS); pulmonary embolism and infarction; pulmonary edema; angina pectoris; arrhythmia including atrial tachycardia and bradycardia; atrial fibrillation; palpitation, Raynaud's phenomenon.

Endocrine
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Digestive
Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular or cholestatic jaundice), liver function abnormalities (see WARNINGS AND PRECAUTIONS), melena, anorexia, dyspepsia, constipation, glossitis, stomatitis, dry mouth.

Hematologic
Rare cases of neutropenia, thrombocytopenia, hemolytic anemia and bone marrow depression.

Metabolic
Rare cases of hypoglycemia in diabetic patients on oral antidiabetic agents or insulin have been reported (see WARNINGS AND PRECAUTIONS).

Musculoskeletal
Muscle cramps.

Nervous System/ Psychiatric
Vertigo, depression, confusion, ataxia, somnolence, insomnia, nervousness, peripheral neuropathy (e.g., paresthesia, dysesthesia), dream abnormality.

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

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

Special Senses
Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing, hearing impairment.

Urogenital
Renal failure, oliguria, renal dysfunction (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION), flank pain, gynecomastia, impotence.

A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive antinuclear antibody (ANA),

elevated erythrocyte sedimentation rate, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur. These symptoms may be reversible upon discontinuation of therapy.

In very rare cases, intestinal angioedema has been reported with angiotensin converting enzyme inhibitors including enalapril.

Laboratory Test Findings: Hyponatremia

DRUG INTERACTIONS

Drug-Drug Interactions

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 (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Agents Increasing Serum Potassium: Since enalapril decreases aldosterone production, elevation of serum potassium may occur. Potassium-sparing diuretics such as spironolactone, eplerenone, triamterene or amiloride, or potassium supplements should be given only for documented hypokalemia and with caution and frequent monitoring of serum potassium particularly in patients with impaired renal function since they may lead to a significant increase in serum potassium. Salt substitutes which contain potassium should also be used with caution (see WARNINGS AND PRECAUTIONS, Hyperkalemia).

Agents Causing Renin Release: The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Agents Affecting Sympathetic Activity: Agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) may be used with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to enalapril.

Lithium Salts: As with other drugs which eliminate sodium, lithium clearance may be reduced. Therefore, the serum lithium levels should be monitored carefully if lithium salts are to be administered.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors: The antihypertensive effect of enalapril may be diminished with concomitant non-steroidal anti-inflammatory drug use including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors). In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs including selective cyclooxygenase-2 inhibitors, the

coadministration of ACE inhibitors or angiotensin II receptor antagonists may result in further deterioration of renal function.

Gold: Nitroid reactions (symptoms include facial flushing, nausea, vomiting and symptomatic hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including enalapril (see WARNINGS AND PRECAUTIONS).

Drug-Food Interactions

The absorption of enalapril is not influenced by the presence of food in the gastrointestinal tract.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- The absorption of enalapril is not affected by food.
- Dosage must be individualized.
- Special attention for dialysis patients.
- The splitting of ENALAPRIL tablets is not advised.

Recommended Dose and Dosage Adjustment

Hypertension: Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation and salt restriction; the dosage of other antihypertensive agents being used with enalapril may need to be adjusted.

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, a diuretic may be added.

The maximum daily dose is 40 mg. Raising the dose above that level is not recommended because of the possibility of increased adverse reactions.

Symptomatic hypotension occasionally may occur following the initial dose of enalapril and is more likely in patients who are currently being treated with a diuretic. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with enalapril to reduce the likelihood of hypotension (see WARNINGS AND PRECAUTIONS).

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used to determine whether excessive hypotension occurs.

To date there is insufficient experience with enalapril in the treatment of accelerated or malignant hypertension. Enalapril, therefore, is not recommended in such situations.

Pediatrics (<16 years of age): 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. Doses above 0.58 mg/kg (or in excess of 40 mg) have not been studied in pediatric patients (see ACTION AND CLINICAL PHARMACOLOGY). Enalapril is not recommended in neonates and in pediatric patients with glomerular filtration rate <30 mL/min/1.73m^2, as no data are available.

Geriatrics (>65 years of age): The starting dose should be 2.5 mg. Some elderly patients may be more responsive to enalapril than younger patients.

Dosing Adjustment in Renal Impairment: (see WARNINGS AND PRECAUTIONS - Anaphylactoid Reactions during Membrane Exposure)

The doses should be reduced in patients with hypertension according to the following guidelines:

Renal Status	**Creatinine Clearance mL/min (mL/s)**	**Initial Dose mg/day**
Normal Renal Function	>80 mL/min (> 1.33 mL/s)	5 mg
Mild Impairment	≤ 80 >30 mL/min (≤ 1.33 > 0.50 mL/s)	5 mg
Moderate to Severe Impairment	≤30 mL/min (≤ 0.50 mL/s)	2.5 mg
Dialysis Patients	-	2.5 mg on dialysis days*

*Enalaprilat is dialyzable. Dosage on nondialysis days should be adjusted depending on the blood pressure response**.**

Congestive Heart Failure: Enalapril is generally used in conjunction with a diuretic and/or digitalis. Blood pressure and renal function should be monitored, both before and during treatment with enalapril because severe hypotension and, more rarely, consequent renal failure have been reported (see WARNINGS and PRECAUTIONS).

Initiation of therapy requires consideration of recent diuretic therapy and the possibility of severe salt/volume depletion. If possible, the dose of diuretic should be reduced before beginning treatment to reduce the likelihood of hypotension. Serum potassium also should be monitored (see DRUG INTERACTIONS, Drug-Drug Interactions).

The recommended initial dose in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction (ejection fraction ≤ 35%) is 2.5 mg once a day, to be administered under close medical supervision to determine the initial effect on blood pressure. After the initial dose, the patient should be observed for at least two hours or until the pressure has stabilized for at least another additional hour (see WARNINGS AND PRECAUTIONS, Hypotension).

In the absence of, or after effective management of symptomatic hypotension following initiation of therapy, the dose should be increased gradually depending on the patient's response. The usual therapeutic dosing range is 5 to 20 mg daily, given as a single dose or two divided doses.

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. The dosage regimen, in patients with symptomatic heart failure, which was effective in reducing mortality and the need for hospitalization in multicentre studies ranged between 16.4 and 18.8 mg/day. The majority of patient experience in clinical studies has been with twice-daily dosage.

The maximum daily dose is 40 mg.

Dosage Adjustment in Patients with Congestive Heart Failure and Renal Impairment or Hyponatremia: In patients with heart failure who have hyponatremia (serum sodium less than 130 mEq/L) or with serum creatinine greater than 1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision (see DOSAGE AND ADMINISTRATION, Congestive Heart Failure and DRUG INTERACTIONS, Drug-Drug Interactions).

The dose may be increased to 2.5 mg b.i.d. then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function.

The maximum daily dose is 40 mg.

OVERDOSAGE

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. 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 ingestion is recent, induce emesis. Enalaprilat may be removed from the general circulation by hemodialysis (see WARNINGS AND PRECAUTIONS, Anaphylactoid Reactions during Membrane Exposure).

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Enalapril is an ACE inhibitor, which is used in the treatment of hypertension and heart failure.

Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyzes the conversion of angiotensin I to the pressor substance, angiotensin II. After absorption, enalapril, a pro-drug, is hydrolyzed to enalaprilat, its active metabolite, which inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release) and decreased aldosterone secretion. Although the latter

decrease is small, it results in a small increase in serum potassium. In patients treated with enalapril and a thiazide diuretic there was essentially no change in serum potassium (see WARNINGS AND PRECAUTIONS).

ACE is identical to kininase II. Thus, enalapril may also block the degradation of bradykinin, a potent vasodepressor peptide. However, the role that this plays in the therapeutic effects of either drug is unknown.

While the mechanism through which enalapril lowers blood pressure is believed to be primarily the suppression of the renin-angiotensin-aldosterone system, enalapril also lowers blood pressure in patients with low-renin hypertension.

Pharmacodynamics

Administration of enalapril to patients with hypertension results in a reduction of both supine and standing blood pressure. Abrupt withdrawal of enalapril has not been associated with a rapid increase in blood pressure. In most patients studied, after oral administration of an individual dose of enalapril, the onset of antihypertensive activity is seen at one hour with peak reduction of blood pressure achieved by 4-6 hours. At recommended doses, the antihypertensive effect has been shown to be maintained for at least 24 hours. In some patients the effect may diminish towards the end of the dosing interval (see DOSAGE AND ADMINISTRATION). On occasion, achievement of optimal blood pressure reduction may require several weeks of therapy.

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 enalapril, there was an increase in renal blood flow; glomerular filtration rate was usually unchanged.

When enalapril is given together with thiazide-type diuretics, its blood pressure lowering effect is approximately additive.

Administration of enalapril to patients with congestive heart failure reduces afterload and preload of the heart, resulting in an increase in cardiac output, without reflex tachycardia.

When used in hypertensive, normolipidemic patients, enalapril had no effect on plasma lipoprotein fractions.

Studies in dogs indicate that enalapril crosses the blood brain barrier poorly, if at all; enalaprilat does not enter the brain.

Pharmacokinetics

Table 3 – Summary of Enalaprilat's Pharmacokinetic Parameters in Healthy Volunteers Further to a 10 mg Oral Dose of Enalapril

	C_{max} ng/mL	$t_{1/2}$ (h)*	$AUC_{0-\infty}$ ng.h/mL
Single Dose Mean	32.3	11	423

*Effective half life of accumulation.

Absorption: 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 enalapril tablets is approximately 60%. The absorption of enalapril is not influenced by the presence of food in the gastrointestinal tract.

Metabolism: Following absorption, enalapril is rapidly and extensively hydrolyzed to enalaprilat, a potent angiotensin converting enzyme inhibitor (which itself is poorly absorbed). Peak serum concentrations of enalaprilat occur 3 to 4 hours after an oral dose of enalapril. Except for conversion to enalaprilat, there is no evidence of significant metabolism of enalapril.

Excretion: Excretion of enalapril 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.

The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently associated with binding to ACE. The effective half-life for accumulation of enalaprilat following multiple doses of enalapril is 11 hours.

In hypertensive children aged 2 months to 15 years the kinetics of enalapril were approximately similar to adults (see DOSAGE AND ADMINISTRATION).

Special Populations and Conditions

Pediatrics: In pediatric patients the antihypertensive effect of enalapril has been studied in hypertensive children aged 6-16 years (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Race: The antihypertensive effect of angiotensin converting enzyme inhibitors is generally lower in black than in non-black patients.

Renal Insufficiency: The disposition of enalapril and enalaprilat in patients with renal insufficiency is similar to that in patients with normal renal function until the glomerular filtration rate is 30 mL/min (0.50 mL/s) or less. With renal function ≤ 30 mL/min (≤ 0.50 mL/s), 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 is prolonged at this level of renal insufficiency (see DOSAGE AND ADMINISTRATION). Enalaprilat is dialyzable at the rate of 62 mL/min (1.03 mL/s).

STORAGE AND STABILITY

Store at controlled room temperature between 15 - 30°C. Keep container tightly closed. Protect from moisture.

NOTE: 100 and 500 tablet bottle: discard remaining tablets six months after opening bottle.

SPECIAL HANDLING INSTRUCTIONS

Keep out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ENALAPRIL (Enalapril) is available as the following:

2.5 mg: White to off-white, oval-shaped, biconvex tablet with "EL | 25" on one side and "ᘐ | ᘐ" on the other side.

5 mg: White to off-white, rounded triangle-shaped, biconvex tablet with "EL | 5" on one side and "ᘐ" on the other side.

10 mg: Peach, rounded triangle-shaped, biconvex tablet with "EL | 10" on one side and "ᘐ" on the other side.

20 mg: Salmon, rounded triangular-shaped, biconvex tablet with "EL | 20" on one side and "ᘐ" on the other side.

The splitting of ENALAPRIL tablets is not advised.

Composition

Each tablet of ENALAPRIL is made with 2.5, 5, 10 or 20 mg of enalapril maleate that appears as 2, 4, 8 or 16 mg of enalapril sodium, respectively in the tablets, and the following non-medicinal ingredients: lactose monohydrate, maize starch, magnesium stearate (vegetable grade), pregelatinized maize starch and sodium bicarbonate.

Colourants are present in the tablets as follows:
10 mg tablets also contain iron oxide red
20 mg tablets also contain iron oxide yellow and iron oxide red

Packaging

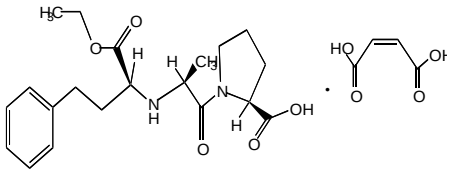
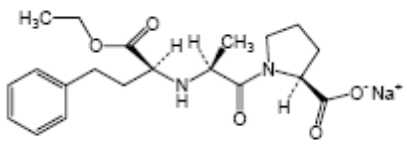
Available in:

2.5 mg -	Blisters of 30's
	HDPE Bottles of 100's and 500's
5 mg -	Blisters of 30's
	HDPE Bottles of 100's and 500's
10 mg -	Blisters of 30's
	HDPE Bottles of 100's and 500's
20 mg -	Blisters of 30's
	HDPE Bottles of 100's and 500's

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	Enalapril Maleate	Enalapril Sodium
Chemical Name:	L-Proline, 1-[*N*-[1-(ethoxycarbonyl) - 3 - phenylpropyl] - L- alanyl]-, (*S*)-, (*Z*)-2-butenedioate (1:1)	L-Proline, 1-[*N*-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-,(S)-, Sodium (1:1)
Molecular Formula:	$C_{20}H_{28}N_2O_5 \bullet C_4H_4O_4$	$C_{20}H_{27}N_2Na\ O_5$
Molecular Mass:	492.53	398.43
Structural Formula:		
Physicochemical Properties:	Enalapril maleate is a white to off-white crystalline powder which melts at ≈ 143ºC to 144ºC. It is sparingly soluble in water (pH 3.4), soluble in ethanol, and freely soluble in methanol and dimethylformamide. The pKa^1 and pKa^2 of the base moiety are 3.0 and 5.4 respectively.	

CLINICAL TRIALS

Study I: A single dose crossover comparative bioavailability study of ENALAPRIL 2 × 2.5 mg tablets and Vasotec® 2 x 2.5 mg Tablets was performed in 26 healthy adult male volunteers under fasted conditions. A summary of the bioavailability data is tabulated below.

Table 4: Summary Table of the Comparative Bioavailability Data Study I

Enalapril (2 x 2.5 mg Enalapril tablets) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	ENALAPRIL* 2.5 mg tablet	Vasotec® † 2.5 mg tablet Merck Frosst Canada Ltd., Canada	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	40.644 42.654 (33.1)	38.800 40.876 (35.2)	104.75	98.72 – 111.15
AUC_∞ (ng·h/mL)	41.226 43.230 (32.7)	39.445 41.513 (34.8)	104.49	98.40 – 110.95
C_{max} (ng/mL)	26.085 27.799 (36.2)	25.064 26.762 (36.6)	104.07	95.51 – 113.40
T_{max} § (h)	0.75 (0.33 – 1.50)	0.83 (0.50 – 2.03)		
$T_{½}$ € (h)	1.02 (38.9)	1.23 (92.3)		

* ENALAPRIL 2.5 mg Tablets (Batch #: E0921; Manufacturing Date: September-2004)
† VASOTEC® 2.5 mg Tablets, Manufacturer: Merck Frosst Canada & Co. was purchased in Canada
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

Study II: A single dose crossover comparative bioavailability Study of ENALAPRIL 1 × 20 mg tablets and Vasotec® 1 x 20 mg Tablets was performed in 26 healthy adult male volunteers under fasted conditions. A summary of the bioavailability data is tabulated below.

Table 5: Summary Table of the Comparative Bioavailability Data Study II

Enalapril (1 x 20 mg Enalapril tablet) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	ENALAPRIL* 20 mg tablet	Vasotec® † 20 mg tablet Merck Frosst Canada Ltd., Canada	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	179.792 190.037 (30.7)	183.774 193.959 (33.9)	97.83	91.67 – 104.41
AUC_∞ (ng·h/mL)	181.628 191.879 (30.5)	185.961 196.440 (34.3)	97.67	91.59 – 104.16
C_{max} (ng/mL)	117.305 122.949 (30.2)	120.793 128.329 (35.9)	97.11	87.94 – 107.25
T_{max} § (h)	0.92 (0.50 – 2.00)	0.83 (0.67 – 1.75)		
$T_{½}$ € (h)	1.34 (27.6)	1.50 (40.1)		

* ENALAPRIL 20 mg Tablets (Batch #: E0808; Manufacturing Date: August-2004)
† VASOTEC® 20 mg Tablets, Manufacturer: Merck Frosst Canada & Co. was purchased in Canada
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

Study Demographics and trial design

Table 6: Summary of Patient demographics for clinical trials

Study	Trial Design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
SOLVD - Treatment	Multicentre, randomized, double blind, placebo-controlled	2.5 or 5 mg twice daily Titrated up to 10 mg twice daily up to 55 months	2569 Placebo: 1284 Enalapril: 1285	60.2 years (20-80)	Male: 2065 Female: 504

Study Results

Table 7: Results of SOLVD-Treatment study

Primary Endpoints	Enalapril N (%)	Placebo N (%)	p-Value
Overall mortality	451 (35.1%)	510 (39.7%)	0.008

In a multicentre, placebo-controlled, double-blind study (SOLVD, see BIBLIOGRAPHY No. 23), 2569 patients with symptomatic heart failure (primarily New York Heart Association Class II and III and ejection fraction ≤ 35%), were randomized to placebo or enalapril given as an adjunct to conventional therapy. Diseases that excluded patients from enrolment in the study included severe stable angina, hemodynamically significant valvular or outflow tract obstruction, renal failure, cerebral vascular disease (e.g., significant carotid artery diseases), advanced pulmonary disease, malignancies, active myocarditis and constrictive pericarditis. The use of enalapril was associated with an 11% reduction in all-cause mortality (which corresponds to a 16% risk reduction in all-cause mortality) and a 30% reduction in hospitalization for heart failure (which corresponds to a 36% risk reduction in hospitalization for heart failure). The chief difference in mortality was in deaths due to progressive heart failure. There was no significant difference in the number of deaths classified as due to arrhythmia without worsening congestive heart failure.

Study demographics and trial design

Table 8: Summary of patient demographics for clinical trials

Study	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
SOLVD - Prevention	Multicentre, randomized, double blind, placebo-controlled	2.5 mg twice daily gradually increased to 10 mg twice daily Follow-up for a minimum of 46 months to a maximum of 62 months	4228 Placebo: 2117 Enalapril: 2111	58.7 years (20-80)	Male: 3752 Female: 476

Study Results

Table 9: Results of SOLVD- Prevention study

Primary Endpoints	Enalapril N (%)	Placebo N (%)	p-value
Overall mortality	306 (14.5%)	332 (15.7%)	0.211

A second multicenter trial used the SOLVD protocol for a study of asymptomatic or minimally symptomatic patients. SOLVD-Prevention patients, who had left ventricular ejection fraction ≤ 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 four 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.

Study Demographics and trial design

Table 10: Summary of Patient demographics for clinical trials

Study	Trial Design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
CONSENSUS	Multicentre, randomized, double blind, placebo-controlled	5 mg twice daily increased to a maximum of 20 mg twice daily	253 Placebo: 126 Enalapril: 127	70 years (36-91)	Male: 179 Female: 74

Study results

Table 11: Results of CONSENSUS study

Primary Endpoints		Enalapril N (%)	Placebo N (%)	p-value
Overall mortality	6 months	33 (26.0%)	55 (43.6%)	0.004
	12 months	46 (36.2%)	66 (52.4%)	0.011
	End of study	50 (39.4%)	68 (54.0%)	0.003

In another multicenter, placebo-controlled trial (CONSENSUS, see BIBLIOGRAPHY No. 22), 253 patients with severe congestive heart failure (New York Heart Association Class IV) were randomized to placebo or enalapril given as an adjunct to conventional therapy. The use of enalapril was associated with an improvement of symptoms and a reduction in mortality from the progression of heart failure. No difference was seen in the incidence of sudden cardiac death.

DETAILED PHARMACOLOGY

MECHANISM OF ACTION					
Study	**Species/Strain**	**No. of Animals /Group**	**Route**	**Dose**	**Results**
Effect of enalapril maleate on total serum ACE in rats and dogs	Male Sprague/ Dawley rats Male beagle hounds	12 experimental 6 placebo 3 dogs 3 dogs	P.O. P.O. P.O	10 mg/kg/day for 7 or 14 days 10 mg/kg (free base) for 7 or 14 days 30 mg/kg/day for 3 days	79% increase in ACE after 7 days & 140% after 14 days. 30% increase in ACE after 7 days & 48% after 14 days 1.5-fold increase in ACE
In vivo ACE inhibition in anesthetized and unanesthetized rats and dogs	Male Sprague/ Dawley rats (Blue Spruce) Mongrel or beagle dogs (male & female)	6 rats 6 dogs per dose	I.V. P.O. I.V.	3, 10, 30 µg/kg 0.1, 0.3, 1.0 and 3.0 mg/kg 30, 130, 430, 1430 µg/kg	The ED_{50} is 14.0 µg/kg I.V. and 0.29 mg/kg p.o. Dose-related inhibition of pressor response to angiotensin. ED_{50}: Enalaprilat: 6.4 µg/kg. Enalapril maleate: 278 µg/kg
Effect of enalaprilat on canine hind limb vasodilator response to bradykinin and vasoconstrictor response to angiotensins	Anesthetized dogs male or female	4 dogs	I.V.	0.3 – 100 µg/kg	Local inhibition of ACE: (enalaprilat) ED_{50} = 4.8 (4.4 to 5.2 µg/kg) I.V.

EFFECTS ON BLOOD PRESSURE					
Study	**Species/strain**	**No. of animals per group**	**Route**	**Dose**	**Results**
Antihypertensive activity in sodium-deficient rats	Male Sprague/ Dawley rats	6 rats/group and at least 8 treatment groups	P.O.	Enalapril 1 to 10 mg/kg	Enalapril produced a dose-dependent decrease in systolic BP for 3 or more hours
Effect on renal hypertensive rats (Grollman technique)	Male Sprague/Dawley rats	Most groups = 6 to 8 rats/treatment group	P.O.	Enalapril 3.0 mg/kg	Enalapril produced a mean decrease in systolic pressure ≈20 mmHg and a slight tachycardia
Relationship between angiotensin I blockade and blood pressure lowering in spontaneous hypertensive rats, renal hypertensive rats, and renal hypertensive dogs and normotensive sodium depleted dogs	Sprague/Dawley rats normotensive dogs (mongrel)	At least 4 to 5 rats/group and at least 3 dogs per group	P.O.	Enalapril 0.1 to 3.0 mg/kg	Time course of blood pressure decrease did not coincide with time course for maximal inhibition of angiotensin 1 pressor response

OTHER EFFECTS					
Study	**Species/strain**	**Number of animals per group**	**Route**	**Dose**	**Results**
Effects in acute renal failure in dogs	Mongrel dogs	4/group	P.O.	1.0 mg/kg b.i.d. for 3 days	No further deterioration of acute renal failure occurred
Whole body autoradiography	Golden hamsters	Min. 16	P.O.	5 mg/kg	No radioactivity was found in the spinal cord or brain of either male or female hamsters

TOXICOLOGY

Acute Toxicity

LD_{50} Values:

Route	Species	Sex	MSDRL[a]	NMB/RL[b]
Oral	Mouse	Male	2 g/kg	3.5 g/kg
		Female	2 g/kg	3.5 g/kg
	Rat	Male	2 g/kg	3.5 g/kg
		Female	2 g/kg	3.0 g/kg
Intravenous	Mouse	Male	--	900 mg/kg
		Female	750 mg/kg	900 mg/kg
	Rat	Male	--	950 mg/kg
		Female	--	850 mg/kg
Subcutaneous	Mouse	Male	--	1150 mg/kg
		Female	--	1500 mg/kg
	Rat	Male	--	1750 mg/kg
		Female	--	1400 mg/kg

[a] Merck Sharp and Dohme Research Laboratories, West Point, PA, USA
[b] Nippon Merck-Banyu Co., Menuma, Japan

Signs of toxicity: ptosis, decreased activity, bradypnea, loss of righting, ataxia, dyspnea, and clonic convulsions.

Sub-Acute and Chronic Toxicity

Species	Duration	Number of animals/ group	Route	Dose	Results
Rat	1-Month	10 M + 10F	Oral	0, 10, 30, 90	**At all Doses:** Slight decrease in body weight gain. **At 30 and 90 mg/kg/day:** Dose-related increase in BUN in males.
Rat	3-Months	15 M + 15 F	Oral	0, 10, 30, 90	**At all doses:** Slight decrease in body weight gain and in serum sodium, slight increase in serum potassium. Small increase in kidney weight and decrease in heart weight. **At 30 & 90 mg/kg/day:** Dose-related increase in BUN.
Rat	1-Year	25 M + 25 F	Oral	0, 10, 30, 90	**6-month interim kill:** Males given 90 mg/kg/day had a significantly ($P \leq 0.05$) greater kidney weight than controls. **1 year:** Dose-related decrease in weight gain (7 to 19%). Dose-related increase in serum urea nitrogen in males given 30 and 90 mg/kg/day (values up to 52.9 and 89.2 mg/100 mL, respectively). Three high dose females showed elevated serum urea nitrogen levels. Serum potassium values were increased (0.1 to 0.8 mEq/L) in male rats on the high dose. Males given 90 mg/kg/day had a significantly ($P \leq 0.05$) greater kidney weight than controls.
Rat	1-Month	20 M + 20 F	Oral	0, 90 & 90 with physiologic saline for drinking	**Unsupplemented:** Less weight gain (8 to 19%), increase in serum urea nitrogen (up to 62.8 mg%). **Supplemented:** Body weight gain and serum urea nitrogen levels similar to controls.
Rat (sodium depleted)	3-Weeks	30 M + 30 F	Oral	0, 90	A marked potentiation in toxicity included: death, weight loss, marked increases in serum urea nitrogen, creatinine and potassium, renal tubular degeneration.
Dog Beagle	1-Month	3 M + 3 F	Oral	0, 10, 30, 90 (4 doses only) reduced to 60 (4 doses only)	**At 30 mg**: One dog showed increase in BUN and renal tubular degeneration. **At high doses**: 6/6: deaths (7 – 12 days) Increase in serum urea nitrogen, glucose, SGOT, SGPT, and potassium; decrease in serum sodium and chloride; renal tubular degeneration and increased hepatocellular fat.

Species	Duration	Number of animals/ group	Route	Dose	Results
Dog Beagle	3-Months	3 M + 3 F	Oral	0, 10, 30, 90 (7 doses only)	**At all Doses:** Slight decrease in serum sodium. **At 30 mg:** 2/6: deaths Increase in BUN and serum glucose; renal tubular degeneration. **At 90 mg:** 5/6: deaths Increase in BUN, serum glucose, SGOT, SGPT, alkaline phosphatase and potassium. Decrease in serum chloride; renal tubular degeneration, increased hepatocellular fat; hepatocellular necrosis.
Dog Beagle	1-Year	5 M + 5 F	Oral	0, 3, 5, 15	No drug-induced changes were seen.
Dog Beagle	15-Days	3 M + 3 F	Oral	0, 60 with and without saline supplementat-ion	**Unsupplemented treated dogs:** 3/6: deaths 4/6: increase in serum urea nitrogen 3/6: decrease in serum chloride increase in SGOT, SGPT and potassium 1/6: increase in alkaline phosphatase 1/6: hepatocellular lesions (in 1st animal which died) 5/6: renal lesions (3 moderate, 2 slight renal tubular necrosis). **Saline supplemented treated dogs:** 0/6: deaths 3/6: increase in serum urea nitrogen 1/6: very slight renal tubular necrosis and moderate renal tubular cell vacuolation
Dog Beagle	15-Days	3 M + 3 F	Oral	0, 90 with and without saline supplementati on	**Unsupplemented treated dogs:** 6/6: deaths 6/6: increase in serum urea nitrogen, creatinine and SGPT 5/6: increase in SGOT 2/6: increase in serum potassium 5/6: marked renal tubular degeneration 1/6: moderate renal tubular degeneration 6/6: slight to marked thymic atrophy 3/6: ulceration of distal esophagus 2/6: oral mucosal lesions **Supplemented treated dogs:** 2/6: deaths 6/6: increase in serum urea nitrogen, creatinine 3/6: increase in SGOT and SGPT 0/6: Increase in potassium 2/6: moderate renal tubular degeneration 4/6: slight to moderate thymic atrophy 3/6: liver degeneration

Teratology Studies

Species	Number of animals/ group	Dose mg/kg/day	Duration of Dosing	Results
Rat (Charles River CD)	20 F	0, 10, 30, 90	Day 15 of gestation through Day 20 of lactation	**At all dosage levels:** - Decreased maternal weight gain during days 15-20 - Dose-related retardation in growth of F1 offspring during lactation **At 90 mg/kg/day:** - Mean Day 1 pup weight/litter was significantly less than that of controls
Rat (Charles River CD)	25 F	0, 10, 100, 200 100 + saline 200 + saline	Days 6 through Day 17 of gestation	Decreased maternal weight gain at 100 and 200 mg/kg/day in Unsupplemented rats. No treatment related effects on reproductive status or teratogenic effects in any of the groups.
Rat (CLEA Japan Inc-JCL:SD)	25 F	0, 12, 120, 1200 1200 + saline	Days 6 through Day 17 of gestation	**Unsupplemented treated rats:** - Average maternal body weight gain significantly reduced at all doses **At 1200 mg/kg/day:** - Slight but significant decrease in fetal weight - Increase in the number of fetuses with the 14th rib skeletal variation - Decrease in the number of fetuses with ossified caudal vertebrae **Supplemented treated rats:** - No evidence of maternotoxicity or fetotoxicity
Rabbit (New Zealand albino)	18 F	0, 3, 10, 30 (with saline)	Days 6 through Day 18 of gestation	**At 3 and 10 mg/kg/day:** - No treatment-related effects on reproductive status or teratogenicity was observed. **At 30 mg/kg/day:** - 4 deaths - Reduced food and water intake - Significant increase in the mean number of resorptions per litter - 2 abortions - No evidence of teratogenicity was observed.

Fertility and Postnatal Evaluation Studies

Species	Number of animals/ group	Dose mg/kg/day	Duration of Dosing	Results
Rat (Charles River CD)	15 M + 30 F	0, 10, 30, 90	Males 70 days prior to mating to termination of females. Females 15 days prior to mating and throughout gestation.	No effects on reproductive status were observed at any dose. **Males at 30 & 90 mg/kg/day:** - At approximately 14 weeks of age, and after 6 weeks of dosing, the FO males started producing an increased number of seminal plugs and lacerated genitalia. - At termination of treatment, weight gain was significantly reduced in FO males - A slight treatment-related reduction in mean post weaning weight gain among F1 males of the 30 & 90 mg/kg/day groups. **Females at 30 & 90 mg/kg/day:** - Decrease weight gain during gestation. **Pups:** Reduced body weights in F1 pups at 90 mg/kg/day on Day 1 postpartum and secondarily a delay in postnatal development. Increased incidence of deaths of F1 pups at 30 and 90 mg/kg/day during lactation.

Mutagenicity Studies

Enalapril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation, in the Rec-Assay, sister chromatid exchange with cultured chinese hamster cells, (up to 20 mg/mL) and the micro-nucleus test with mice.

In vitro chromosomal aberration test = enalapril was clastogenic at 10 and 20 mg/mL but not at 5 mg/mL.

Carcinogenicity Studies

There was no evidence of a carcinogenic effect when enalapril was administered for 106 weeks to rats (Charles River CD-1) at doses up to 90 mg/kg/day (150 times the maximum daily human dose).

Enalapril has also been administered for 94 weeks to male and female mice (Charles River CD-1) at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times the maximum daily dose for humans) and no evidence of carcinogenicity was noted.

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PART III: CONSUMER INFORMATION

Pr ENALAPRIL
Enalapril Tablets

This leaflet is part III of a three-part "Product Monograph" published when ENALAPRIL was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ENALAPRIL. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

ENALAPRIL is available **only** on prescription from your physician.

What the medication is used for:
ENALAPRIL is used for:
- reducing high blood pressure

When **blood pressure** is high, the workload of the heart and arteries increases so that over time, these organs may not function as they should. In turn, this could lead to damage of the "vital organs": brain – heart – kidneys, and result in stroke, heart failure, heart attack, blood vessel disease or kidney disease.

ENALAPRIL is used for:
- treating patients with heart failure

Enalapril may also be used to treat patients with **heart failure**. This is a condition where the heart cannot pump adequate amounts of blood to satisfy the needs of the body.

If your physician has recommended a particular diet, for instance- less salt- follow the diet carefully. This could help your medicine to better control your blood pressure. Your physician may also recommend weight loss. Do follow these suggestions.

What it does:
Enalapril is part of a class of medicines known as angiotensin converting enzyme (ACE) inhibitors. They lower blood pressure by specifically blocking a naturally occurring substance called angiotensin II. Angiotensin II normally tightens your blood vessels. Enalapril allows them to relax and therefore help lower high blood pressure.

This medicine does not cure high blood pressure, **but does help control it.** So, it is important to continue taking the tablets regularly to keep your blood pressure down. You may have to take high blood pressure medicine for life.

Keep your regular appointments with your physician, even if you feel well. High blood pressure may not be easily recognized by you, because you may not "feel any symptoms"; but your physician can measure your blood pressure very easily, and check how the medicine is controlling it.

Read the following information carefully. **If you need any explanations or further information, ask your physician or pharmacist.**

When it should not be used:
Do not take ENALAPRIL if you:
- are allergic to enalapril or any other component of ENALAPRIL (see What the important non-medicinal ingredients are).
- have a history of swelling of the face, lips, tongue, throat, or sudden difficulty breathing or swallowing.
- have been diagnosed with swelling of the face, lips, tongue, throat, or sudden difficulty breathing or swallowing due to genetic factors or unknown reasons (please refer to Side Effects and What to do About Them).

What the medicinal ingredient is:
Each tablet of ENALAPRIL is made with enalapril maleate that appears as enalapril sodium in the tablets.

What the important nonmedicinal ingredients are:
ENALAPRIL contains the following non-medicinal ingredients: lactose monohydrate, maize starch, magnesium stearate (vegetable grade), pregelatinized maize starch and sodium bicarbonate.

Colourants are present in the tablets as follows:
10 mg tablets also contain iron oxide red
20 mg tablets also contain iron oxide yellow & iron oxide red

What dosage forms it comes in:
ENALAPRIL is available in 4 strengths, namely: tablets
2.5 mg (white, oval-shaped), 5 mg (white, rounded triangle-shaped), 10mg (peach, rounded triangle-shaped), and 20 mg (salmon, rounded triangle-shaped).

WARNINGS AND PRECAUTIONS

Serious Warning and Precautions
ENALAPRIL should not be used during pregnancy. If you discover that you are pregnant while taking ENALAPRIL, stop the medication and contact your physician as soon as possible.

This medicine may not be suitable for certain people. Tell your physician or pharmacist if you think **any** of the following applies to you:
- You have previously taken enalapril or other medication of the same type -Angiotensin Converting Enzyme (ACE) inhibitors such as enalapril, lisinopril, captopril, and you were allergic or reacted badly to it, particularly if you experienced swelling of the face, lips, tongue, or throat, or had sudden difficulty breathing or swallowing. These are symptoms of conditions called hereditary angioedema or idiopathic angioedema.
- **You should not take this medicine if you have been diagnosed with hereditary angioedema or idiopathic angioedema (angioedema of unknown cause).**
- Dizziness or drowsiness may occasionally occur when taking medications to lower blood pressure. Therefore, before you perform tasks which may require special attention (driving a car or operating dangerous machinery), wait until you know how you respond to your medicine.

- You should be aware that black patients are at increased risk of these types of reactions to ACE inhibitors.
- **You are pregnant, breast-feeding or thinking of becoming pregnant.** Taking ENALAPRIL during pregnancy can cause injury and even death to your developing baby. This medicine should **not** be used during pregnancy. If you become pregnant while taking ENALAPRIL, stop the medication and report to your physician as soon as possible. It is possible that ENALAPRIL passes into breast milk. You should not breast-feed while taking ENALAPRIL.
- You suffer from low blood pressure (you may notice this as faintness or dizziness, especially when standing).
- You are undergoing dialysis
- You have any of these conditions:
  - diabetes
  - heart or blood vessel disease
  - liver disease
  - kidney disease
- You are receiving gold (sodium aurothiomalate) injections.
- You are taking "water pills" or potassium supplements.
- You use potassium containing salt substitutes with your food.

You should also inform your physician or pharmacist if you have recently suffered from excessive vomiting or diarrhea.

If you have diabetes and are taking oral medicines to treat diabetes or insulin, you should closely monitor for low blood glucose levels, especially during the first month of treatment with ENALAPRIL.

If you have to undergo any dental or other surgery, inform the dentist or the physician in charge that you are taking this medicine.

Remember – This medicine is prescribed for the particular condition that you have. **Do not give this medicine to other people, nor use it for any other condition.**

Do not use outdated medicine.

INTERACTIONS WITH THIS MEDICATION

Do not take any other medicines unless you have discussed the matter with your physician or pharmacist. Certain medications tend to increase your blood pressure, for example, non-prescription preparations for appetite control, asthma, colds, coughs, hay fever and sinus problems, or may also react badly with ENALAPRIL.

Your physician or pharmacist also needs to know if you are taking any other medication, whether on prescription or otherwise. It is particularly important to inform your physician or pharmacist if you are taking:

- Diuretics or "water pills"; any other medicines to reduce blood pressure.
- Diabetes medicine and/or insulin
- Potassium-containing medicines, potassium supplements.
- Salt substitutes that contain potassium, as these may lead to increased levels of potassium in the blood which can be serious. In these cases, your physician may need to adjust the dosage of ENALAPRIL or monitor your blood level of potassium.
- Lithium (a drug used to treat a certain kind of depression).
- Certain pain and arthritis medicines, including gold therapy and non-steroidal anti-inflammatory drugs.

PROPER USE OF THIS MEDICATION

Usual dose:

- Take this medicine exactly as your physician ordered.
- The absorption of this medicine is not affected by food; so it can be taken with or without a meal.
- Try to take your medicine every day at the same time. This way it becomes easy to remember your doses.
- The splitting of ENALAPRIL tablets is not advised.

For patients with high blood pressure:

Adults:
Your physician may adjust the dose according to your blood pressure response. The usual dose range is 10 mg to 40 mg per day given in a single dose or two divided doses. The maximum daily dose for ENALAPRIL is 40 mg.

Children (less than 16 years):
The usual starting dose is up to 5 mg once daily. Doses above 40 mg have not been studied.

For patients with congestive heart failure:
The initial dose is 2.5 mg taken once a day. Your physician will closely monitor you to determine the initial effect on your blood pressure. The usual daily dose is 5 mg to 20 mg given in a single dose or two divided doses. The maximum daily dose is 40 mg.

Overdose:

- In case of an overdose, contact your physician or pharmacist immediately so that medical attention may be given promptly. The most likely symptom would be a feeling of lightheadedness or dizziness due to a sudden or excessive drop in blood pressure.

For management of a suspected drug overdose, contact your regional Poison Control Center.

Missed Dose:

- If you miss a dose of this medicine, take it as soon as possible. However, if no more than six hours have elapsed since the missed dose, you may take that day's dose of medication and then go back to your regular dosing schedule. **Do not take a double dose.**

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its intended action, any medication, including ENALAPRIL, may cause side effects. Most people do not experience any problem when taking these medicines; but if you notice any of the following, have other side effects or if the

condition persists or worsens, seek medical attention.

- Dry cough, sore throat.
- The initial dose may cause a greater fall in blood pressure than will occur following continued treatment. You may notice this as faintness or dizziness and it may help to lie down. If concerned, please consult your physician or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Fatigue	✓		
	Dizziness/Fainting/ Lightheadedness, especially following exercise, and/or when it is hot and you have lost a lot of water by sweating			✓
	Low blood pressure		✓	
	Headache	✓		
	Rash/Itching		✓	
	Nausea/ Vomiting/ Diarrhea	✓		
	Lasting Cough		✓	
	Chest Pain		✓	
	Shortness of breath		✓	
Uncommon	Allergic reactions/ Angioedema (sudden difficulty in breathing or swallowing, swelling of face, eyes, lips, tongue and/or throat, hands or feet)			✓
	Flu-like symptoms (fever, malaise, muscle pain, rash, itching, abdominal pain, nausea, vomiting, diarrhea, jaundice, loss of appetite)			✓
	Liver impairment such as jaundice, dark/ brown urine		✓	
	Abdominal pain	✓		
	Low blood sugars in diabetic patients	✓		
	Loss of appetite	✓		

This is not a complete list of side effects. For any unexpected effects while taking ENALAPRIL, contact your doctor or pharmacist.

HOW TO STORE IT

ENALAPRIL should be stored at room temperature between 15 - 30°C. Keep container tightly closed, away from heat and direct light, and out of damp places, such as the bathroom or kitchen. Protect from moisture.

Note: 100 and 500 tablet bottle: discard remaining tablets six months after opening bottle.

Keep all medicines out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701C
    Ottawa, ON K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Cobalt Pharmaceuticals Inc. at: 1-866-254-6111.

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