PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr ENALAPRIL

Enalapril Tablets

Tablets, 2.5 mg, 5 mg, 10 mg and 20 mg, Oral

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

Angiotensin Converting Enzyme Inhibitor

Sivem Pharmaceuticals ULC
4705 Dobrin Street
Saint-Laurent, Quebec, Canada
H4R 2P7
www.sivem.ca

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RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS Error! Bookmark not defined.

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 7 WARNINGS AND PRECAUTIONS).

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 14 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 14 CLINICAL TRIALS for details and limitations of survival trials).

1.1 Pediatrics

Pediatrics (<16 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ENALAPRIL in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use. See 4 DOSAGE AND ADMINISTRATION

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see 4 DOSAGE AND ADMINISTRATION).

2 CONTRAINDICATIONS

ENALAPRIL is contraindicated in:

- Patients who are hypersensitive to these products or to any ingredient in their formulation. For a complete listing, see the 6 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.
- Combination with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR <60 ml/min/1.73 m2) (see 7 WARNINGS AND PRECAUTIONS).
- Combination with a neprilysin inhibitor (e.g., sacubitril). Do not administer ENALAPRIL within 36 hours of switching to or from sacubitril/valsartan, a product containing a neprilysin inhibitor (See 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS.)

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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.

4 DOSAGE AND ADMINISTRATION

4.1 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.

4.2 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 7 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 10 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 7 WARNINGS AND PRECAUTIONS - Anaphylactoid Reactions during Membrane Exposure)

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

Table 1 - Dosing Adjustment in Renal Impairment

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	30 to 80 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 7 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 9 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 7 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 4 DOSAGE AND ADMINISTRATION and 9 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.

4.4 Administration

See 4 DOSAGE AND ADMINISTRATION.

4.5 Missed Dose

Patients should be instructed that if they miss a dose of ENALAPRIL, they should take the next dose as soon as possible. If no more than six hours have elapsed since the missed dose, the patient can take that day's dose of medication and then return to the regularly scheduled time. The Patient should not double the dose.

5 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 7 WARNINGS AND PRECAUTIONS).

For management of a suspected drug overdose, contact your regional poison control center.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
oral	Tablet* / 2.5 mg, 5 mg, 10 mg and 20 mg	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

* 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.

Description

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 "ᗤ | ᗤ" on the other side.

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

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

20 mg: Salmon, rounded triangular-shaped, biconvex tablet with "EL | 20" on one side and "ᗤ" 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 - HDPE Bottles of 100's
5 mg - HDPE Bottles of 100's
10 mg - HDPE Bottles of 100's
20 mg - HDPE Bottles of 100's

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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 2 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 2 CONTRAINDICATIONS).

Patients receiving coadministration of ACE inhibitor and mTOR (mammalian target of rapamycin) inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema. Caution should be used when these drugs are used concomitantly (see 9 DRUG INTERACTIONS).

Patients receiving concomitant ACE inhibitor and neprilysin inhibitor therapy may be at increased risk for angioedema (see 2 CONTRAINDICATIONS and 9 DRUG INTERACTIONS).

Patients receiving concomitant ACE inhibitor and dipeptidyl peptidase IV (DPP-IV_ inhibitors such as alogliptin, linagliptin, saxagliptin, and sitagliptin may be at increased risk for angioedema (see 9 DRUG INTERACTIONS). Caution should be used when these drugs are used concomitantly.

Anaphylactoid Reactions during Membrane Exposure: Anaphylactoid reactions have been reported in patients dialysed 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 8 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.

Dual Blockade of the Renin-Angiotensin System (RAS)
There is evidence that co-administration of angiotensin converting enzyme inhibitors (ACEIs), such as ENALAPRIL or of angiotensin receptor antagonists (ARBs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR <60 ml/min/1.73 m^2). Therefore, the use of ENALAPRIL, in combination with aliskiren-containing drugs is contraindicated in these patients (see 2 CONTRAINDICATIONS). Further, co-administration of ACEIs, including ENALAPRIL with other agents blocking the RAS, such as ARBs or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.

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 hypoglycemia 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 hypoglycemia, especially during the first month of combined use. In addition, hypoglycemia appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment (see 8 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 8 ADVERSE REACTIONS). In most cases the changes were reversed on discontinuation of the drug.

Should the patient receiving ENALAPRIL experience any unexplained symptoms (see PATIENT MEDICATION 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 9 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.

The use of ACEIs – including of ENALAPRIL – or ARBs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR <60 ml/min/1.73 m^2).(See 2 CONTRAINDICATIONS and 9 DRUG INTERACTIONS, Dual Blockade of the Renin- Angiotensin-System (RAS) with ACEIs, ARBs or aliskiren-containing drugs).

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, potassium-containing salt substitutes or other drugs that may increase serum potassium (e.g., trimethoprim-containing products). The use of potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that may increase serum potassium, 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 9 DRUG INTERACTIONS).

7.1 Special Populations

7.1.1 Pregnant Women

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.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

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 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, 10.3 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.

7.1.4 Geriatrics

See 4 DOSAGE AND ADMINISTRATION.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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%.

In congestive heart failure patients, hypotension occurred in 4.4% and syncope in 0.8%.

The most frequent clinical adverse reactions were: headache (4.8%), dizziness (4.6%) and fatigue (2.8%).

8.2 Clinical Trial Adverse Reactions

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 may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Hypertension

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 3 - 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

Heart Failure

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 4 – Congestive Heart Failure

	Enalapril n = 2314	Placebo n = 230
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

8.3 Less Common Clinical Trial Adverse Reactions

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

Heart Failure
Cardiovascular: Palpitations
Musculoskeletal: Muscle cramps
Nervous System/Psychiatric: Insomnia
Skin: Pruritus
Special Senses: Taste disturbance
Urogenital: Renal failure, impotence

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Hyperkalemia: (See 7 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 7 WARNINGS AND PRECAUTIONS).

Clinical Trial Findings
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 Findings
Laboratory Test Findings: Hyponatremia

8.5 Post-Market Adverse 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 7 WARNINGS AND PRECAUTIONS).

Cardiovascular
Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see 7 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 7 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 7 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 7 WARNINGS AND PRECAUTIONS and 4 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.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

See Drug-Drug Interactions table

9.4 Drug-Drug Interactions

Table 5- Established or Potential Drug-Drug Interactions

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Agents Affecting Sympathetic Activity		Beta-adrenergic blocking drugs add some further antihypertensive effect to enalapril	Agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) may be used with caution.
Agents Causing Renin Release		The antihypertensive effect of ENALAPRIL is augmented by antihypertensive agents that cause renin release (e.g., diuretics)	
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, potassium supplements or other drugs that may increase serum potassium (e.g., trimethoprim-containing products) 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

			7 WARNINGS AND PRECAUTIONS).
Dual Blockade of the Renin-Angiotensin System (RAS) with ACEIs, ARBs or aliskiren-containing drugs		Increased incidence of severe hypotension, renal failure, and hyperkalemia	Dual Blockade of the Renin-Angiotensin System (RAS) with ACEIs, ARBs or aliskiren-containing drugs is contraindicated in patients with diabetes and/or renal impairment, and is generally not recommended in other patients. See 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS
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 7 WARNINGS AND PRECAUTIONS
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 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).
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.
Mammalian Target of Rapamycin (mTOR) Inhibitors		Patients taking concomitant mTOR inhibitor (e.g.,	Caution should be used when these drugs are used concomitantly (see 7 WARNINGS and PRECAUTIONS).

		temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema	
Neprilysin Inhibitors		Patients taking a concomitant neprilysin inhibitor (e.g., sacubitril) may be at increased risk for angioedema	(see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS)
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-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. Cases of acute renal failure, usually reversible, have also been reported	The antihypertensive effect of enalapril may be diminished with concomitant non-steroidal anti-inflammatory drug use including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors).. This combination should therefore be administered with caution in this patient population
Dipeptidyl peptidase IV (DPP-IV) inhibitors (e.g. alogliptin, linagliptin, saxagliptin, sitagliptin)	C	Patients taking concomitant DPP-IV inhibitors may be at increased risk for angioedema	Caution should be used when using DPP-IV and ACE inhibitors concomitantly (see 7 WARNING AND PRECAUTIONS).

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions
The absorption of enalapril is not influenced by the presence of food in the gastrointestinal tract.

9.6 Drug-Herb Interactions
Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions
Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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 7 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.

10.2 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 4 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.

10.3 Pharmacokinetics

Table 6 – 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.

Elimination:
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 4 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 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, 10.3 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 4 DOSAGE AND ADMINISTRATION). Enalaprilat is dialyzable at the rate of 62 mL/min (1.03 mL/s).

11 STORAGE, STABILITY AND DISPOSAL

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

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

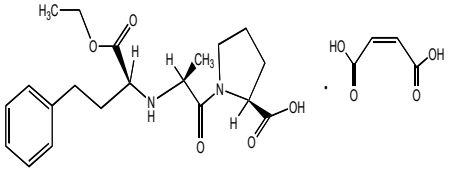
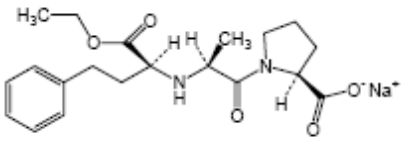
12 SPECIAL HANDLING INSTRUCTIONS

Keep out of the reach and sight of children.

PART II: SCIENTIFIC INFORMATION

13 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 g/mol	398.43 g/mol
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.	

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 7 - Summary of patient demographics for clinical trials SOLVD – Treatment study

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
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

Table 8 - Summary of patient demographics for clinical trials SOLVD-Prevention study

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
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

Table 9 - Summary of Patient demographics for clinical trials

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
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

14.2 Study Results

Table 10 - Results of study SOLVD – Treatment study

Primary Endpoints	Associated value and statistical significance for Enalapril N (%)	Associated value and statistical significance for Placebo N (%)	p-Value
Overall mortality	451 (35.1%)	510 (39.7%)	0.008

In a multicentre, placebo-controlled, double-blind study (SOLVD), 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.

Table 11– 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 multicentre 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.

Table 12 – 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 multicentre, 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.

14.3 Comparative Bioavailability Studies

Study I: A randomized, single dose, two-way crossover comparative bioavailability study of ENALAPRIL tablets, 2.5 mg (Sivem Pharmaceuticals ULC) and VASOTEC® tablets, 2.5 mg (Merck Frosst Canada & Co.) was conducted in 26 healthy, adult male subjects under fasting conditions. A summary of the comparative bioavailability data is presented in the following table.

Table 13: Summary Table of the Comparative Bioavailability Data Study I

Enalapril (2 x 2.5 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	40.64 42.65 (33.1)	38.80 40.88 (35.2)	104.8	98.7 – 111.2
AUC_I (ng·h/mL)	41.23 43.23 (32.7)	39.44 41.51 (34.8)	104.5	98.4 – 111.0
C_{max} (ng/mL)	26.08 27.80 (36.2)	25.06 26.76 (36.6)	104.1	95.5 – 113.4
T_{max}[3] (h)	0.75 (0.33 – 1.50)	0.83 (0.50 – 2.03)	Not applicable	Not applicable
$T_{½}$[4] (h)	1.02 (38.9)	1.23 (92.3)	Not applicable	Not applicable

[1] ENALAPRIL (enalapril as enalapril maleate) tablets, 2.5 mg (Sivem Pharmaceuticals ULC)
[2] VASOTEC® (enalapril as enalapril maleate) tablets, 2.5 mg (Merck Frosst Canada & Co.)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV%) only

Study II: A randomized, single dose, two way crossover comparative bioavailability Study of ENALAPRIL tablets, 20 mg (Sivem Pharmaceuticals ULC) and VASOTEC® tablets, 20 mg (Merck Frosst Canada & Co.) was conducted in 26 healthy, adult male volunteers under fasting conditions. A summary of the comparative bioavailability data is presented in the following table.

Table 14: Summary Table of the Comparative Bioavailability Data Study II

Enalapril (1 x 20 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	179.79 190.04 (30.7)	183.78 193.96 (33.9)	97.8	91.7 – 104.4
AUC_I (ng·h/mL)	181.63 191.88 (30.5)	185.96 196.44 (34.3)	97.7	91.6 – 104.2
C_{max} (ng/mL)	117.30 122.95 (30.2)	120.79 128.33 (35.9)	97.1	87.9 – 107.2
T_{max}[3] (h)	0.92 (0.50 – 2.00)	0.83 (0.67 – 1.75)	Not applicable	Not applicable
$T_{½}$[4] (h)	1.34 (27.6)	1.50 (40.1)	Not applicable	Not applicable

[1] ENALAPRIL (enalapril as enalapril maleate) tablets, 20 mg (Sivem Pharmaceuticals ULC)
[2] VASOTEC® (enalapril as enalapril maleate) tablets, 20 mg (Merck Frosst Canada & Co.)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Table 15 – Mechanism of Action

Study	Species/Strain	No. of Animals/Group	Route	Dose	Results
Effect of enalapril maleate on total	Male Sprague/ Dawley rats	12 experimental 6 placebo	P.O.	10 mg/kg/day for 7 or 14 days	79% increase in ACE after 7 days & 140% after 14 days.

serum ACE in rats and dogs	Male beagle hounds	3 dogs	P.O	10 mg/kg (free base) for 7 or 14 days	30% increase in ACE after 7 days & 48% after 14 days
		3 dogs	P.O	30 mg/kg/day for 3 days	1.5-fold increase in ACE
In vivo ACE inhibition in anesthetized and unanesthetized rats and dogs	Male Sprague/ Dawley rats (Blue Spruce)	6 rats	I.V. P.O.	3, 10, 30 mcg/kg 0.1, 0.3, 1.0 and 3.0 mg/kg	The ED_{50} is 14.0 mcg/kg I.V. and 0.29 mg/kg p.o.
	Mongrel or beagle dogs (male & female)	6 dogs per dose	I.V.	30, 130, 430, 1430 mcg/kg	Dose-related inhibition of pressor response to angiotensin.
					ED_{50}: Enalaprilat: 6.4 mcg/kg. Enalapril maleate: 278 mcg/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 mcg/kg	Local inhibition of ACE: (enalaprilat) ED_{50} = 4.8 (4.4 to 5.2 mcg/kg) I.V.

Table 16 – 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 angiotensin1	Sprague/Dawley rats normotensive	At least 4 to 5 rats/group and at least 3 dogs per	P.O.	Enalapril 0.1 to 3.0 mg/kg	Time course of blood pressure decrease did not coincide with time

blockade and blood pressure lowering in spontaneous hypertensive rats, renal hypertensive rats, and renal hypertensive dogs and normotensive sodium depleted dogs	dogs (mongrel)	group			course for maximal inhibition of angiotensin 1 pressor response

Table 17 – 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

General Toxicology

Acute Toxicity

Table 18 – LD_{50} Values:

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

	Rat	Male Female	-- --	1750 mg/kg 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.

Table 19 – Sub-Acute and Chronic Toxicity

Species	Duration	Number of animals/ group	Route	Dose mg/kg/day	Effects
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

Species	Duration	Number of animals/ group	Route	Dose mg/kg/day	Effects
					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.
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

Species	Duration	Number of animals/ group	Route	Dose mg/kg/day	Effects
					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 supplementation	**Unsupplemented treated dogs:** 6/6: deaths 6/6: increase in serum urea

Species	Duration	Number of animals/ group	Route	Dose mg/kg/day	Effects
					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 renal tubular degeneration 4/6: slight to moderate thymic atrophy 3/6: liver degeneration

Table 20 – 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

Species	Number of animals/ group	Dose mg/kg/day	Duration of Dosing	Results
				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 14^{th} 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

Species	Number of animals/ group	Dose mg/kg/day	Duration of Dosing	Results
				water intake - Significant increase in the mean number of resorptions per litter - 2 abortions - No evidence of teratogenicity was observed.

Table 21 – 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:
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:
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.

17 SUPPORTING PRODUCT MONOGRAPH

1. VASOTEC® (Tablets, 5 mg, 10 mg and 20 mg), submission control #247519, Product Monograph, Organon Canada Inc. (June 21, 2021)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr ENALAPRIL
Enalapril Tablets

Read this carefully before you start taking **ENALAPRIL** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ENALAPRIL**.

Serious Warnings and Precautions

ENALAPRIL should **not** be used during pregnancy. Taking it during pregnancy can cause injury or even death to your baby. If you discover that you are pregnant while taking ENALAPRIL, stop the medication and contact your healthcare professional **as soon as possible**.

What is ENALAPRIL used for?
ENALAPRIL is used to treat:

- children (less than 16 years of age) and adults with high blood pressure
- adults with heart failure

It can be used alone or along with other medications to treat your condition.

How does ENALAPRIL work?
ENALAPRIL belongs to a group of medicines called Angiotensin-Converting Enzyme (ACE) inhibitors. These types of medicines block your body from making a chemical called angiotensin II. When angiotensin II enters your blood:

- your blood vessels become narrower. When this happens, your blood has less space to move in.
- it also triggers a hormone that makes your body hold on to water.

Having more fluid in your body, in a narrow space will cause your blood pressure to go up.

ACE inhibitors help to lower your blood pressure by:

- reducing the amount of angiotensin II in your body. This allows your blood vessels to relax and become wider. It makes it easier for your blood to flow through your blood vessels.
- lowering the amount of water your body retains.

The lowering of your blood pressure makes it easier for your heart to pump blood. It can also help your heart work better if you have heart failure.

This medicine does not cure high blood pressure or congestive heart failure but it helps control these conditions**.**

What are the ingredients in ENALAPRIL?
Medicinal ingredient: Enalapril maleate that appears as enalapril sodium in the tablets.
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

ENALAPRIL comes in the following dosage forms:
ENALAPRIL tablets: 2.5 mg (white, oval-shaped), 5 mg (white, rounded triangle-shaped), 10 mg (peach, rounded triangle-shaped), and 20 mg (salmon, rounded triangle-shaped) of enalapril maleate that appears as 2 mg, 4 mg, 8 mg and 16 mg of enalapril sodium in the tablets respectively.

Do not use ENALAPRIL if:

- You are allergic to enalapril or to any of the other ingredients in ENALAPRIL.
- You have had an allergic reaction (angioedema):
    - to any other ACE inhibitor. You can tell you are taking or have taken an ACE inhibitor because these types of medicines have ingredients that end with **"-PRIL"**.
    - have been diagnosed with hereditary angioedema. This is an increased risk of getting an allergic reaction that is passed down through your family.
    - where the reason for it is not known. This is called idiopathic angioedema.

Signs of an allergic reaction include

- swelling of the hands, feet, ankles, face, lips, tongue and throat
- sudden having trouble breathing or swallowing

Make sure that you tell your healthcare professional that this has happened to you before.

- You have diabetes or kidney disease and are already taking a blood pressure-lowering medicine that contains aliskiren.
- You are taking a medicine containing a neprilysin inhibitor (e.g., sacubitril). Do not take ENALAPRIL for at least 36 hours before or after you take sacubitril/valsartan, a medicine containing a neprilysin inhibitor.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ENALAPRIL. Talk about any health conditions or problems you may have, including if you:

- previously had airway surgery (e.g., in your nose, throat, trachea or lungs)
- have a history of allergic reactions (angioedema). You should be aware that black patients have a higher risk of experiencing these types of reactions while taking ACE inhibitors.
- are undergoing dialysis
- have recently received or are planning to have allergy shots for bee or wasp stings
- are undergoing low-density lipoprotein (LDL)-apheresis, a treatment that removes cholesterol from your blood
- have recently suffered from excessive vomiting or severe diarrhea
- have heart or blood vessel disease
- have narrowing of an artery or a heart valve
- have liver disease
- have low blood pressure
- are planning to have dental or any other type of surgery and will be given anesthesia. Tell your healthcare professional that you are taking this medicine
- are taking anti-cancer or anti-rejection medicines such as temsirolimus, everolimus and sirolimus. Use of ACE inhibitors, such as ENALAPRIL, with these drugs may increase the chance of having an allergic reaction (angioedema).
- are taking a medicine containing a neprilysin inhibitor (e.g., sacubitril).
- are taking dipeptidyl peptidase IV (DPP-IV) inhibitors. You can recognize a DPP-IV inhibitor because its medicinal ingredient ends in **"-GLIPTIN"**
- are taking other blood pressure-lowering medicines
- are on a low-salt diet
- are taking an angiotensin receptor blockers (ARBs). You can recognize an ARB because its medicinal ingredient ends in **"-SARTAN"**
- are taking a medicine that contains aliskiren
- are receiving gold (in the form of sodium aurothiomalate) injections.
- are at risk for developing high levels of potassium in your blood. This can be serious and can happen if you:

- are taking:
    - a salt substitute that contains potassium
    - potassium supplements
    - potassium-sparing diuretic (a specific kind of "water pills" that makes your body hold onto potassium such as spironolactone, eplerenone, triamterene or amiloride)
    - other medications that may increase potassium in your blood (e.g., trimethoprim-containing products)
- have diabetes or any kidney problems

Other warnings you should know about:

ENALAPRIL can cause serious side effects, including:

- **Allergic reaction / Angioedema:** Some patients have reported experiencing allergic reactions (angioedema) while taking ENALAPRIL This may happen at any time during treatment with ENALAPRIL and can be life threatening. Very rarely, cases have resulted in death. If you experience an allergic reaction, **stop** taking ENALAPRIL and tell your healthcare professional **right away**.
- **Hypotension** (low blood pressure): You may feel dizzy or light-headed:
    - Particularly in the first few days after you start taking ENALAPRIL or when your dose is increased.
    - When you exercise or when the weather is hot.

  You should lie down if this happens. If you faint, **stop** taking ENALAPRIL and talk to your healthcare professional. Before doing any tasks that require special attention, wait until you know how you respond to ENALAPRIL.
- **Blood disorders**: ACE inhibitors, such as ENALAPRIL may cause:
    - **Neutropenia / Agranulocytosis** (decrease in white blood cells)
    - **Bone marrow depression** (a large decrease in the production of blood cells and platelets by the bone marrow)
- **Hypoglycemia** (low blood sugar): ENALAPRIL may cause low blood sugar in patients with
    - Diabetes who are taking oral antidiabetic medicines or insulin.
    - Kidney problems

  You should closely monitor your blood sugar level, especially during the first month of your treatment with ENALAPRIL.

See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Cough: You may develop a dry and persistent cough while taking ENALAPRIL. This usually goes away once you stop taking ENALAPRIL or when the dose is lowered. Tell your healthcare professional if you experience this symptom.

Breastfeeding: ENALAPRIL passes into breastmilk and could harm a breastfed baby. ENALAPRIL is not recommended during breastfeeding. Talk to your healthcare professional about ways to feed your baby if you are planning to breastfeed while taking ENALAPRIL.

Laboratory tests and monitoring: Your healthcare professional may do blood tests before you take ENALAPRIL and/or during treatment. These tests will check:

- The level of white blood cells in your body.
- That your liver or kidneys are working properly.
- The potassium levels in your blood.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ENALAPRIL:

- Medicines that lower your blood pressure. These include:
  - Angiotensin-Converting Enzyme (ACE) inhibitors
  - diuretics ("water pills")
  - aliskiren-containing medicines
  - Angiotensin Receptor Blockers (ARBs)
  - beta blockers
- Medicines that can increase the levels of potassium in your blood. These include:
  - potassium-sparing medicines (such as spironolactone, eplerenone, triamterene or amiloride)
  - potassium supplements
  - salt substitutes that contain potassium
  - other medicines that may increase serum potassium (e.g., trimethoprim-containing medicines)
- Medicines used to treat diabetes. These include:
  - DPP-IV inhibitors, such as aligliptin, linagliptin, saxagliptin and sitagliptin
  - Insulin
  - Other oral antidiabetic medicines
- Gold (in the form of sodium aurothiomalate) injections – used to treat arthritis
- Lithium - used to treat bipolar disorder
- Temsirolimus, everolimus, sirolimus – used to treat certain cancers and/or used to prevent rejection of organ transplants
- Medicines containing a neprilysin inhibitor (e.g., sacubitril)
- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), such as naproxen, ibuprofen and celecoxib – used to treat pain and swelling
- Certain medicines that you can buy without a prescription are known to cause your blood pressure to go up. These include medicines:
  - to control your hunger
  - for asthma
  - to treat colds and coughs
  - to treat allergies (such as hayfever)
  - to treat sinus problems

How to take ENALAPRIL:

- Keep your regular appointments with your health care professional, even if you feel well. You may not easily recognize signs of high blood pressure. Your healthcare professional will measure your blood pressure and check how the medicine is controlling it.
- If your healthcare professional has given you specific instructions to follow, for example to eat a low-salt diet or to lose weight, you should follow them.
- Swallow the tablet **whole. You should not split or break ENALAPRIL tablets.**
- **Take ENALAPRIL**
  - exactly as your healthcare professional tells you
  - with or without food
  - at about the same time every day

Usual dose:
Your healthcare professional will decide the best dose for you based on your needs.

Overdose:

If you think you, or a person you are caring for, have taken too much ENALAPRIL, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Symptoms of an overdose include feeling light-headed or dizzy. This can happen because of a sudden or extreme drop in blood pressure.

Missed Dose:

- If it has been **less** than 6 hours since you missed taking it, take your dose as soon as possible and then go back to your regular schedule.
- If it has been **more** than 6 hours since you missed taking it, skip the missed dose. Take the next dose at your usual time.

Do not take two doses at the same time.

What are possible side effects from using ENALAPRIL?
These are not all the possible side effects you may have when taking ENALAPRIL. If you experience any side effects not listed here, tell your healthcare professional.

Side effects include:

- Headache
- Feeling weak or tired
- Dry Cough
- Sore throat
- Runny nose
- Abdominal pain
- Muscle pain
- Joint pain
- Difficulty sleeping
- Sleepiness
- Nervousness
- Decreased urination
- Impotence (not able to have an erection)
- Bladder infection
- Difficulty swallowing
- Eating disorder (anorexia)
- Indigestion
- Nausea
- Vomiting
- Bloating
- Cramps
- Constipation
- Tongue changing colour
- Dry mouth
- Mouth sores
- Changes in taste
- Abnormal dreams
- Confusion
- Hair loss
- Flushed skin
- Sensitivity to light
- Tingling of the skin
- Excessive sweating
- Loss of smell
- Ringing in the ears
- Hearing loss
- Blurred vision
- Pink eye
- Dry eyes

- Watery eyes
- Breast growth in males

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Diarrhea	✓		
Electrolyte imbalance: feeling weak or tired, muscle pain or cramps, irregular heartbeat	✓		
Hypotension (Low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up, following exercise and/or when it is hot and you have lost a lot of water by sweating)			✓
Rash/Itching		✓	
UNCOMMON			
Allergic reactions / Angioedema: difficulty swallowing or breathing; swollen face, hands and feet, genitals, tongue, throat; wheezing; hives or rash; swelling of the digestive tract causing diarrhea, nausea or vomiting			✓
Hypoglycemia (low blood sugar): thirst, frequent urination, hunger, nausea and dizziness, fast heartbeat, tingling trembling, nervousness, sweating, low energy	✓		
Kidney disorder: change in frequency of urination, nausea, vomiting, swelling of the hands and feet, fatigue			✓
Liver disorder: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness		✓	
Loss of appetite	✓		
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat.			✓
Stroke (bleeding or blood clot in the brain): sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body,			✓

sudden headache, blurry vision, difficulty swallowing or speaking, or lethargy, dizziness, fainting, vomiting, trouble understanding, trouble with walking and loss of balance			
Rare			
Bone marrow depression (a large decrease in the production of blood cells and platelets by the bone marrow): bleeding, bruising, chills, fatigue, fever, infections, weakness, shortness of breath or other signs of infection			✓
Neutropenia / Agranulocytosis (decrease in white blood cells): frequent infection, fatigue, fever, aches, pains and flu-like symptoms		✓	
Stevens-Johnson syndrome (SJS) / Toxic Epidermal Necrolysis (TEN) / pemphigus (severe skin reactions): redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, can be accompanied with fever, chills, headache, cough, body aches or swollen glands			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- ENALAPRIL should be stored at room temperature between 15 - 30ºC.
- Keep container tightly closed, away from heat and direct light, and out of damp places, such as the bathroom or kitchen.
- Protect from moisture.
- Discard remaining tablets six months after opening bottle.
- Keep all medicines out of reach and sight of children.

If you want more information about ENALAPRIL:

- Talk to your healthcare professional
  Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-

canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.sivem.ca or by calling 1-855-788-3153.

This leaflet was prepared by,
Sivem Pharmaceuticals ULC
4705 Dobrin Street
Saint-Laurent, Quebec, Canada
H4R 2P7

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