PRODUCT MONOGRAPH

PrENALAPRILAT INJECTION, USP

Solution for Injection,1.25 mg/mL

Angiotensin Converting Enzyme Inhibitor

SteriMax Inc.
1-2735 Matheson Blvd E
Mississauga, ON L4W 4M8

Submission Control No : 171566

Date of Revision:
February 18, 2014

Table of Contents

PrENALAPRILAT INJECTION, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intravenous	Solution for Injection, 1.25 mg/mL	Benzyl Alcohol, Sodium Chloride, Sodium Hydroxide and Water for Injection.

INDICATIONS AND CLINICAL USE

Enalaprilat Injection, USP is indicated for:

- Treatment of hypertension when oral therapy is not practical.

Enalaprilat injection has been studied with only one other antihypertensive agent, furosemide, which showed approximately additive effects on blood pressure.

Due to insufficient experience with Enalaprilat injection in the treatment of accelerated or malignant hypertension, this drug is not recommended in such situations (see **DOSAGE AND ADMINISTRATION**).

The product should be administered under the supervision of a qualified health professional who is experienced in the use of antihypertension IV agents and in the management of patients with severe hypotension or heart failure. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

Pediatrics (<16 years of age):
Enalaprilat Injection, USP has not been studied in children and, therefore, use in this group is not recommended.

CONTRAINDICATIONS

Enalaprilat Injection, USP is contraindicated in:

- Patients who are hypersensitive to this product or to any ingredient in its 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.

Concomitant use of angiotensin converting enzyme (ACE) inhibitors – including Enalaprilat Injection, USP, with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR < 60 mL/min/1.73m^2) is contraindicated (see WARNINGS and PRECAUTIONS, Dual blockade of the Renin-Angiotensin System (RAS) and Renal and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) with ACE inhibitors, ARBs, or aliskiren-containing drugs).

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, Enalaprilat Injection, USP 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 Enalaprilat injection. 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 patient airway should be administered promptly when indicated.

If angioedema occurs, Enalaprilat Injection, USP 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 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 sulphate 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 Enalaprilat injection, 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.

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 **ADVERSE REACTIONS**).

HEMATOLOGIC

Neutropenia/Agranulocytosis: Agranulocytosis and bone marrow depression have been caused by angiotensin converting enzyme inhibitors. 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: There are no adequate studies in patients with cirrhosis and/or liver dysfunction. Enalaprilat Injection, USP 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 Enalaprilat injection (see **DRUG INTERACTIONS**).

Dual blockade of the Renin-Angiotensin System (RAS)

There is evidence that the co-administration of angiotensin converting enzyme (ACE) inhibitors, such as Enalaprilat Injection, USP, 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/1.73m^2). Therefore, the use of Enalaprilat Injection, USP, in combination with aliskiren-containing drugs is contraindicated in these patients (see CONTRAINDICATIONS). Further, co-administration of ACE inhibitors, including Enalaprilat Injection, USP, 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.

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 ACE inhibitors – including Enalaprilat Injection, USP – or ARBs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 mL/min/1.73m^2). (See CONTRAINDICATIONS and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) with ARBs, ACE inhibitors, or aliskiren-containing drugs).

SPECIAL POPULATIONS

Pregnant Women: ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, Enalaprilat Injection, USP 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.

Animal Data

No reproductive or teratogenicity studies have been performed with Enalaprilat injection.

Pediatrics (<16 years of age): Enalaprilat Injection, USP has not been studied in children and, therefore, use in this age group is not recommended.

ADVERSE REACTIONS

ENALAPRIL TABLET:

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 tablets in controlled clinical trials are shown below. In patients treated with enalapril tablets, the maximum duration of therapy was three years; in placebo-treated patients the maximum duration of therapy was 12 weeks.

Table 1 – Hypertension

	Enalapril Tablets 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 tablets 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 tablets and placebo, respectively.

Table 2 – Congestive Heart Failure

	Enalapril Tablets 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 tablets 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 tablets 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 tablets, 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.

POSTMARKET 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.

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

ENALAPRILAT INJECTION

ADVERSE DRUG REACTION OVERVIEW

Since enalapril is converted to enalaprilat, those adverse reactions associated with enalapril tablets might also be expected to occur with Enalaprilat Injection, USP.

The incidence of symptomatic hypotension is 3.4% with Enalaprilat injection. Other adverse experiences occurring in greater than one percent of patients were headache (2.9%) and nausea (1.1%).

Adverse reactions occurring in 0.5 to 1.0% of patients in controlled clinical trials include myocardial infarct, fatigue, dizziness, fever, rash and constipation.

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 enalaprilat. The possibility of hypotensive effects with enalaprilat can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalaprilat (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). If the diuretic cannot be discontinued, patients should be placed under close medical supervision for at least one hour after the initial dose of Enalaprilat Injection, USP (see **WARNINGS AND PRECAUTIONS**).

Agents Increasing Serum Potassium: Since enalaprilat 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.

Agents Causing Renin Release: The antihypertensive effect of Enalaprilat injection 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.

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.

NonSteroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors: In some patients with compromised renal function who are being treated with nonsteroidal anti-inflammatory drugs including selective cyclooxygenase-2 inhibitors, the coadministration of ACE inhibitors may result in further deterioration of renal function.

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 enalaprilat (Enalaprilat injection) (see **WARNINGS AND PRECAUTIONS**).

Dual Blockade of the Renin-Angiotensin System (RAS) with ACE inhibitors, ARBs or aliskiren-containing drugs
Dual blockade of the Renin-Angiotensin System with ACE inhibitors, ARBs or aliskiren-containing drugs is contraindicated in patients with diabetes and/or renal impairment, and is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia. See CONTRAINDICATIONS and WARNINGS AND PRECAUIONS, Dual Blockade of the Renin-Angiotensin System (RAS).

DOSAGE AND ADMINISTRATION

Enalaprilat Injection, USP is for Intravenous Administration Only

DOSING CONSIDERATIONS
• Special attention for dialysis patients.

RECOMMENDED DOSE AND DOSAGE ADJUSTMENT
The dose is 1.25 mg every six hours administered intravenously over at least five minutes. A clinical response is usually seen within 15 minutes. Peak effects after the first dose may not occur for up to four hours after dosing. The peak effects of the second and subsequent doses may exceed those of the first.

No dosage regimen for Enalaprilat injection has been clearly demonstrated to be more effective in treating hypertension than 1.25 mg every six hours. However, in controlled clinical studies in hypertension, doses as high as 5 mg every six hours were well tolerated for up to 36 hours. There has been inadequate experience with doses greater than 20 mg per day.

In studies of patients with hypertension, Enalaprilat injection has not been administered for periods longer than 48 hours. In other studies, patients have received Enalaprilat injection for as long as seven days. The dose for patients being converted to Enalaprilat injection from oral therapy for hypertension with enalapril is 1.25 mg every six hours administered intravenously over at least five minutes. For conversion from intravenous to oral therapy, the recommended

initial dose of enalapril tablets is 5 mg once a day with subsequent dosage adjustments as necessary.

Patients on Diuretic Therapy: For patients on diuretic therapy the recommended starting dose for hypertension is 0.625 mg administered intravenously over at least five minutes. A clinical response is usually seen within 15 minutes. Peak effects after the first dose may not occur for up to four hours after dosing, although most of the effect is usually apparent within the first hour. If after one hour there is an inadequate clinical response, the 0.625 mg dose may be repeated. Additional doses of 1.25 mg may be administered at six hour intervals.

For conversion from intravenous to oral therapy, the recommended initial dose of enalapril tablets for patients who have responded to 0.625 mg of enalaprilat every 6 hours is 2.5 mg once a day with subsequent dosage adjustments as necessary.

Dosage Adjustment in Renal Impairment: The usual dose of 1.25 mg of enalaprilat every six hours is recommended for patients with a creatinine clearance >30 mL/min [>0.50 mL/s] (serum creatinine of up to approximately 3 mg/dL [265.2 μmol/L]). For patients with creatinine clearance ≤30 mL/min [≤0.50 mL/s] (serum creatinine ≥3 mg/dL [≥265.2 μmol/L]), the initial dose is 0.625 mg (see **WARNINGS AND PRECAUTIONS**).

If after one hour there is an inadequate clinical response, the 0.625 mg dose may be repeated. Additional doses of 1.25 mg may be administered at six hour intervals.

For dialysis patients, the initial dose should be 0.625 mg every six hours (see **WARNINGS AND PRECAUTIONS**, **Anaphylactoid Reactions during Membrane Exposure**).

For conversion from intravenous to oral therapy, the recommended initial dose of enalapril tablets is 5 mg once a day for patients with creatinine clearance > 30 mL/min [> 0.50 mL/s] and 2.5 mg once daily for patients with creatinine clearance ≤ 30 mL/min [≤ 0.50 mL/s]. Dosage should then be adjusted according to blood pressure response.

ADMINISTRATION

Enalaprilat Injection, USP may be administered intravenously as supplied, or mixed with up to 50 mL of one of the following diluents:

Dextrose Injection 5%
Sodium Chloride Injection 0.9%
Sodium Chloride Injection 0.9% in 5% Dextrose
Dextrose 5% in Lactated Ringer's Injection

Diluted solutions should be used within 24 hours.

Parenteral Products: As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitation, discolouration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.

OVERDOSAGE

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

Limited data are available for overdosage in humans.

The recommended treatment of overdosage is intravenous infusion of normal saline solution. Enalaprilat may be removed from the general circulation by hemodialysis (see **WARNINGS AND PRECAUTIONS**, **Anaphylactoid Reactions during Membrane Exposure**).

ACTION AND CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Enalaprilat injection is an active metabolite of enalapril and is used in the treatment of hypertension.

Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyzes the conversion of angiotensin I to the pressor substance, angiotensin II. Enalaprilat is an ACE inhibitor. 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.

ACE is identical to kininase II. Thus, Enalaprilat injection 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 Enalaprilat injection lowers blood pressure is believed to be primarily the suppression of the renin-angiotensin-aldosterone system, Enalaprilat injection also lowers blood pressure in patients with low-renin hypertension.

PHARMACODYNAMICS

Administration of Enalaprilat injection to patients with hypertension results in a reduction of both supine and standing blood pressure. Abrupt withdrawal of Enalaprilat injection has not been associated with a rapid increase in blood pressure. Following administration of Enalaprilat injection, the onset of action usually occurs within 15 minutes, with the maximum effect occurring within one to four 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.

Studies in dogs indicate that enalaprilat does not enter the brain.

SPECIAL POPULATIONS AND CONDITIONS

Pediatrics: Enalaprilat injection has not been studied in children and, therefore, use in this age group is not recommended.

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

Renal Insufficiency: The disposition of 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. Enalaprilat is dialyzable at the rate of 62 mL/min (1.03 mL/s).

STORAGE AND STABILITY

Store between 15 and 30°C. Protect from light. Multi-dose vial: discard 28 days after initial puncture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Enalaprilat Injection, USP 1.25 mg per mL, is a clear, colourless solution and is supplied in vials containing 1 mL and 2 mL.

Each millilitre of Enalaprilat Injection, USP contains enalaprilat 1.25 mg (anhydrous equivalent), sodium chloride 6.2 mg to adjust tonicity, sodium hydroxide to adjust pH, benzyl alcohol 9 mg, as a preservative and water for injection q.s..

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

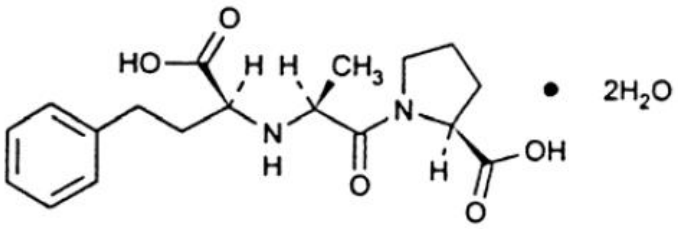
Proper name: Enalaprilat

Chemical name: L-Proline, 1-[*N*-(1-carboxy-3-phenylpropyl)-L-alanyl]-,dihydrate, (*S*)-.

Molecular formula: $C_{18}H_{24}N_2O_5 \bullet 2H_2O$

Molecular mass: 384.43 g/mol

Structural formula:



Physicochemical properties: Enalaprilat is a white to off-white, hygroscopic crystalline powder. It is sparingly soluble in methanol and in dimethylformamide; slightly soluble in water and in isopropyl alcohol; very slightly soluble in acetone, in alcohol, and in hexane; practically insoluble in acetonitrile and in chloroform.

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	12 experimental 6 placebo	PO	10 mg/kg/day for 7 or 14 days	79% increase in ACE after 7 days & 140% after 14 days
	Male beagle hounds	3 dogs	PO	10 mg/kg (free base) for 7 or 14 days	30% increase in ACE after 7 days & 48% after 14 days
		3 dogs	PO	30 mg/kg/day for 3 days	1.5-fold increase in ACE

In vivo ACE inhibition in anesthetised and unanesthetised rats and dogs	Male Sprague/Dawley rats (Blue Spruce)	6 rats	IV PO	3, 10, 30 mcg/kg 0.1, 0.3, 1.0 and 3.0 mg/kg	The ED_{50} is 14.0 mcg/kg IV and 0.29 mg/kg PO
	Mongrel or beagle dogs (male & female)	6 dogs per dose	IV	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	IV	0.3 – 100 mcg/kg	Local inhibition of ACE: (enalaprilat) ED_{50} = 4.8 (4.4 to 5.2 mcg/kg) IV

EFFECTS ON BLOOD PRESSURE

Study	**Species/Strain**	**No. of Animals/Group**	**Route**	**Dose**	**Results**
Antihypertensive activity in sodium-deficient rats	Male Sprague/Dawley rats	6 rats/group and at least 8 treatment groups	PO	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	PO	Enalapril 3.0 mg/kg	Enalapril produced a mean decrease in systolic pressure of ≈20 mmHg and a slight tachycardia
Relationship between angiotensin 1 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	PO	Enalapril 0.1 to 3 mg/kg	Time course of blood pressure decrease did not coincide with time course for maximal inhibition of angiotensin I pressor response

OTHER EFFECTS

Study	Species/Strain	No. of Animals/Group	Route	Dose	Results
Effects in acute renal failure in dogs	Mongrel dogs	4/group	PO	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	PO	5 mg/kg	No radioactivity was found in the spinal cord or brain of either male or female hamsters

TOXICOLOGY

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.

SUBACUTE AND CHRONIC TOXICITY

Species	Duration	No. of Animals/ Group	Route	Dose mg/kg/day	Effects
Rat	1 month	10 M + 10 F	Oral	0, 10, 30, 90	**At all doses:** Slight decrease in body weight gain. **At 30 & 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 (7to 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 physiological 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 + 3F	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.

SUBACUTE AND CHRONIC TOXICITY

Species	Duration	No. Of Animals/ Group	Route	Dose Mg/kg/day	Effects
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 supplementation	**Unsupplemented treated dogs:** 3/6: deaths 4/6: increase in serum urea nitrogen 3/6: decrease in sodium 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 tubular cell vacuolation
Dog Beagle	15 days	3 M + 3 F	Oral	0, 90 with and without saline supplement	**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 renal tubular degeneration 4/6: slight to moderate thymic atrophy 3/6: liver degeneration

TERATOLOGY STUDIES

Species	No. 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-JLC: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 rub 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 were 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	No. 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 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 postweaning weight gain among F1 males of the 30 and 90 mg/kg/day groups **Females at 30 & 90 mg/kg/day:** - Decreased 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 showed 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.

REFERENCES

1. Biollaz J, Burnier M, Turini GA, Brunner DB, Porchet M, Gomez HJ, Jones KH. Three new long-acting converting-enzyme inhibitors: relationship between plasma converting-enzyme activity and response to angiotensin I. Clin Pharmacol Ther 1981;29:665-70.

2. Biollaz J, Schelling JL, Jacot des Combes B, Brunner DB, Desponds G, Brunner HR. Enalapril maleate and a lysine analogue (MK-521) in normal volunteers; relationship between plasma drug levels and the renin angiotensin system. Br J Clin Pharmacol 1982;14:363-8.

3. Biollaz J, Brunner HR, Gavras I, Waeber B, Gavras H. Antihypertensive therapy with MK- 421: Angiotensin II - Renin relationships to evaluate efficacy of converting enzyme blockade. J Cardiovasc Pharmacol 1982;4:966-72.

4. Brunner DB, Desponds G, Biollaz J, Keller I, Ferber F, Gavras H, Brunner HR, Schelling JL. Effect of a new angiotensin converting enzyme inhibitor MK-421 and its lysine analogue on the components of the renin system in healthy subjects. Br J Clin Pharmacol 1981;11:461-7.

5. Cleary JP, Taylor JW. Enalapril: a new angiotensin converting enzyme inhibitor. Drug Intell Clin Pharm 1986;20(3)177-86.

6. Cleland JGF, Dargie HJ, McAlpine H, Ball SG, Morton JJ, Robertson JIS, Ford I. Severe hypotension after first dose of enalapril in heart failure. Br Med J 1985;291:1309-12.

7. Cody RJ, Covit AB, Schaer GL, Laragh JH. Evaluation of a long-acting converting enzyme inhibitor (enalapril) for the treatment of chronic congestive heart failure. J Am Coll Cardiol 1983;1(4):1154-9.

8. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman WB, Loeb H, Wong M, Bhat G, Goldman S, Fletcher RD, Doherty J, Hughes CV, Carson P, Cintron G, Shabetai R, Haakenson C. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Eng J Med 1991;325:303-10.

9. Gavras H, Biollaz J, Waeber B, Brunner HR, Gavras I, Davies RO. Antihypertensive effect of the new oral angiotensin converting enzyme inhibitor "MK-421". Lancet 1981;ii:543-7.

10. Gomez HJ, Cirillo VJ. Angiotensin converting enzyme inhibitors: the clinical pharmacology of captopril and enalapril maleate. Clinical pharmacology and therapeutics (International Congress Series No. 604), Velasco, M. ed., Excerpta Medica, Amsterdam. 1983;52-7.

11. Hodsman GP, Brown JJ, Davies DL, Fraser R, Lever AF, Morton JJ, Murray GD, Robertson JIS. Converting-enzyme inhibitor enalapril (MK-421) in treatment of hypertension with renal artery stenosis. Br Med J 1982;285:1697-9.

12. Hodsman GP, Brown JJ, Cumming AMM, Davies DL, East BW, Lever AF, Morton JJ, Murray GD, Robertson JIS. Enalapril (MK-421) in the treatment of hypertension with renal artery stenosis, (Symposium: on the renin-angiotensin-aldosterone system: treatment of hypertension and heart failure, Milan, Italy, 28 May 1983). J Hypertension 1(Suppl. 1)1983;109-17.

13. Ibsen H, Egan B, Osterziel K, Vander A, Julius S. Reflex-hemodynamic adjustments and baroreflex sensitivity during converting enzyme inhibition with MK-421 in normal humans. Hypertension 1983;5(Suppl. I):184-91.

14. Larochelle P, Carruthers SG, Krip G. Comparison of monotherapy with enalapril and atenolol in mild to moderate hypertension. Can Med Assoc J 1987;(37):803-8.

15. McNabb WR, Brooks BA, Noormohamed F, Lant AF. The effect of enalapril on serum prolactin. Br J Clin Pharmacol 1983;15:752-4.

16. Millar JA, Derx FHM, McLean K, Reid JL. Pharmacodynamics of converting enzyme inhibition: the cardiovascular, endocrine and autonomic effects of MK-421 (enalapril) and MK-521. Br J Clin Pharmacol 1982;14:347-55.

17. Oberman A, Cutter GR, Rogers WJ, Mantle JA. Clinical Endpoints. 1982;341-55 in Congestive Heart Failure; ed. Braunwald E, Mock M, Watson J. Grune & Stratton.

18. Packer M, Hung Lee W, Yushak M, Medina N. Comparison of captopril and enalapril in patients with severe chronic heart failure. N Engl J Med 1986;315:847-53.

19. Packer M, Hung Lee W, Medina N, Yushak M, Kessler PD. Functional renal insufficiency during long-term therapy with captopril and enalapril in severe chronic heart failure. Ann Intern Med 1987;106(3):346-54.

20. Packer M, ed. Do vasodilators prolong life in heart failure? N Engl J Med 1987;316:1471-73.

21. Turini GA, Waeber B, Brunner HR. The renin-angiotensin system in refractory heart failure: Clinical, hemodynamic and hormonal effects of captopril and enalapril. Eur Heart J 1983;4:189-97.

22. Wilkins LH, Dustan HP, Walker JF, Oparil S. Enalapril in low-renin essential hypertension, Clin Pharmacol Ther 1983;34(3):297-302.

23. Vasotec IV® Product Monograph, Version dated September 20, 2013.

PART III: CONSUMER INFORMATION

Enalaprilat Injection, USP

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

ABOUT THIS MEDICATION

Enalaprilat Injection, USP is available **only on prescription** from your physician. Enalaprilat Injection, USP is only administered under the supervision of a qualified health professional.

Enalaprilat Injection, USP 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.

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:

Enalaprilat Injection, USP 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. Enalaprilat Injection, USP allows them to relax and therefore help lower high blood pressure.

Enalaprilat Injection, USP is an active substance of enalapril produced during metabolism and is used in the treatment of high blood pressure.

This medicine does not cure high blood pressure, **but does help control it**. 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 Enalaprilat Injection, USP if you:

- are allergic to enalaprilat or any other component of Enalaprilat Injection, USP (see **What the 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**).
- **are already taking a blood pressure-lowering medicine that contains aliskiren (such as Rasilez) and you have diabetes or kidney disease.**

What the medicinal ingredient is:

Each millilitre of Enalaprilat Injection, USP contains 1.25 mg enalaprilat.

What the non-medicinal ingredients are:

Each millilitre of Enalaprilat Injection, USP contains the following non-medicinal ingredients: sodium chloride 6.2 mg to adjust tonicity, sodium hydroxide to adjust pH (to approximately 7.0), water for injection, q.s.; with benzyl alcohol 9 mg, as preservative.

What dosage forms it comes in:

Enalaprilat Injection, USP 1.25 mg/mL in vials containing 1 and 2 mL.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Enalaprilat Injection, USP should not be used during pregnancy. If you discover that you are pregnant while taking Enalaprilat Injection, USP, stop the medication and please contact your physician as soon as possible.

This medicine may not be suitable for certain people. BEFORE you use Enalaprilat Injection, USP talk to your doctor, nurse or pharmacist if:]

- You have previously taken Enalaprilat Injection, USP 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 medication 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 Enalaprilat Injection, USP 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 Enalaprilat Injection, USP, stop the medication and report to your physician as soon as possible. It is possible that Enalaprilat Injection, USP passes into breast milk. You should not breast feed while taking Enalaprilat Injection, USP
- 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 are taking a medicine that contains aliskiren, such as Rasilez, used to lower blood pressure. The combination with Enalaprilat Injection, USP is not recommended.
• You are taking an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in "-SARTAN".

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 Enalaprilat Injection, USP.

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.**

Enalaprilat Injection, USP is not for use in children.
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 Enalaprilat Injection, USP.

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 Enalaprilat Injection, USP 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 nonsteroidal anti-inflammatory drugs.

The following may also interact with Enalaprilat Injection, USP:
• Blood pressure-lowering drugs, including diuretics ("water pills"), aliskiren-containing products (e.g. Rasilez), or angiotensin receptor blockers (ARBs).

PROPER USE OF THIS MEDICATION

Usual dose:
Your physician will determine the best dosing regimen for you based on your specific condition and blood pressure readings. The usual dose of Enalaprilat Injection, USP is 1.25 mg given every 6 hours by intravenous infusion.

Your physician will determine if and when you should convert from Enalaprilat Injection, USP to enalapril tablets. When this is appropriate, the usual initial dose of enalapril tablets is 5 mg once a day.

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.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its intended action, any medication, including Enalaprilat Injection, USP, 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 Enalaprilat Injection, USP, contact your doctor or pharmacist.

HOW TO STORE IT

Store vials between 15 and 30°C. Protect from light. Multi-dose vial: discard 28 days after initial puncture.

Once diluted, solution should be used within 24 hours.

Keep all medicines out of 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 0701E
    Ottawa, Ontario
    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 found at:
http://www.sterimaxinc.com

or by contacting the sponsor, SteriMax Inc., at:
1-877-546-7667
1-2735 Matheson Blvd E
Mississauga, ON L4W 4M8

This leaflet was prepared by SteriMax Inc.

Last revised: February 18, 2014