PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

VASERETIC®

(enalapril and hydrochlorothiazide)
Tablets 10 mg/25 mg oral
Each tablet is made with 10 mg of enalapril maleate that appears as 8 mg of enalapril sodium in the tablet and 25 mg of hydrochlorothiazide.

Organon Standard
Angiotensin Converting Enzyme Inhibitor / Diuretic

Organon Canada Inc.
16766 route Transcanadienne
Kirkland, QC Canada
H9H 4M7
www.organon.ca

Date of Initial Authorization:
Jul 4, 1990

Date of Revision:

Nov 04, 2022

Internal Revision:

Sep 09, 2024

Submission Control Number: 265020

RECENT MAJOR LABEL CHANGES

1 INDICATIONS, 1.1 Pediatrics	06/2021
1 INDICATIONS, 1.2 Geriatrics	06/2021
4 DOSAGE AND ADMINISTRATION, 4.4 Administration	06/2021
4 DOSAGE AND ADMINISTRATION, 4.5 Missed dose	06/2021
7 WARNINGS AND PRECAUTIONS	11/2022

TABLE OF CONTENTS

RECENT MAJOR LABEL CHANGES 2

TABLE OF CONTENTS 2

PART I: HEALTH PROFESSIONAL INFORMATION 4

1 INDICATIONS 4

1.1 Pediatrics 4

1.2 Geriatrics 4

2 CONTRAINDICATIONS 4

3 SERIOUS WARNINGS AND PRECAUTIONS BOX 5

4 DOSAGE AND ADMINISTRATION 5

4.1 Dosing Considerations 5

4.2 Recommended Dose and Dosage Adjustment 5

4.4 Administration 6

4.5 Missed Dose 7

5 OVERDOSAGE 7

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING 7

7 WARNINGS AND PRECAUTIONS 8

7.1 Special Populations 14

7.1.1 Pregnant Women 14

7.1.2 Breast-feeding 14

7.1.3 Pediatrics 15

7.1.4 Geriatrics 15

8 ADVERSE REACTIONS 15

8.1 Adverse Reaction Overview 15
8.2 Clinical Trial Adverse Reactions 15
8.3 Less Common Clinical Trial Adverse Reactions 17
8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data 17
8.5 Post-Market Adverse Reactions 18
9 DRUG INTERACTIONS 19
9.1 Serious Drug Interactions 19
9.2 Drug Interactions Overview 20
9.4 Drug-Drug Interactions 20
9.5 Drug-Food Interactions 28
9.6 Drug-Herb Interactions 28
9.7 Drug-Laboratory Test Interactions 28
10 CLINICAL PHARMACOLOGY 29
10.1 Mechanism of Action 29
10.2 Pharmacodynamics 29
10.3 Pharmacokinetics 30
11 STORAGE, STABILITY AND DISPOSAL 32
12 SPECIAL HANDLING INSTRUCTIONS 32
PART II: SCIENTIFIC INFORMATION 33
13 PHARMACEUTICAL INFORMATION 33
14 CLINICAL TRIALS 34
14.1 Clinical Trials by Indication 34
15 MICROBIOLOGY 35
16 NON-CLINICAL TOXICOLOGY 35
PATIENT MEDICATION INFORMATION 48

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

VASERETIC® (enalapril and hydrochlorothiazide) is indicated for:

- Treatment of essential hypertension in patients for whom this combination therapy with enalapril and hydrochlorothiazide is appropriate.

In using VASERETIC® consideration should be given to the risk of angioedema (see 7 WARNINGS AND PRECAUTIONS - General).

VASERETIC® is not indicated for initial therapy.

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of VASERETIC® has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

2 CONTRAINDICATIONS

VASERETIC® is contraindicated in:

- Patients who are hypersensitive to this product or to any ingredient in the 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.
- Patients with anuria or hypersensitivity to other sulfonamide-derived drugs due to the hydrochlorothiazide component
- Concomitant use of angiotensin converting enzyme inhibitors (ACEIs) – including the enalapril component of VASERETIC® 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 m^2) is contraindicated (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular, and 9.4 DRUG-DRUG INTERACTIONS).
- VASERETIC® is contraindicated in combination with a neprilysin inhibitor (e.g. , sacubitril). Do not administer VASERETIC® within 36 hours of switching to or from sacubitril/valsartan, a product containing a neprilysin inhibitor. (See 7 WARNINGS AND

PRECAUTIONS - General and 9.4 DRUG-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, VASERETIC® should be discontinued as soon as possible.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Dosage must be individualized.
- The fixed combination is not for initial therapy.
- Special attention for dialysis patients.
- The splitting of VASERETIC® 10 mg/25 mg tablets is not advised.

4.2 Recommended Dose and Dosage Adjustment

The dose of VASERETIC® should be determined by the titration of the individual components. If the fixed combination represents the dose and dosing frequency determined by this titration, the use of VASERETIC® may be more convenient in the management of patients. If during maintenance therapy dosage adjustment is necessary, it is advisable to use the individual drugs.

Once the patient has been successfully titrated with the individual components as described below, VASERETIC® may be substituted if the titrated doses and dosing schedule can be achieved by the fixed combination.

Patients usually do not require doses in excess of 50 mg of hydrochlorothiazide daily, particularly when combined with antihypertensive agents. Therefore, since each tablet of VASERETIC® contains 25 mg of hydrochlorothiazide (in combination with 10 mg of enalapril respectively), the total daily dosage of VASERETIC® should not exceed two tablets of VASERETIC® 10 mg/25 mg. If further blood pressure control is indicated, additional doses of enalapril or other nondiuretic, antihypertensive agents should be considered.

For enalapril monotherapy the recommended initial dose in patients not on diuretics is 5 mg of enalapril once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range of enalapril is 10 to 40 mg per day administered in a single dose or two divided doses. In some patients treated once daily, the antihypertensive effects may diminish toward the end of the dosing interval. In such patients an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with enalapril alone, a diuretic may be added.

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of enalapril. 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 - Cardiovascular). If the patient's blood pressure is not controlled with enalapril alone, diuretic therapy may be resumed.
If the diuretic cannot be discontinued, an initial dose of 2.5 mg of enalapril should be used to determine whether excessive hypotension occurs.

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

Dosing Adjustment in Renal Impairment: In patients with mild to moderate renal impairment (creatinine clearance > 30 mL/min), the usual dose titration of the individual components is required. The recommended initial dose of enalapril, when used alone in patients with mild renal impairment, is 5 mg. In patients with moderate renal impairment, the initial dose of enalapril, when used alone, is 2.5 mg.

When concomitant diuretic therapy is required in patients with severe renal impairment, a loop diuretic, rather than a thiazide diuretic is preferred for use with enalapril. Therefore, for patients with severe renal dysfunction, VASERETIC® is not recommended (see 7 WARNINGS AND PRECAUTIONS - Renal).

Drug Discontinuation
If angioedema occurs, VASERETIC® should be promptly discontinued and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient (see 7 WARNINGS AND PRECAUTIONS - General).
If increasing azotemia and oliguria occur during treatment of severe progressive renal disease the diuretic should be discontinued (see 7 WARNINGS AND PRECAUTIONS - Renal).
VASERETIC should be discontinued and appropriate treatment should be given if the patient presents with acute respiratory distress (see 7 WARNINGS AND PRECAUTIONS - Respiratory)
When pregnancy is detected, VASERETIC® should be discontinued as soon as possible (see 7 WARNINGS AND PRECAUTIONS – Pregnant Women).
If photosensitivity reactions occur during treatment with hydrochlorothiazide-containing drugs, treatment should be stopped (see 7 WARNINGS AND PRECAUTIONS - Photosensitivity).

4.4 Administration
VASERETIC® is for oral administration. VASERETIC® can be taken with or without food. The splitting of VASERETIC® 10 mg/25 mg tablets is not advised

4.5 Missed Dose

Patients should be instructed that if they miss a dose of Vaseretic, they should take the next dose at the regularly scheduled time. The Patient should not double the dose.

5 OVERDOSAGE

No specific information is available on the treatment of overdosage with VASERETIC®. Treatment is symptomatic and supportive. Therapy with VASERETIC® should be discontinued and the patient observed closely. Suggested measures include induction of emesis and/or gastric lavage, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

Enalapril: The most prominent feature of overdosage reported to date is marked hypotension, beginning some six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system, and stupor. Serum enalaprilat levels 100 times and 200 times higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of enalapril, respectively. Enalaprilat may be removed from the general circulation by hemodialysis (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular).

The recommended treatment of overdosage is intravenous infusion of normal saline solution.

Hydrochlorothiazide: The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered hypokalemia may accentuate cardiac arrhythmias.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table -1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
oral	Tablet* 10 mg/25 mg**	corn starch, lactose, magnesium stearate, pregelatinized starch, sodium bicarbonate and the following colouring agent: red ferric oxide

* Each tablet is made with 10 mg of enalapril maleate that appears as 8 mg of enalapril sodium in the tablet and 25 mg of hydrochlorothiazide.

** The splitting of VASERETIC® 10 mg/25 mg tablets is not advised.

VASERETIC® 10 mg/25 mg tablets are rust, oval-shaped, scored tablets, with MSD 720 on one side. Available in blister packages of 28.

Composition
Each tablet of VASERETIC® is made with 10 mg of enalapril maleate that appears as 8 mg of enalapril sodium in the tablets and 25 mg of hydrochlorothiazide.

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 VASERETIC®. 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.

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 9.4 DRUG-DRUG INTERACTIONS).

Patients receiving concomitant ACE inhibitor and neprilysin inhibitor therapy may be at increased risk for angioedema (see 2 CONTRAINDICATIONS and 9.4 DRUG-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 9.4 DRUG-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.

Carcinogenesis and Mutagenesis

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin] after hydrochlorothiazide therapy was reported in some epidemiological studies. The risk may be higher with increasing cumulative use (see 8.5 Post-Market Adverse Reactions). The photosensitizing action of hydrochlorothiazide may be a possible mechanism for NMSC (see 16 NON-CLINICAL TOXICOLOGY).

Patients taking hydrochlorothiazide should be informed of the potential risk of NMSC. They should be advised to regularly check their skin for new lesions as well as changes to existing ones, and to promptly report any suspicious skin lesions. Patients should also be advised to limit exposure to sunlight, to avoid the use of indoor tanning equipment, and to use adequate protection (e.g. a broad spectrum sunscreen with a SPF of 30 or higher, clothing, and a hat) when exposed to sunlight or UV light to minimize the risk of skin cancer.

Alternatives to hydrochlorothiazide may be considered for patients who are at a particularly high risk for NMSC (e.g., light coloured skin, known personal or family history of skin cancer, ongoing immunosuppressive therapy, etc.) (see 8.5 Post Market Adverse Reactions).

Cardiovascular

Hypotension: Patients in whom enalapril and diuretic are initiated simultaneously can develop symptomatic hypotension (see 9.4 DRUG-DRUG INTERACTIONS).

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. Therefore, VASERETIC® should not be used to start therapy or when a dose change is needed. 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 with enalapril 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 hydrochlorothiazide is increased. In patients with ischemic heart or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (see 8.5 Post-Market 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 the enalapril component of VASERETIC®, 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 m2). Therefore, the use of VASERETIC®, in combination with aliskiren-containing drugs is contraindicated in these patients (see 2 CONTRAINDICATIONS). Further, co-administration of ACEIs, including the enalapril component of VASERETIC®, 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.

Driving and Operating Machinery

Occasionally dizziness and fatigue may occur, especially when starting therapy (see 8 ADVERSE REACTIONS). Therefore, exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Ear/Nose/Throat

Cough: A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of VASERETIC®, has been reported.
Such possibility should be considered as part of the differential diagnosis of the cough.

Endocrine and Metabolism

Initial and periodic determination of serum electrolytes should be performed at appropriate intervals to detect possible electrolyte imbalance.

Metabolism: Hyperuricemia may occur, or acute gout may be precipitated in certain patients receiving thiazide therapy.
Thiazides may decrease serum protein-bound iodine (PBI) levels without signs of thyroid disturbance.
Thiazides have been shown to increase excretion of magnesium; this may result in hypomagnesemia.
Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.
Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

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 VASERETIC® 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 VASERETIC® should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. VASERETIC® 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.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

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 (including VASERETIC®) (see 9.4 DRUG-DRUG INTERACTIONS).

Ophthalmologic

Choroidal effusion, Acute Myopia and Secondary Angle-Closure Glaucoma: Hydrochlorothiazide, a sulphonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion, acute transient myopia and/or secondary acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity, blurred vision or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

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.
Thiazides may increase the responsiveness to tubocurarine.

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 the enalapril component of VASERETIC® – or ARBs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 ml/min/1.73 m2). (See 2 CONTRAINDICATIONS and 9.4 DRUG-DRUG INTERACTIONS).

Use of VASERETIC® should include appropriate assessment of renal function.

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 mL/min or below (i.e., moderate or severe renal insufficiency).

Azotemia: Azotemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired 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 alone. 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 VASERETIC® and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see 9.4 DRUG-DRUG INTERACTIONS).

Respiratory

Very rare severe cases of acute respiratory distress including pneumonitis and pulmonary edema have been reported after taking hydrochlorothiazide. (See 8.5 Post-market adverse reactions).

Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Sensitivity/Resistance

Hypersensitivity Reactions: Sensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported in patients treated with hydrochlorothiazide.

Photosensitivity

Photosensitivity reactions have been reported with the use of thiazide diuretics.

7.1 Special Populations

7.1.1 Pregnant Women

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

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.

7.1.2 Breast-feeding

Both enalapril and thiazides appear in human milk. Use of ACE inhibitors (VASERETIC®) is not recommended during breast-feeding.

7.1.3 Pediatrics

Pediatrics (0-18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

See 4 DOSAGE AND ADMINISTRATION.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse Drug Reaction Overview

In clinical trials involving 1580 hypertensive patients, including over 300 patients treated for one year or more, the most severe adverse reactions were: angioedema (0.3%), syncope (1.3%) and renal failure (0.1%).

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6%), headache (5.5%), fatigue (3.9%) and cough (3.5%).

Adverse experiences that have occurred have been those that were previously reported with enalapril or hydrochlorothiazide when used separately for the treatment of hypertension.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse reactions occurring in greater than one percent of patients treated with VASERETIC® in controlled trials are shown below.

Table 2: Hypertension

	Percent of Patients in Controlled Studies	
	VASERETIC® (n = 1580) Incidence (%)	Placebo (n = 230) Incidence (%)
Body as a Whole		
Fatigue	3.9	2.6
Orthostatic Effects	2.3	0.0
Asthenia	2.4	0.9
Cardiovascular		
Chest Pain	1.1	*
Syncope	1.3	*
Orthostatic Hypotension	1.5	*
Palpitations	1.0	*
Dermatologic		
Rash	1.3	*
Digestive		
Diarrhea	2.1	1.7
Nausea	2.5	1.7
Vomiting	1.6	*
Abdominal Pain	1.1	*
Musculoskeletal		
Muscle Cramps	2.7	0.9
Nervous/Psychiatric		
Headache	5.5	9.1
Dizziness	8.6	4.3
Paresthesia	1.1	*
Respiratory		
Cough	3.5	0.9
Urogenital		
Impotence	2.2	0.5

* No data available

8.3 Less Common Clinical Trial Adverse Reactions

Cardiovascular: Hypotension, myocardial infarction, tachycardia
Digestive: Dysphagia, dyspepsia, constipation, flatulence, dry mouth
Hearing: Tinnitus
Hematologic: Anemia
Hypersensitivity: Angioedema
Metabolic and Nutritional: Gout
Musculoskeletal: Back pain, arthralgia
Nervous System/Psychiatric: Insomnia, nervousness, somnolence, vertigo
Respiratory: Dyspnea
Skin: Pruritus, hyperhidrosis, diaphoresis
Special Senses: Taste disturbance
Urogenital: Renal failure, oliguria, proteinuria, decreased libido, urinary tract infection

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

Clinical Trial Findings

Hyperkalemia: (see 7 WARNINGS AND PRECAUTIONS - Renal)

Creatinine, Blood Urea Nitrogen (BUN): In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6% of patients with essential hypertension treated with VASERETIC®.
In patients treated with enalapril alone, 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.

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

Others: Elevations of liver enzymes and/or serum bilirubin have occurred (see 7 WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic).

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 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 - General), asthenia

Cardiovascular

Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular), pulmonary embolism and infarction, pulmonary edema, angina pectoris, arrhythmia including atrial tachycardia and bradycardia, atrial fibrillation, hypotension, palpitation, Raynaud's phenomenon.

Digestive

Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular or cholestatic jaundice), liver function abnormalities (see 7 WARNINGS AND PRECAUTIONS - Hepatic/Biliary/Pancreatic), melena, anorexia, dyspepsia, constipation, flatulence, glossitis, stomatitis, dry mouth.

Endocrine

Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Hematologic

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

Metabolic and Nutritional

Gout

Musculoskeletal

Muscle cramps, arthralgia.

Non-melanoma skin cancer

Some pharmacoepidemiological studies have suggested a higher risk of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) of the skin with increasing use of hydrochlorothiazide. A systematic review and meta-analysis undertaken by Health Canada suggested that, with important uncertainty, the use of hydrochlorothiazide for several years (>3 years) could lead to:

• 122 additional cases (95% CI, from 112 to 133 additional cases) of SCC per 1000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 3 observational studies);

• 31 additional cases (95% CI, from 24 to 37 additional cases) of BCC per 1000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 2 observational studies).

Nervous/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, respiratory distress, pneumonitis and pulmonary edema. Acute respiratory distress has been reported in very rare instances.

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, decreased libido.

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

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
• Concomitant use of lithium and VASERETIC® is not recommended
• Concomitant use of angiotensin converting enzyme inhibitors (ACEIs) – including the enalapril component of VASERETIC® 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 m^2) is contraindicated

- VASERETIC® is contraindicated in combination with a neprilysin inhibitor (e.g. , sacubitril). Do not administer VASERETIC® within 36 hours of switching to or from sacubitril/valsartan, a product containing a neprilysin inhibitor.

9.2 Drug Interactions Overview

See Drug-Drug Interaction table

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the potential magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 - Established or Potential Drug-Drug Interactions

Proper Name	Source of Evidence	**Effect**	**Clinical comment**
Agents Increasing Serum Potassium	T	Concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium or other drugs that may increase serum potassium (e.g., trimethoprim-containing products), may lead to increases in serum potassium	Since enalapril decreases the production of aldosterone, potassium-sparing diuretics 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. If concomitant use of VASERETIC® and any of these agents is deemed appropriate, they should be used with caution and frequent monitoring of serum potassium. Potassium containing salt substitutes

Proper Name	Source of Evidence	**Effect**	**Clinical comment**
			should also be used with caution.
Agents Affecting Sympathetic Activity		Agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) may be used with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to enalapril.	Effect: Beta-adrenergic blocking drugs add some further antihypertensive effect to enalapril. Clinical Outcome: Agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) may be used with caution
Alcohol, barbiturates, or narcotics	C	Potentiation of orthostatic hypotension may occur.	Avoid alcohol, barbiturates or narcotics, especially with initiation of therapy.
Amphotericin B	T	Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics	Monitor serum potassium level.
Antidiabetic agents (e.g. CT insulin and oral hypoglycemic agents)	CT	Thiazide-induced hyperglycemia may compromise blood sugar control. Depletion of serum potassium augments glucose intolerance	Monitor glycemic control, supplement potassium if necessary, to maintain potassium levels, and adjust diabetes medications as required.
Antihypertensive drugs	CT	Hydrochlorothiazide may potentiate the action of other antihypertensive drugs (e.g. guanethidine, methyldopa, betablockers, vasodilators, calcium channel blockers,	

Proper Name	Source of Evidence	**Effect**	**Clinical comment**
		ACEI, ARB, and direct renin inhibitors).	
Antineoplastic drugs, including cyclophosphamide and methotrexate	C	Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.	Hematological status should be closely monitored in patients receiving this combination. Dose adjustment of cytotoxic agents may be required.
Bile acid sequestrants, e.g. cholestyramine and Cholestipol Resins	CT	Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively. Administration of thiazide 4 hours after a bile acid sequestrant reduced absorption of hydrochlorothaizide by 30–35%.	Give thiazide 2–4 hours before or 6 hours after the bile acid sequestrant. Maintain a consistent sequence of administration. Monitor blood pressure, and increase dose of thiazide, if necessary.
Calcium and vitamin D supplements	C	Thiazides decrease renal excretion of calcium and increase calcium release from bone.	Monitor serum calcium, especially with concomitant use of high doses of calcium supplements. Dose reduction or withdrawal

Proper Name	Source of Evidence	**Effect**	**Clinical comment**
			of calcium and/or vitamin D supplements may be necessary.
Carbamazepine	C	Carbamazepine may cause clinically significant hyponatremia. Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Corticosteroids, and adrenocorticotropic hormone (ACTH)	T	Intensified electrolyte depletion, particularly hypokalemia, may occur	Monitor serum potassium, and adjust medications, as required.
Digoxin	CT	Thiazide-induced electrolyte disturbances, i.e. hypokalemia, hypomagnesemia, increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events.	Concomitant administration of hydrochlorothiazide and digoxin requires caution. Monitor electrolytes and digoxin levels closely. Supplement potassium or adjust doses of digoxin or thiazide, as required.
Diuretics	CT	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.

Proper Name	Source of Evidence	**Effect**	**Clinical comment**
Drugs that alter GI motility, i.e., anti- cholinergic agents, such as atropine and prokinetic agents, such as. metoclopramide, domperidone	CT, T	Bioavailability of thiazide diuretics may be increased by anticholinergic agents due to a decrease in gastrointestinal motility and gastric emptying. Conversely, prokinetic drugs may decrease the bioavailability of thiazide diuretics.	Dose adjustment of thiazide may be required.
Dual blockade of the Renin-Angiotensin System (RAS) with ACEIs, ARBs or aliskiren-containing drugs		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, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.	See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Dual Blockade of the Renin-Angiotensin System (RAS).
Gold		Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and symptomatic	See 7 WARNING AND PRECAUTIONS – Hepatic/Biliary/Pancreatic

Proper Name	Source of Evidence	**Effect**	**Clinical comment**
		hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including enalapril	
Gout medications (allopurinol, uricosurics, xanthine oxidase inhibitors)	T, RC	Thiazide-induced hyperuricemia may compromise control of gout by allopurinol and probenecid. The co-administration of hydrochlorothiazide and allopurinol may increase the incidence of hypersensitivity reactions to allopurinol.	Dose adjustment of gout medications may be required.
Lithium	CT	Thiazide diuretics reduce the renal clearance of lithium and add a high risk of lithium toxicity.	Concomitant use of thiazide diuretics with lithium is generally not recommended. If such use is deemed necessary, reduce lithium dose by 50% and monitor lithium levels closely.
Mammalian target of rapamycin (mTOR) inhibitors (e.g., temsirolimus, sirolimus, everolimus)	C, RCS	Patients taking concomitant mTOR inhibitor therapy may be at increased risk for angioedema.	Caution should be used when these drugs are used concomitantly (see WARNINGS and PRECAUTIONS).
Neprilysin Inhibitors (e.g., sacubitril)		Patients taking a concomitant neprilysin inhibitor	see CONTRAINDICATIONS and WARNINGS and PRECAUTIONS.

Proper Name	Source of Evidence	**Effect**	**Clinical comment**
		may be at increased risk for angioedema.	
Nonsteroidal anti-inflammatory drugs (NSAID) Including Cyclooxygenase-2 Inhibitors	CT	The antihypertensive effect of enalapril may be diminished with concomitant non-steroidal anti-inflammatory drug use including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors). In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted including those on diuretic therapy) who are being treated with NSAIDS including selective COX-2 inhibitors, the co-administration 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. This combination should therefore be administered with	If combination use is necessary, monitor renal function, serum potassium, and blood pressure closely. Dose adjustments may be required.

Proper Name	Source of Evidence	**Effect**	**Clinical comment**
		caution in this patient population. It has been reported in the literature that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, dual blockade of the renin-angiotensin-aldosterone system is associated with a higher frequency of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure) as compared to use of a single renin-angiotensin aldosterone system agent.	
Pressor Amines (e.g., norepinephrine)	T	In the presence of thiazide diuretics, possible decreased response to pressor amines may be seen but not sufficient to preclude their use.	
Probenecid		The rate of elimination of hydrochlorothiazide is decreased somewhat by the coadministration of	

Proper Name	Source of Evidence	Effect	Clinical comment
		probenecid without, however, an accompanying reduction in diuresis.	
Selective serotonin reuptake inhibitors (SSRIs, e.g. citalopram, escitalopram, sertraline)	T, C	Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Skeletal muscle relaxants of the curare family, e.g., tubocurare	C	Thiazide drugs may increase the responsiveness of some skeletal muscle relaxants, such as curare derivatives	
Topiramate	CT	Additive hypokalemia. Possible thiazide-induced increase in topiramate serum concentrations.	Monitor serum potassium and topiramate levels.
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).

C = Case Study; RCS = Retrospective Cohort Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

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

VASERETIC® combines the action of an angiotensin converting enzyme inhibitor, enalapril, and that of a diuretic, hydrochlorothiazide.

Enalapril: Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyses 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 enalapril 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.

Hydrochlorothiazide: Hydrochlorothiazide is a diuretic and antihypertensive which interferes with the renal tubular mechanism of electrolyte reabsorption. It increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. While this compound is predominantly a saluretic agent, *in vitro* studies have shown that it has a carbonic anhydrase inhibitory action which seems to be relatively specific for the renal tubular mechanism. It does not appear to be concentrated in erythrocytes or the brain in sufficient amounts to influence the activity of carbonic anhydrase in those tissues.

10.2 Pharmacodynamics

Enalapril

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 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.

Hydrochlorothiazide is useful in the treatment of hypertension. It may be used alone or as an adjunct to other antihypertensive drugs. Hydrochlorothiazide does not affect normal blood pressure.
Onset of the diuretic action following oral administration occurs in 2 hours and the peak action in about 4 hours. Diuretic activity lasts about 6 to 12 hours.

10.3 Pharmacokinetics

Table 4: Summary of Enalaprilat's Pharmacokinetic Parameters in Healthy Volunteers Further to a 10 mg Oral Dose of Enalapril

	Cmax ng/mL	t½ (h)*	AUC0-∞ ng • h/mL
Single dose mean	32.3	11	423

* Effective half-life of accumulation.

Table 5: Summary of Hydrochlorothiazide's Pharmacokinetic Parameters in Healthy Volunteers Further to a 25 mg Oral Dose of Hydrochlorothiazide

	Cmax ng/mL	t½ (h)	AUC0-36 (ng • h/mL)	Renal Clearance (mL/min)	Volume of distribution (L/kg)
Single dose mean	127	5.6–14.8	978	257	0.83

Enalapril

Absorption

Following oral administration, enalapril is rapidly absorbed with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery the extent of absorption of enalapril 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.

Hydrochlorothiazide
Absorption: Hydrochlorothiazide is rapidly absorbed from the gastrointestinal tract with an oral bioavailability of about 65% to 75%. Peak concentrations of hydrochlorothiazide were reached approximately 2 hours after dosing.

Distribution: Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk. Its apparent volume of distribution is 0.83 L/kg.

Metabolism: Hydrochlorothiazide is not metabolized.

Elimination: Hydrochlorothiazide is eliminated rapidly by the kidney. The plasma half-life is 5.6–14.8 hours when the plasma levels can be followed for at least 24 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours.

Enalapril – Hydrochlorothiazide
Concomitant administration of enalapril and hydrochlorothiazide has little, or no effect on the bioavailability of either drug. The combination tablet is bioequivalent to concomitant administration of the separate entities.

Special Populations and Conditions

Pediatrics: Safety and effectiveness in pediatric patients have not been established.

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 (15°C–30°C). Protect from moisture

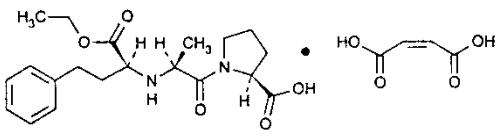
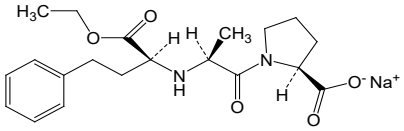
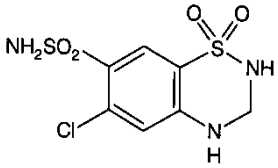
12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions necessary for this medicinal product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

	Enalapril maleate	Enalapril sodium	Hydrochlorothiazide
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).	6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
Molecular formula:	$C_{20}H_{28}N_2O_5.C_4H_4O_4$	$C_{20}H_{27}N_2NaO_5$	$C_7H_8ClN_3O_4S_2$
Molecular mass:	492.53	398.43	297.74
Structural formula:			
Physicochemical properties:	Enalapril maleate is a white to off-white crystalline powder which melts at ≈ 143°C to 144°C. 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.		Hydrochlorothiazide is a white or practically white crystalline compound with low solubility in water but is readily soluble in dilute aqueous sodium hydroxide.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Hypertension

Table 6 - Summary of patient demographics for clinical trials in hypertension

Study	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (range)
2951	Multicenter, double-blind randomized, parallel, active controlled study (24 investigators)	Oral Enalapril 10 mg twice daily Or HCTZ 25 mg twice daily Or Enalapril 10/HCTZ 25 twice daily The dose was titrated from 1 to 2 tablets twice daily after 4 weeks if DBP ≥ 90 mm Hg. Total Duration on Treatment: 8 weeks	546 (221 in enalapril, 222 in HCTZ and 103 in enalapril/HCTZ combination groups)	21 to 65 years
16	Multicenter, double-blind randomized, parallel, active controlled study (6 investigators)	Oral Enalapril 10/ Hydrochlorothiazide 25 once daily Or Propranolol 40/HCTZ 25 twice daily The dose was titrated after 4 and 8 weeks if DBP > 85 mm Hg. Total Duration on Treatment: 12 weeks	151 (76 in enalapril/HCTZ and 75 in propranolol HCTZ groups)	20 to 68 years

HCTZ: Hydrochlorothiazide

Table 7: Results of study 2951 in patients with hypertension

Primary endpoints	Associated value and statistical significance for enalapril/HCTZ	Associated value and statistical significance for enalapril alone	Associated value and statistical significance for HCTZ alone
Mean Change from baseline in supine DBP at 4 weeks	-19.9[*,+]	-11.4	-11.4
Mean Change from baseline in supine DBP at 8 weeks	-21.4[*,+]	-11.5	-13.2

[*,+] Significantly greater than HCTZ and enalapril respectively, ($p < 0.01$)

Table 8: Results of study 16 in patients with hypertension

Primary endpoints	Associated value and statistical significance for enalapril/HCTZ	Associated value and statistical significance for active control/HCTZ
Mean Change from baseline in supine DBP at 4 weeks	-14.4	-12.6
Mean Change from baseline in supine DBP at 8 weeks	-14.9	-13.6
Mean Change from baseline in supine DBP at 12 weeks	-16.8	-16.5

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Enalapril Maleate

Table 9 – Mechanism of Action

Study	Species/Strain	Number of Animals/Group	Route	Dose	Results
Effect of enalapril maleate on	Male Sprague/ Dawley rats	12 experimental 6 placebo	P.O.	10 mg/kg/day	79% increase in ACE after 7 days & 140% after 14 days

total serum ACE in rats and dogs				for 7 or 14 days	
	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 µg/kg 0.1, 0.3, 1.0 and 3.0 mg/kg	The ED50 is 14.0 µg/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 µg/kg	Dose related inhibition of pressor response to angiotensin ED50: Enalaprilat: 6.4 µg/kg Enalapril maleate: 278 µg/kg
Effect of enalaprilat on canine hind limb vasodilator response to bradykinin and vasoconstrictor response to angiotensins	Anesthetized dogs male or female	4 dogs	I.V.	0.3–100 µg/kg	Local inhibition of ACE: (enalaprilat) ED50 = 4.8 (4.4 to 5.2 µg/kg) I.V.

Table 10 – Effects on Blood Pressure

Study	Species/Strain	Number 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	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 of ≈ 20 mmHg and a slight tachycardia
Relationship between angiotensin I blockade and blood pressure lowering in spontaneous hypertensive rats, renal hypertensive rats, and renal hypertensive dogs and normotensive sodium depleted dogs	Sprague/ Dawley rats normotensive dogs (mongrel)	At least 4 to 5 rats/group and at least 3 dogs per group	P.O.	Enalapril 0.1 to 3 mg/kg	Time course of blood pressure decrease did not coincide with time course for maximal inhibition of angiotensin I pressor response

Table 11 – Other Effects

Study	Species/Strain	Number of Animals/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.

Enalapril Maleate and Hydrochlorothiazide

In unanesthetized spontaneously hypertensive rats (7–8/group) enalapril alone when given orally at a dose of 3.0 mg/kg twice daily for three consecutive days reduced mean arterial blood pressure by 10–15 mmHg. A substantially greater fall in mean arterial blood pressure averaging 20, 41 and 34 mmHg (from the pretreatment value on Day 1) was observed in a similar 3-day experiment when enalapril, 3 mg/kg/day orally, was coadministered with an oral dose of hydrochlorothiazide, 50 mg/kg/day.

A similar enhanced antihypertensive response was observed in chronic perinephritic hypertensive dogs when enalapril, 10 mg/kg orally was coadministered with an oral dose of hydrochlorothiazide, 15 mg/kg.

In a renal study in conscious dogs (6 dogs/group) the combination of enalapril 3 mg/kg plus hydrochlorothiazide (0.1, 0.3 and 1.0 mg/kg) given orally over three days showed no synergistic effect of the two compounds on urinary sodium excretion.

When hydrochlorothiazide, 10 mg/kg p.o., was given in combination with enalapril, at doses of 3, 10 and 30 mg/kg orally, only the combination of 10 mg/kg hydrochlorothiazide plus 10 or 30 mg/kg of enalapril orally for three days produced increases in sodium excretion which were greater than the sum of the effects of hydrochlorothiazide plus enalapril. Decreases in plasma potassium were observed at oral doses of 3 and 10 mg/kg but not at 30 mg/kg.

A 16-fold increase in plasma renin activity was observed with the combination treatment of enalapril 30 mg/kg and hydrochlorothiazide 10 mg/kg orally.

General Toxicology:

Table 12 – Enalapril Maleate – Acute Toxicity – LD_{50} Values:

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

		Female	750 mg/kg	900 mg/kg
	Rat	Male	-	950 mg/kg
		Female	-	850 mg/kg
Subcutaneous	Mouse	Male	-	1150 mg/kg
		Female	-	1500 mg/kg
	Rat	Male	-	1750 mg/kg
		Female	-	1400 mg/kg

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

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

Table 13 – Sub-Acute and Chronic Toxicity

Species	Duration	Number 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

Species	Duration	Number of Animals/Group	Route	Dose (mg/kg/day)	Effects
					($p \leq 0.05$) greater kidney weight than controls. 1 year: Dose-related decrease in weight gain (7 to 19%) Dose-related increase in serum urea nitrogen in males given 30 and 90 mg/kg/day (values up to 52.9 and 89.2 mg/100 mL respectively). Three high dose females showed elevated serum urea nitrogen levels. Serum potassium values were increased (0.1 to 0.8 mEq/L) in male rats on the high dose. Males given 90 mg/kg/day had a significantly ($p \leq 0.05$) greater kidney weight than controls.
Rat	1-Month	20 M + 20 F	Oral	0, 90 & 90 with physiologic saline for drinking	Unsupplemented: Less weight gain (8 to 19%), increase in serum urea nitrogen (up to 62.8 mg%). Supplemented: Body weight gain and serum urea nitrogen levels similar to controls.
Rat (sodium depleted)	3 Weeks	30 M + 30 F	Oral	0, 90	A marked potentiation in toxicity included: death, weight loss, marked increases in serum urea nitrogen, creatinine and potassium, renal tubular degeneration.

Species	Duration	Number of Animals/Group	Route	Dose (mg/kg/day)	Effects
Dog Beagle	1-Month	3 M + 3 F	Oral	0, 10, 30, 90 (4 doses only) reduced to 60	At 30 mg: One dog showed increase in BUN and renal tubular degeneration (4 doses only). 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 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	Unsupplemented treated dogs:

Species	Duration	Number of Animals/Group	Route	Dose (mg/kg/day)	Effects
				supplementation	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 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

Species	Duration	Number of Animals/Group	Route	Dose (mg/kg/day)	Effects
					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 14 – Teratology Studies

Species	Number of Animals/Group	Dose (mg/kg/day)	Duration of Dosing	Results
Rat (Charles River CD)	20 F	0, 10, 30, 90	Day 15 of gestation through Day 20 of lactation	At all dosage levels: Decreased maternal weight gain during days 15–20 Dose-related retardation in growth of F1 offspring during lactation At 90 mg/kg/day: Mean Day 1 pup weight/litter was significantly less than that of controls
Rat	25 F	0, 10, 100, 200, 100 +	Days 6 through Day 17 of gestation	Decreased maternal weight gain at 100 and 200

Species	Number of Animals/Group	Dose (mg/kg/day)	Duration of Dosing	Results
(Charles River CD)		saline, 200 + saline		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)	25F	0, 12, 120, 1200, 1200 + saline	Days 6 through Day 17 of gestation	Unsupplemented treated rats: Average maternal body weight gain significantly reduced at all doses
				At 1200 mg/kg/day Slight but significant decrease in fetal weight Increase in the number of fetuses with the 14th rib skeletal variation Decrease in the number of fetuses with ossified caudal vertebrae Supplemented treated rats: No evidence of maternotoxicity or fetotoxicity
Rabbit (New Zealand albino)	18 F	0, 3, 10, 30 (with saline)	Days 6 through Day 18 of gestation	At 3 and 10 mg/kg/day: No treatment-related effects on reproductive status or teratogenicity was observed At 30 mg/kg/day: 4 deaths Reduced food and water intake Significant increase in the mean number of resorptions per litter 2 abortions No evidence of teratogenicity was observed

Table 15 - 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 postweaning weight gain among F1 males of the 30 and 90 mg/kg/day groups Females at 30 & 90 mg/kg/day: Decrease weight gain during gestation Pups: Reduced body weights in F1 pups at 90 mg/kg/day on Day 1 postpartum and secondarily a delay in postnatal development. Increased incidence of deaths of F1 pups at 30 and 90 mg/kg/day during lactation.

Mutagenicity Studies: Enalapril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation, in the Rec-Assay, sister chromatid exchange with cultured chinese hamster cells, (up to 20 mg/mL) and the micro-nucleus test with mice.
In vitro chromosomal aberration test – enalapril was clastogenic at 10 and 20 mg/mL but not at 5 mg/mL.
Carcinogenicity: 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.

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. Enalapril crosses the placental barrier in rats and hamsters.

Hydrochlorothiazide
According to the experimental data available, hydrochlorothiazide revealed inconsistent evidence of carcinogenic activity in rats and mice, with conflicting evidence of hepatic adenoma in male mice at the highest dose and adrenal pheocytochroma in one rat study but not in another. Current evidence is inadequate to draw a clear conclusion for a carcinogenic effect of hydrochlorothiazide in animals.

The mutagenic potential was assessed in a series of in vitro and in vivo test systems. While some positive results were obtained in vitro, all in vivo studies provided negative results. Hydrochlorothiazide enhanced the UVA-induced formation of pyrimidine dimers in vitro and in the skin of mice following oral treatment. It is therefore concluded that although there is no relevant mutagenic potential in vivo, hydrochlorothiazide could enhance the genotoxic effects of UVA light. This mechanism of photosensitization could be associated with a higher risk for non-melanoma skin cancer.

Enalapril Maleate - Hydrochlorothiazide
The acute LD50 of hydrochlorothiazide (479–551 mg/kg) was lowered (390–353 mg/kg) by one hour pretreatment with orally administered enalapril (14–211 mg/kg). This change was slight and at doses which would not be of clinical significance. No effect was seen on the acute oral

toxicity of enalapril in mice by the prior oral administration of 900 mg/kg of hydrochlorothiazide.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrVASERETIC®

enalapril and hydrochlorothiazide tablets

Read this carefully before you start taking **VASERETIC®** 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 **VASERETIC®**.

Serious Warnings and Precautions
VASERETIC® 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 VASERETIC®, stop the medication and contact your healthcare professional **as soon as possible**.

What is VASERETIC® used for?
VASERETIC® is used to treat adults with high blood pressure.

How does VASERETIC® work?

VASERETIC® contains two medicinal ingredients:

- **Enalapril**: It is an Angiotensin-Converting Enzyme (ACE) inhibitor. This type of drug blocks 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.

- **Hydrochlorothiazide**: It is a diuretic. This type of drug helps your body eliminate salt and water through your urine. Having less fluid in your body will cause your blood pressure to go down.

This medicine does not cure high blood pressure but it helps control this condition.

What are the ingredients in VASERETIC®?
Medicinal ingredients: Enalapril maleate that appears as enalapril sodium in the tablets, and hydrochlorothiazide.
Non-medicinal ingredients: Corn starch, lactose, magnesium stearate, pregelatinized starch, red ferric oxide and sodium bicarbonate.

VASERETIC® comes in the following dosage forms:
Tablet: 10 mg of enalapril maleate, that appears as 8 mg of enalapril sodium in the tablets, and 25 mg of hydrochlorothiazide.

Do not use VASERETIC® if:

- You are allergic to enalapril, hydrochlorothiazide or to any of the other ingredients in VASERETIC®. VASERETIC® contains lactose.
- 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
    - suddenly 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 VASERETIC® for at least 36 hours before or after you take sacubitril/valsartan, a medicine containing a neprilysin inhibitor.
- You have difficulty urinating or produce no urine.
- You are allergic to sulphonamide-derived medicines (sulfa drugs). Most of them have a medicinal ingredient that ends in "-**MIDE**".

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VASERETIC®. 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 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
- have a history of allergies
- have a history of bronchial asthma
- have lupus or gout
- have a greater chance of developing skin cancer because you:
    - had skin cancer or have a family history of skin cancer
    - have light coloured skin
    - get sunburned easily, or
    - are taking medicines to suppress your immune system
- 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
- 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 allergic to penicillin or sulphonamide-derived medicines
- 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 pill” 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:

- **Breastfeeding**: VASERETIC® passes into breastmilk and could harm a breastfed baby. VASERETIC® is **not** recommended during breastfeeding. Talk to your healthcare professional about ways to feed your baby if you are planning to breastfeed while taking VASERETIC®.
- **Driving and using machines:** VASERETIC® may impair your ability to drive or to use machines. Wait until you know how VASERETIC® affects you before driving or using machines. Do not drive or use machines if VASERETIC® impairs your ability to do so safely.
- **Laboratory tests and monitoring**: Your healthcare professional may do blood tests before you take VASERETIC® and/or during treatment. These tests will check:
  - The amount of blood cells in your body.
  - That your thyroid gland, liver and kidneys are working properly.
  - The levels of electrolytes in your blood.
  - The levels of cholesterol and triglycerides (types of fat) in your blood

VASERETIC® can cause serious side effects, including:

- **Allergic reaction / Angioedema**: Some patients have reported experiencing allergic reactions (angioedema) while taking VASERETIC®. This may happen at any time during treatment with VASERETIC® and can be life threatening. Very rarely, cases have resulted in death. If you experience an allergic reaction, **stop** taking VASERETIC® and tell your healthcare professional **right away**.
- **Blood disorders**: ACE inhibitors, such as the enalapril component of VASERETIC®, may cause:
  - **Bone marrow depression** (a large decrease in the production of blood cells and platelets by the bone marrow)
  - **Neutropenia / Agranulocytosis** (decrease in white blood cells)
- **Breathing Problems:** The hydrochlorothiazide component of VASERETIC may cause severe shortness of breath or difficulty breathing after taking VASERETIC. Stop taking VASERETIC and get immediate medical help.
- **Cough**: You may develop a dry and persistent cough while taking VASERETIC®. This usually goes away once you stop taking VASERETIC® or when the dose is lowered. Tell your healthcare professional if you experience this symptom.
- **Eyes:** The hydrochlorothiazide component of VASERETIC® may cause:

    - **Choroidal effusion** (abnormal accumulation of fluid in your eyes)
    - **Glaucoma** (increased pressure in your eyes). This may lead to permanent vision loss if left untreated.
    - **Myopia** (near sightedness)
- These eye disorders can develop within hours to weeks of starting VASERETIC®. If you experience eye problems, **stop** taking VASERETIC® 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 VASERETIC® 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, talk to your healthcare professional **as soon as possible**. Before doing any tasks that require special attention, wait until you know how you respond to VASERETIC®.
- **Kidney disorders:** The hydrochlorothiazide component of VASERETIC may cause or worsen kidney problems. This includes kidney damage and/or decreased production of urine. If you experience signs of kidney problems, tell your healthcare professional **right away**.
- **Skin**: Treatment with hydrochlorothiazide, a component of VASERETIC®, may increase your risk of developing non-melanoma skin cancer. The risk is higher if you have been taking VASERETIC® for many years (more than 3) or at a high dose.

  While taking VASERETIC®:
    - Regularly check your skin for any new lesions such as patches of pigmented skin, lumps, bumps, sores or moles. Check areas that are most exposed to the sun, such as the face, ears, hands, shoulders, upper chest and back.
    - You may become sensitive to the sun.
    - Limit your exposure to sun and avoid indoor tanning. Always use sunscreen (SPF-30 or higher) and wear protective clothing when going outside.

  Talk to your healthcare professional **right away** if you become more sensitive to the sun or UV light or if you develop any new skin lesions while taking VASERETIC®.

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

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 VASERETIC®:

- 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 alogliptin, linagliptin, saxaglitpin and sitagliptin
    - insulin
    - other oral antidiabetic medicines
- Medicines that lower your blood pressure. These include:
    - guanethidine
    - methyldopa
    - beta blockers
    - vasodilators
    - calcium channel blockers
    - Angiotensin-Converting Enzyme (ACE) inhibitors
    - Angiotensin Receptor Blockers (ARBs)
    - aliskiren-containing medicines
    - diuretics (“water pills”)
- Alcohol
- Lithium - used to treat bipolar disorder
- Barbiturates – used to treat anxiety, insomnia and seizures
- Carbamazepine, topiramate – used to prevent and control seizures
- Narcotics – used to relieve pain
- Amphotericin B – used to treat fungal infections
- Adrenocorticotropic hormone (ACTH) – used to treat West Syndrome
- Corticosteroids – used to treat joint pain and swelling and other conditions
- Digoxin – used to treat heart conditions
- Calcium and vitamin D supplements
- Gout medicines, including allopurinol, uricosurics, xanthine oxidase inhibitors and probenecid
- Anticancer medicines, including cyclophosphamide and methotrexate – used to treat cancer
- Gold (in the form of sodium aurothiomalate) injections – used to treat arthritis
- Temsirolimus, everolimus, sirolimus – used to treat certain cancers and/or used to prevent rejection of organ transplants
- Bile acid resins, such as cholestyramine and cholestipol resins – used to lower cholesterol
- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), such as naproxen, ibuprofen and celecoxib – used to treat pain and swelling
- Medicines that slow down or speed up bowel functions, such as atropine, metoclopramide, and domperidone

- Medicines containing a neprilysin inhibitor (e.g., sacubitril)
- Pressor amines, such as norepinephrine
- Antidepressants, in particular Selective Serotonin Reuptake Inhibitors (SSRIs), such as citalopram, escitalopram and sertraline
- Skeletal muscle relaxants used to relieve muscle spasms, including tubocurare

How to take VASERETIC®:

- Swallow the tablet whole. You should not split or break VASERETIC® tablets.
- Take VASERETIC®:
    - exactly as your healthcare professional tells you
    - at the same time every day
    - with or without food. If VASERETIC® upsets your stomach, take it with food or milk.

Usual dose:
Take VASERETIC® as directed by your healthcare professional.

The maximum daily dosage should not exceed two tablets of VASERETIC® 10 mg/25 mg.

Overdose:

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

Symptoms of an overdose include:

- Light-headedness and dizziness. This is due to a sudden or extreme drop in blood pressure.
- Feeling weak, feeling sleepy, irregular heartbeat, muscle pain or cramps. These are signs of an electrolyte imbalance.
- Dehydration. This is due to an increase or extreme production of urine.

Missed dose:
If you have forgotten to take your dose during the day, take the next dose at the usual time. Do not double dose.

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

Side effects may include:
- Fever

- Feeling weak or tired
- Skin rash
- Feeling sick
- Vomiting
- Abdominal pain
- Muscle cramps
- Bladder infection
- Headache
- Dizziness
- Tingling of the skin
- Dry cough
- Impotence (not able to have an erection)
- Difficulty swallowing
- Indigestion
- Constipation
- Passing Gas, gas
- Dry mouth
- Ringing in the ears
- Gout (Intense joint pain, pain after the intense pain in not longer there, inflamation and redness of the affected joint, limited movement of the affected joint.
- Back pain
- Joint pain, joint stiffness
- Difficulty sleeping
- Nervousness
- Sleepiness
- Vertigo (you have a spinning or moving sensation)
- Itching
- Excessive sweating
- Changes in taste
- Decreased libido
- Eating disorder (anorexia)
- Abnormal dreams
- Confusion
- Hair loss
- Flushed skin
- Sensitivity to light
- Loss of smell
- Pink eye

- Dry eyes
- Watery eyes
- Loss of hearing
- Breast growth in males

VASERETIC® can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

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			
Breathing problems, shortness of breath		**√**	
Chest pain		**√**	
Decreased or increased levels of potassium in the blood: irregular heartbeats, muscle weakness, generally feeling unwell		**√**	
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)	**√**		
Non-melanoma skin cancer: lump or discoloured patch on the skin that stays after a few weeks and slowly changes. Cancerous lumps are red/pink and firm and sometimes turn into ulcers. Cancerous patches are usually flat and scaly.		**√**	
Tachycardia (abnormally fast heartbeat)	**√**		
UNCOMMON			
Allergic Reaction / Angioedema: difficulty swallowing or breathing; swollen face, hands and feet, genitals, tongue, throat; wheezing; hives or rash; swelling			**√**

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	
of the digestive tract causing diarrhea, nausea or vomiting			
Anemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness		√	
Electrolyte Imbalance: weakness, drowsiness, muscle pain or cramps, irregular heartbeat		√	
Hyperglycemia: (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue	√		
Kidney Disorder: decreased urination, nausea, vomiting, swelling of extremities, fatigue		√	
Liver Disorder: yellowing of the skin or eyes (jaundice), dark urine, abdominal pain, nausea, vomiting, 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.			√
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heart beat, nausea, vomiting, tenderness when touching the abdomen			√
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			√

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	
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		**√**	
Pulmonary edema (excess fluid in the lungs): difficulty breathing that worsens with activity or when lying down, extreme shortness of breath, wheezing or gasping for breath, cold clammy skin, irregular heartbeat, cough that produces frothy sputum, blue-tinged lips			**√**
Raynaud's phenomenon (episodes of reduced blood flow): cold feeling in fingers and toes (and sometimes nose, lips and ears), prickly or stinging feeling, change in skin colour to white then blue			**√**
VERY RARE			
Acute Respiratory Distress Syndrome (ARDS): Severe difficulty breathing, including shortness of breath. fever, weakness, or confusion.			**√**
Stevens-Johnson syndrome (SJS) / Toxic Epidermal Necrolysis			**√**

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	
(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			
SIADH—syndrome of inappropriate antidiuretic hormone secretion: concentrated urine (dark in colour), feel or are sick, have muscle cramps, confusion and fits (seizures) which may be due to inappropriate secretion of ADH (antidiuretic hormone).			√
UNKNOWN			
Ataxia (lack of muscle coordination): difficulty with fine motor tasks such as eating, writing or buttoning shirt; difficulty walking; loss of balance; slurring speech		√	
Eye Disorders: **Choroidal effusion** (abnormal accumulation of fluid in your eyes): changes in your vision, can be accompanied with eye pain. **Glaucoma:** increased pressure in your eyes, eye and head pain, swelling or redness in or around the eye, and changes in vision (Hazy or blurred vision, sudden sight loss). **Myopia** (near sightedness): blurred vision, difficulty focusing on objects far away, need to squint, headache caused by eyestrain, fatigue.			√
Herpes Zoster virus (shingles): a painful skin rash of fluid-filled	√		

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	
blisters, blisters appear along a strip of skin, itching			
Pulmonary embolism (blood clot in the lung): chest pain that may increase with deep breathing, cough, coughing up bloody sputum, shortness of breath			√

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:

- Store your tablets between 15°C - 30°C.
- Protect from moisture.
- Keep out of reach and sight of children.

If you want more information about VASERETIC®:

- 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://health-products.canada.ca/dpd-bdpp/index-eng.jsp the manufacturer's website www.organon.ca , or by calling 1-844-820-5468.

This leaflet was prepared by Organon Canada Inc.
Last Revised November 04, 2022