

PRODUCT MONOGRAPH

**Pr TEVA-ENALAPRIL/HCTZ**

Enalapril / Hydrochlorothiazide Tablets

5 mg/12.5 mg and 10 mg/25 mg

Professed Standard

Each tablet is made with 5 or 10 mg of enalapril maleate that appears as 4 or 8 mg of enalapril sodium, and 12.5 mg or 25 mg of hydrochlorothiazide, respectively

Angiotensin Converting Enzyme Inhibitor / Diuretic

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**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form/Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
Oral	Tablets/ 5 mg/12.5 mg and 10 mg/25 mg	Lactose <i>For a complete listing, see Dosage Forms, Composition and Packaging section.</i>

**INDICATIONS AND CLINICAL USE**

TEVA-ENALAPRIL/HCTZ (enalapril and hydrochlorothiazide) is indicated for:

- treatment of essential hypertension in patients for whom this combination therapy is appropriate

In using TEVA-ENALAPRIL/HCTZ consideration should be given to the risk of angioedema (see WARNINGS AND PRECAUTIONS).

TEVA-ENALAPRIL/HCTZ is not indicated for initial therapy. Patients in whom enalapril and diuretic are initiated simultaneously can develop symptomatic hypotension (see DRUG INTERACTIONS).

Patients should be titrated on individual drugs. If the fixed combination represents the dose and dosing frequency determined by this titration, the use of TEVA-ENALAPRIL/HCTZ 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.

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

**Pediatrics (<18 years of age):** TEVA-ENALAPRIL/HCTZ is not recommended in this age group.

**CONTRAINDICATIONS**

TEVA-ENALAPRIL/HCTZ is contraindicated in:

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

For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

- Patients with a history of angioneurotic edema relating to previous treatment with an angiotensin converting enzyme inhibitor.
- Patients with hereditary or idiopathic angioedema.

Because of the hydrochlorothiazide component, this product is contraindicated in:

- Patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

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

#### General

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

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

If angioedema occurs, TEVA-ENALAPRIL should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since this may be life threatening and treatment with antihistamines and corticosteroids may not be sufficient.

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

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

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see CONTRAINDICATIONS).

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

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

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

### **Cardiovascular**

**Hypotension:** Symptomatic hypotension has occurred after administration of enalapril, usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Therefore, TEVA-ENALAPRIL/HCTZ 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 ADVERSE REACTIONS).

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

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

### **Ear/Nose/Throat**

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

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

### **Endocrine and Metabolism**

**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 ADVERSE REACTIONS). In most cases the changes were reversed on discontinuation of the drug.

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

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. TEVA-ENALAPRIL/HCTZ 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 (see DRUG INTERACTIONS).

### **Peri-Operative Considerations**

**Surgery/Anesthesia:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril blocks angiotensin II formation, secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

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.

Use of TEVA-ENALAPRIL/HCTZ (enalapril and hydrochlorothiazide) 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. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the diuretic should be discontinued.

**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 the concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes. The use of potassium

supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function should be given only for documented hypokalemia and with caution and frequent monitoring of serum potassium since they may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal, arrhythmias. If concomitant use of TEVA-ENALAPRIL/HCTZ and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see DRUG INTERACTIONS, Agent Increasing Serum Potassium).

### **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.

### **Special Populations**

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

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

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

Infants with a history of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit.

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

### **Animal Data**

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



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

**Nursing Women:** Both enalapril and thiazides appear in human milk. Use of ACE inhibitors (TEVA-ENALAPRIL/HCTZ) is not recommended during breast-feeding.

**Pediatrics:** TEVA-ENALAPRIL/HCTZ has not been studied in children and, therefore, use in this age group is not recommended.

## **ADVERSE REACTIONS**

### **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.

### **Clinical Trial Adverse Drug Reactions**

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

Adverse reactions occurring in greater than one percent of patients treated with enalapril and hydrochlorothiazide tablets in controlled trials are shown below.

**Table 1: Hypertension**

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

\* No data available

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

**Abnormal Hematologic and Clinical Chemistry Findings**

**Hyperkalemia:** (see WARNINGS AND PRECAUTIONS)

**Creatinine, Blood Urea Nitrogen:** 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 enalapril and hydrochlorothiazide tablets.

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 WARNINGS AND PRECAUTIONS).

**Post-Market Adverse Drug Reactions**

**Adverse Reactions Reported in Uncontrolled Trials and/or Marketing Experience:**

**Enalapril Tablets**

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 WARNINGS AND PRECAUTIONS).

**Cardiovascular**

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

**Digestive**

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

**Hematologic**

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

**Musculoskeletal**

Muscle cramps.

**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.

**Skin**

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

**Special Senses**

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

**Urogenital**

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

A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive antinuclear antibody (ANA), elevated erythrocyte sedimentation rate, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur. These symptoms may be reversible upon discontinuation of therapy. In very rare cases, intestinal angioedema has been reported with angiotensin converting enzyme inhibitors including enalapril.

**Laboratory Test Findings:** Hyponatremia

### **Enalapril and Hydrochlorothiazide Tablets (Marketing Experience Only)**

Arthralgia  
Asthenia  
Constipation  
Decreased libido  
Dry mouth  
Dyspepsia  
Flatulence  
Gout  
Hypotension  
Tachycardia  
Tinnitus  
Vertigo

### **DRUG INTERACTIONS**

#### **Serious Drug Interactions**

- Concomitant use of lithium and TEVA-ENALAPRIL/HCTZ Tablets is not recommended.

### **Drug-Drug Interactions**

**Hypotension - Patients on Diuretic Therapy:** Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril (see WARNINGS AND PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

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

**Agents Causing Renin Release:** The antihypertensive effect of TEVA-ENALAPRIL/HCTZ is augmented by antihypertensive agents that cause renin release (e.g. diuretics).

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

**Lithium:** Diuretic agents and ACE inhibitors reduce the renal clearance of lithium and add a high risk of lithium toxicity. Concomitant use is not recommended.

**d-Tubocurarine:** Thiazide drugs may increase the responsiveness to tubocurarine.

**Insulin:** Insulin requirements in diabetic patients treated with thiazide diuretics may be increased. Diabetes mellitus which has been latent may become manifest during thiazide administration.

**Alcohol, Barbiturates, or Narcotics:** In the presence of thiazide diuretics, potentiation of orthostatic hypotension may occur.

**Corticosteroids, ACTH:** Intensified electrolyte depletion, particularly hypokalemia may occur when given concomitantly with thiazide diuretics.

**Cholestyramine and Colestipol Resins:** 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%, respectively.

**Pressor Amines** (e.g. norepinephrine): In the presence of thiazide diuretics, possible decreased response to pressor amines may be seen but not sufficient to preclude their use.

**Non-steroidal Anti-inflammatory Drugs:** In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when TEVA-ENALAPRIL/HCTZ and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

The antihypertensive effect of enalapril may be diminished with concomitant non-steroidal anti-inflammatory drug use. In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of ACE inhibitors may result in further deterioration of renal function.

**Probenecid:** The rate of elimination of hydrochlorothiazide is decreased some what by the coadministration of probenecid without, however, an accompanying reduction in diuresis.

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

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

- **Dosage must be individualized.**
- **The fixed combination is not for initial therapy.**
- **The dose of TEVA-ENALAPRIL/HCTZ (enalapril and hydrochlorothiazide) should be determined by the titration of the individual components.**
- **Special attention for dialysis patients.**

### Recommended Dose and Dosage Adjustment

Once the patient has been successfully titrated with the individual components as described below, TEVA-ENALAPRIL/HCTZ may be substituted if the titrated doses and dosing schedule can be achieved by the fixed combination (see INDICATIONS AND CLINICAL USE and WARNINGS AND PRECAUTIONS).

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 TEVA-ENALAPRIL/HCTZ contains either 12.5 mg or 25 mg of hydrochlorothiazide (in combination with 5 mg or 10 mg of enalapril respectively), the total daily dosage of TEVA-ENALAPRIL/HCTZ should not exceed four tablets of TEVA-ENALAPRIL/HCTZ 5/12.5 or two tablets of TEVA-ENALAPRIL/HCTZ 10/25. 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 WARNINGS AND PRECAUTIONS). 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, TEVA-ENALAPRIL/HCTZ is not recommended (see WARNINGS AND PRECAUTIONS, Anaphylactoid Reactions during Membrane Exposure).

## **OVERDOSAGE**

No specific information is available on the treatment of overdosage with enalapril and hydrochlorothiazide. Treatment is symptomatic and supportive. Therapy with TEVA-ENALAPRIL/HCTZ 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.

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

**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.

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.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

TEVA-ENALAPRIL/HCTZ 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 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.

## **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 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.

### **Pharmacokinetics**

**Table 2: Summary of Enalaprilat's Pharmacokinetic Parameters in Healthy Volunteers Further to a 10 mg Oral Dose of Enalapril**

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

\* Effective half life of accumulation.

**Table 3: Summary of Hydrochlorothiazide's Pharmacokinetic Parameters in Healthy Volunteers Further to a 25 mg Oral Dose of Hydrochlorothiazide**

	$C_{max}$ ng/mL	$t_{1/2}$ (h)	$AUC_{0-36}$ (ng.h/mL) <sub>∞</sub>	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.

**Excretion:** Excretion of enalapril is primarily renal. Approximately 94% of the dose is recovered in the urine and feces as enalaprilat or enalapril. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril.

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

### **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.

**Excretion:** 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  $\leq 30$  mL/min ( $\leq 0.50$  mL/s), peak and trough enalaprilat levels increase, time to peak concentration increases and time to steady state may be delayed. The effective half-life of enalaprilat following multiple doses of enalapril is prolonged at this level of renal insufficiency (see DOSAGE AND ADMINISTRATION). Enalaprilat is dialyzable at the rate of 62 mL/min (1.03 mL/s).

### **STORAGE AND STABILITY**

Store at controlled room temperature (15°C - 30°C). Protect from moisture.

### **DOSAGE FORMS, COMPOSITION AND PACKAGING**

TEVA-ENALAPRIL/HCTZ 5/12.5 mg tablets are green, squared, capsule-shaped, compressed tablets, engraved with N on one side and 5 on the other. Each tablet contains 5 mg of enalapril maleate that appears as 4 mg of enalapril sodium and 12.5 mg of hydrochlorothiazide. Available in blister packages of 30 tablets.

TEVA-ENALAPRIL/HCTZ 10/25 mg tablets are rust, oval-shaped, scored tablets, engraved with N on one side and 10 scoreline 25 (10|25) on the scored side. Each tablet contains 10 mg of

enalapril maleate that appears as 8 mg of enalapril sodium and 25 mg of hydrochlorothiazide. Available in bottles of 100 tablets and blister packages of 30 tablets.

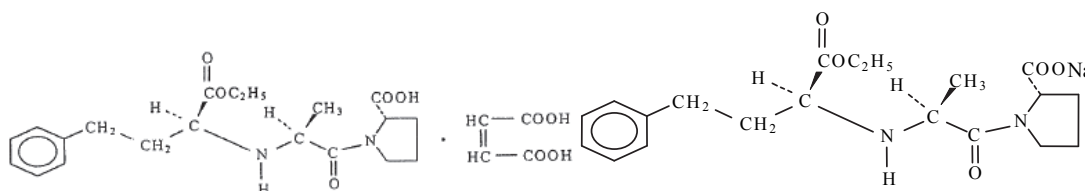
In addition to the active ingredients, enalapril maleate that appears as enalapril sodium in the final tablet and hydrochlorothiazide, each tablet contains as non-medicinal ingredients: corn starch, lactose, magnesium stearate, pregelatinized starch, sodium bicarbonate powder and the following colouring agents: The 5/12.5 mg tablets contain FD&C Blue No. 2 Aluminum Lake and yellow ferric oxide and the 10/25 mg tablets contain red ferric oxide.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name:	Enalapril maleate	Enalapril sodium
Chemical name:	L-Proline, 1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-, (S)-, (Z)-2-butenedioate (1:1)	L-Proline, 1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-, (S)-, Sodium (1:1)
Molecular formula:	$C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$	$C_{20}H_{27}N_2O_5 \cdot Na$
Molecular mass:	492.53	398.43
Structural formula:		



**Physicochemical Properties:** Enalapril maleate is a white to off-white crystalline powder which melts at  $\approx 143^\circ\text{C}$  to  $\approx 144^\circ\text{C}$ . It is sparingly soluble in water (pH 3.4), soluble in ethanol, and freely soluble in methanol and dimethylformamide. The  $\text{pK}_a^1$  and  $\text{pK}_a^2$  of the base moiety are 3.0 and 5.4 respectively.

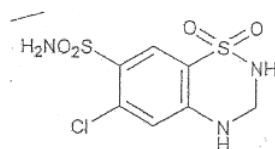
Proper name: Hydrochlorothiazide

Chemical name: 1. 1,2,4-Benzothiadiazine-7-sulfonamide,6-chloro-3,4-dihydro-,1,1-dioxide  
2. 2. 6-Chloro-3,4 dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

Molecular formula:  $C_7H_8ClN_3O_4S_2$

Molecular mass: 297.74

Structural formula:



Physicochemical Properties Hydrochlorothiazide is a white to off-white crystalline powder with low solubility in water, but is readily soluble in dilute aqueous sodium hydroxide.

## CLINICAL TRIALS

### Comparative Bioavailability Data

This is a blinded, single-dose, randomized, two-period, two-sequence, two-treatment, crossover comparative bioavailability study between TEVA-ENALAPRIL/HCTZ 10/25 mg Tablets (Teva Canada Limited, Canada) and Vaseretic® 10/25 mg Tablets (Merck Frosst Canada & Co., Canada) after a single-dose in 24 healthy subjects (male and female) under fasting conditions.

### Enalapril Data

Enalapril (1 x 10/25 mg) From measured data <b>uncorrected for potency</b> Geometric Mean Arithmetic Mean (CV%)				
Parameter	Teva- Enalapril/HCTZ *	Vaseretic® †	<sup>a</sup> % Ratio of Geometric Means	<sup>a</sup> Confidence Interval, 90%
AUC <sub>T</sub> (ng x h/mL)	93.096 99.762 (35)	92.430 98.671 (30)	100.72	89.80 - 112.97
AUC <sub>I</sub> (ng x h/mL)	93.893 100.419 (35)	93.048 99.269 (30)	100.91	89.89 - 113.27
C <sub>max</sub> (ng/mL)	61.780 65.287 (31)	63.533 67.065 (28)	97.24	85.78 - 110.23
T <sub>max</sub> <sup>§</sup> (h)	0.81 (28)	0.80 (18)		
T <sub>½</sub> <sup>§</sup> (h)	1.18 (76)	1.07 (62)		

\* Teva-Enalapril/HCTZ 10 mg/25 mg tablets (Teva Canada Limited, Canada).

† Vaseretic® 10 mg/25 mg tablets (Merck Frosst Canada & Co., Canada); purchased in Canada.

§ Expressed as arithmetic mean (CV%) only.

<sup>a</sup> Based on least-square means estimates.

### Hydrochlorothiazide Data

Hydrochlorothiazide (1 x 10/25 mg) From measured data <b>uncorrected for potency</b> Geometric Mean Arithmetic Mean (CV%)				
Parameter	Teva- Enalapril/HCTZ *	Vaseretic® †	<sup>a</sup> % Ratio of Geometric Means	<sup>a</sup> Confidence Interval, 90%
AUC <sub>T</sub> (ng x h/mL)	1252.770 1291.135 (23)	1212.296 1265.263 (24)	103.34	95.06 - 112.33
AUC <sub>I</sub> (ng x h/mL)	1273.661 1311.391 (22)	1229.829 1282.837 (24)	103.56	95.38 - 112.45
C <sub>max</sub> (ng/mL)	201.953 211.348 (30)	184.337 193.900 (31)	109.56	99.39 - 120.76
T <sub>max</sub> <sup>§</sup> (h)	1.94 (54)	2.54 (51)		
T <sub>½</sub> <sup>§</sup> (h)	8.93 (14)	9.08 (16)		

\* Teva-Enalapril/HCTZ 10 mg/25 mg tablets (Teva Canada Limited, Canada).

† Vaseretic® 10 mg/25 mg tablets (Merck Frosst Canada & Co., Canada); purchased in Canada.

§ Expressed as arithmetic mean (CV%) only.

<sup>a</sup> Based on least-square mean estimates.



## Study demographics and trial design

**Table 4: Summary of patient demographics for clinical trials in specific indication**

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 $\geq$ 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)	20-68 years

HCTZ: Hydrochlorothiazide

## Study Results

**Table 5 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 <sup>*,†</sup>	-11.4	-11.4
Mean Change from baseline in supine DBP at 8 weeks	-21.4 <sup>*,†</sup>	-11.5	-13.2

<sup>\*,†</sup> Significantly greater than HCTZ and enalapril respectively, (p<0.01)

**Table 6 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

## DETAILED PHARMACOLOGY

### Enalapril Maleate

#### Mechanism of Action

Study	Species/Strain	Number of Animals/Group	Route	Dose	Results
Effect of enalapril maleate on total serum ACE in rats and dogs	Male Sprague/Dawley rats	12 experimental 6 placebo	P.O.	10 mg/kg/day for 7 or 14 days	79% increase in ACE after 7 days & 140% after 14 days
	Male beagle hounds	3 dogs	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
<i>In vivo</i> ACE inhibition in anesthetized and unanesthetized rats and dogs	Male Sprague/Dawley rats (Blue Spruce)	6 rats	I.V. P.O.	3, 10, 30 $\mu$ g/kg 0.1, 0.3, 1.0 and 3.0 mg/kg	The ED <sub>50</sub> is 14.0 $\mu$ g/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 $\mu$ g/kg	Dose related inhibition of pressor response to angiotensin ED <sub>50</sub> : Enalaprilat: 6.4 $\mu$ g/kg Enalapril maleate: 278 $\mu$ g/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 $\mu$ g/kg	Local inhibition of ACE: (enalaprilat) ED <sub>50</sub> = 4.8 (4.4 to 5.2 $\mu$ g/kg) I.V.

## 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 $\approx$ 20 mmHg and a slight tachycardia
Relationship between angiotensin 1 blockade and blood pressure lowering in spontaneous hypertensive rats, renal hypertensive rats, and renal hypertensive dogs and normotensive sodium depleted dogs	Sprague/Dawley rats normotensive dogs (mongrel)	At least 4 to 5 rats/group and at least 3 dogs per group	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 1 pressor response

## 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.

## TOXICOLOGY

### Enalapril Maleate

#### Acute Toxicity

LD<sub>50</sub> Values:

Route	Species	Sex	MSDRL <sup>a</sup>	NMB/RL <sup>b</sup>
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

<sup>a</sup> Merck Sharp and Dohme Research Laboratories, West Point, PA, USA

<sup>b</sup> Nippon Merck-Banyu Co., Menuma, Japan

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

#### Sub-Acute and Chronic Toxicity

Species	Duration	Number of Animals/Group	Route	Dose mg/kg/day	Effects
Rat	1-Month	10 M + 10 F	Oral	0, 10, 30, 90	<b>At all doses:</b> Slight decrease in body weight gain.  <b>At 30 &amp; 90 mg/kg/day:</b> Dose-related increase in BUN

					in males.
Rat	3-Months	15 M + 15 F	Oral	0, 10, 30, 90	<p><b>At all doses:</b> 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.</p> <p><b>At 30 &amp; 90 mg/kg/day:</b> Dose-related increase in BUN.</p>
Rat	1-Year	25 M + 25 F	Oral	0, 10, 30, 90	<p><b>6-month interim kill:</b> Males given 90 mg/kg/day had a significantly (<math>P \leq 0.05</math>) greater kidney weight than controls.</p> <p><b>1 year:</b> 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 (<math>P \leq 0.05</math>) greater kidney weight than controls.</p>
Rat	1-Month	20 M + 20 F	Oral	0, 90 & 90 with physiologic saline for drinking	<p><b>Unsupplemented:</b> Less weight gain (8 to 19%), increase in serum urea nitrogen (up to 62.8 mg%).</p> <p><b>Supplemented:</b> Body weight gain and serum urea nitrogen levels similar to controls.</p>
Rat (sodium depleted)	3 Weeks	30 M + 30 F	Oral	0, 90	A marked potentiation in toxicity included: death, weight loss, marked increases in serum urea nitrogen, creatinine and potassium, renal tubular degeneration.
Dog Beagle	1-Month	3 M + 3 F	Oral	0, 10, 30, 90 (4 doses only) reduced to 60	<p><b>At 30 mg:</b> One dog showed increase in BUN and renal tubular degeneration (4 doses only).</p>

					<p><b>At high doses:</b>  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.</p>
Dog Beagle	3-Months	3 M + 3 F	Oral	0, 10, 30, 90 (7 doses only)	<p><b>At all doses:</b>  Slight decrease in serum sodium.</p> <p><b>At 30 mg:</b>  2/6: deaths  Increase in BUN and serum glucose; renal tubular degeneration.</p> <p><b>At 90 mg:</b>  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.</p>
Dog Beagle	1-Year	5 M + 5 F	Oral	0, 3, 5, 15	No drug-induced changes were seen.
Dog Beagle	15-days	3 M + 3 F	Oral	0, 60 with and without saline supplementation	<p><b>Unsupplemented treated dogs:</b>  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)</p> <p><b>Saline supplemented treated dogs:</b>  0/6: deaths  3/6: increase in serum urea nitrogen</p>



					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	<p><b>Unsupplemented treated dogs:</b>  6/6: deaths  6/6: increase in serum urea nitrogen, creatinine and SGPT  5/6: increase in SGOT  2/6: increase in serum potassium  5/6: marked renal tubular degeneration  1/6: moderate renal tubular degeneration  6/6: slight to marked thymic atrophy  3/6: ulceration of distal esophagus  2/6: oral mucosal lesions</p> <p><b>Supplemented treated dogs:</b>  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</p>

### 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	<p><b>At all dosage levels:</b></p> <ul style="list-style-type: none"> <li>- Decreased maternal weight gain during days 15-20</li> <li>- Dose-related retardation in growth of F1 offspring during lactation</li> </ul> <p><b>At 90 mg/kg/day:</b></p> <ul style="list-style-type: none"> <li>- Mean Day 1 pup weight/litter was significantly less than that of controls</li> </ul>

Rat (Charles River CD)	25 F	0, 10, 100, 200, 100 + saline, 200 + saline	Days 6 through Day 17 of gestation	Decreased maternal weight gain at 100 and 200 mg/kg/day in unsupplemented rats. No treatment-related effects on reproductive status or teratogenic effects in any of the groups.
Rat (CLEA Japan Inc-JCL:SD)	25F	0, 12, 120, 1200, 1200 + saline	Days 6 through Day 17 of gestation	<b>Unsupplemented treated rats:</b> - Average maternal body weight gain significantly reduced at all doses  <b>At 1200 mg/kg/day</b> - 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  <b>Supplemented treated rats:</b> - 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	<b>At 3 and 10 mg/kg/day:</b> - No treatment-related effects on reproductive status or teratogenicity was observed  <b>At 30 mg/kg/day:</b> - 4 deaths - Reduced food and water intake - Significant increase in the mean number of resorptions per litter - 2 abortions - No evidence of teratogenicity was observed

### **Fertility and Postnatal Evaluation Studies**

Species	Number of Animals/Group	Dose mg/kg/day	Duration of Dosing	Results
Rat (Charles River CD)	15 M + 30 F	0, 10, 30, 90	Males 70 days prior to mating to termination of females. Females 15 days prior to mating and throughout gestation.	No effects on reproductive status were observed at any dose.  <b>Males at 30 &amp; 90 mg/kg/day:</b> - 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

				<p>reduced in FO males</p> <ul style="list-style-type: none"> <li>- A slight treatment-related reduction in mean postweaning weight gain among F1 males of the 30 and 90 mg/kg/day groups</li> </ul> <p><b>Females at 30 &amp; 90 mg/kg/day:</b></p> <ul style="list-style-type: none"> <li>- Decrease weight gain during gestation</li> </ul> <p><b>Pups:</b>  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.</p>
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### **Mutagenicity Studies**

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

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

### **Carcinogenicity Studies**

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

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

### **Enalapril Maleate - Hydrochlorothiazide**

The acute LD<sub>50</sub> 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.

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PART III: CONSUMER  
INFORMATION

Pr TEVA-ENALAPRIL/HCTZ

**Enalapril / Hydrochlorothiazide Tablets**

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

**ABOUT THIS MEDICATION**

TEVA-ENALAPRIL/HCTZ is the brandname for the combination of the substances - enalapril and hydrochlorothiazide. Enalapril is one of a class of medicines known as angiotensin converting enzyme inhibitors and hydrochlorothiazide is a thiazide diuretic, often termed a "water pill". This combination is available **only on prescription** from your physician. It is usually prescribed to reduce **high blood pressure**.

**What the medication is used for:**

- reducing high blood pressure

**What it does:**

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

TEVA-ENALAPRIL/HCTZ does not cure high blood pressure, **but does help control it**. Enalapril is one of a class of medicines known as angiotensin converting enzyme inhibitors (ACE). Its action is to lower blood pressure by blocking the vasoconstrictor and aldosterone-secreting effects of angiotensin II. Hydrochlorothiazide is a diuretic (water pill) that helps reduce angioedema (the swelling caused by water retention).

**When it should not be used:**

Do not take TEVA-ENALAPRIL/HCTZ if you:

- are allergic to TEVA-ENALAPRIL/HCTZ or any of its components
- have a history of swelling of the face, lips, tongue, throat, or sudden difficulty breathing or swallowing.
- have been diagnosed with swelling of the face, lips, tongue, throat, or sudden difficulty breathing or swallowing due to genetic factors or unknown reasons (please refer to Side Effects and What to do About Them).
- have a history of angioneurotic edema
- have a hereditary or idiopathic angioedema

**What the medicinal ingredients are:**

Enalapril maleate and Hydrochlorothiazide. Each tablet is made with 5 or 10 mg of enalapril maleate that appears as 4 or 8 mg of enalapril sodium, and 12.5 mg or 25 mg of hydrochlorothiazide, respectively.

**What the important nonmedicinal ingredients are:**

Corn starch, lactose, magnesium stearate, pregelatinized starch, sodium bicarbonate and the following colouring agents: the 5/12.5 mg tablets contain FD&C Blue No. 2 Aluminum Lake and yellow ferric oxide and the 10/25 mg tablets contain red ferric oxide.

**What dosage forms it comes in:**

Tablet 5/12.5 mg (green), 10/25 mg (rust).

**WARNINGS AND PRECAUTIONS**

**Serious Warning and Precautions**

TEVA-ENALAPRIL/HCTZ should not be used during pregnancy. If you discover that you are pregnant while taking TEVA-ENALAPRIL/HCTZ, please discuss stopping this medication with your physician.

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

This medicine may not be suitable for certain people. So, tell your physician or pharmacist if you think any of the following applies to you:

## IMPORTANT: PLEASE READ

- You have previously taken **any** of the following and were allergic or reacted badly to it: hydrochlorothiazide or any other diuretic or "water pill"; sulfonamides (sulfa medicine); enalapril or any other medication of the same type - Angiotensin Converting Enzyme (ACE) inhibitors with the names usually ending with 'pril' such as enalapril, lisinopril, captopril, particularly if you experienced swelling of the face, eyes, lips, tongue and/or throat, hands or feet, or had sudden difficulty breathing or swallowing.
- **You should also not take this medicine if you have been diagnosed with hereditary angioedema or idiopathic angioedema (angioedema of unknown cause).**
- **You are pregnant, breast-feeding or thinking of becoming pregnant.** Taking TEVA-ENALAPRIL/HCTZ during pregnancy can cause injury and even death to your developing baby. This medicine should not be used during pregnancy. If you become pregnant while taking TEVA-ENALAPRIL/HCTZ, stop the medication and report to your physician as soon as possible. It is possible that TEVA-ENALAPRIL/HCTZ passes into breast milk. You should not breast-feed while taking TEVA-ENALAPRIL/HCTZ.
- You suffer from low blood pressure (you may notice this as faintness or dizziness, especially when standing). Tell your physician if you experience lightheadedness especially during the first few days of therapy. If actual fainting occurs, discontinue the drug until having consulted with your prescribing physician.
- You are undergoing dialysis.
- You have any of these conditions:
  - diabetes
  - heart or blood vessel disease
  - liver disease
  - kidney disease, or difficulty in producing urine
  - bronchial asthma
  - lupus erythematosus or a history of this condition
  - gout or history of gout

- you are receiving gold (sodium aurothiomalate) injections
- you are taking "water pills" or potassium supplements
- you use potassium containing salt substitutes with your food

You should also inform your physician or pharmacist if you are vomiting or have severe diarrhea.

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

**Do not use outdated medicine.**

**This medicine is not recommended for children.**

### INTERACTIONS WITH THIS MEDICATION

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

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

Your physician or pharmacist also needs to know if you are taking any other medication, whether they be prescription medications or over-the-counter products. It is particularly important to inform your physician or pharmacist if you are taking:

- Diuretics or "water pills"
- Any other medicines to reduce blood pressure
- Potassium-containing medicines, potassium supplements, or salt substitutes that contain potassium
- Diabetes medicine and/or insulin
- Lithium (a drug used to treat a certain kind of depression)
- Non-steroidal anti-inflammatory drugs (NSAIDs) used to relieve pain
- Alcohol

## IMPORTANT: PLEASE READ

- Corticosteroids
- Cholestyramine and colestipol resins (to treat high cholesterol)
- Probenecid (a drug used to treat gout)
- D-tubocurarine (a muscle relaxant)
- Barbiturates
- Narcotics

### PROPER USE OF THIS MEDICATION

#### Usual dose:

- Take this medicine exactly as your physician ordered.
- The absorption of this medicine is not affected by food; so it can be taken with or without a meal.
- Try to take your medicine every day at the same time. This way it becomes easy to remember your doses.
- The usual dosage range is between 10-40 mg, taken once or twice daily as per your physician's instructions.

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

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

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

#### Overdose:

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

#### Missed dose:

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

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its intended action, any medication, including enalapril with hydrochlorothiazide, may cause side effects. Most people do not experience any problem when taking this medicine; but if you notice any of the following, medical attention may be needed.

- Symptoms of angioedema include: sudden difficulty in breathing or swallowing, swelling of face, eyes, lips, tongue and/or throat, hands or feet. You should be aware that black patients are at increased risk of these types of reactions to ACE inhibitors.
- Dizziness, lightheadedness or fainting following exercise, and/or when it is hot and you have lost a lot of water by sweating.
- Flu-like symptoms such as sore throat, fever, malaise, muscle pain, rash, itching, abdominal pain, nausea, vomiting, diarrhea, jaundice, loss of appetite.

**Stop taking the medication and contact your physician or pharmacist at once. You may require immediate care. If condition worsens seek medical attention.**

**If any fainting occurs, stop taking the medicine. If dizzy, avoid driving or any activity/jobs requiring alertness. Use extra care during exercise or hot weather.**

- You may experience increased skin sensitivity to sunlight. Avoid too much sunlight and do not use a sunlamp.
- Dry cough, sore throat
- Unusual tiredness and/or weakness
- Chest pain
- Impotence



## IMPORTANT: PLEASE READ

- Headache
- Palpitations
- Tingling of the skin

If you notice any of the above or have other side effects, contact your physician or your pharmacist. If the condition persists or worsens, seek medical attention.

***This is not a complete list of side effects. For any unexpected effects while taking TEVA-ENALAPRIL/HCTZ, contact your physician or pharmacist.***

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

Symptom/effect	Talk with your physician or Pharmacist		Stop taking drug and call your physician or pharmacist
	Only if severe	In all cases	
Common			
Chest Pain		✓	
Dizziness/Lightheadedness			✓
Dyspnea		✓	
Fatigue	✓		
Headache	✓		
Hypotension		✓	
Lasting Cough		✓	
Nausea/Vomiting/Diarrhea	✓		
Rash/Itching		✓	
Uncommon			
Abdominal Pain	✓		
Allergic Reactions/Angioedema			✓
Fainting			✓
Flu-like symptoms such as fever, malaise, muscle pain			✓
Liver Impairment such as jaundice, dark /brown urine		✓	
Loss of Appetite	✓		

### HOW TO STORE IT

Store your tablets at 15°C - 30°C, away from heat and direct light, and out of damp places, such as the bathroom or kitchen. **Keep all medicines out of the reach of children.**

### REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: 1-866-234-2345

Toll-free fax: 1-866-678-6789

By email: [cadrmp@hc-sc.gc.ca](mailto:cadrmp@hc-sc.gc.ca)

By regular mail:

National AR Centre

Marketed Health Products Safety and Effectiveness Information Division

Marketed Health Products Directorate

Tunney's Pasture, AL 0701C

Ottawa, ON K1A 0K9

***NOTE: Before contacting Health Canada you should contact your physician or pharmacist.***

### MORE INFORMATION

This document plus the full Product Monograph prepared for health professionals can be found by contacting Teva Canada Limited at:

1-800-268-4127 ext. 1255005

or [druginfo@tevacanada.com](mailto:druginfo@tevacanada.com)

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