PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] TEVA-LISINOPRIL/HCTZ (TYPE Z)

Lisinopril and Hydrochlorothiazide Tablets

Tablets, 10 mg / 12.5 mg, 20 mg / 12.5 mg and 20 mg / 25 mg, Oral

Angiotensin Converting Enzyme Inhibitor / Diuretic (C09BA03)

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada M1B 2K9
www.tevacanada.com

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RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions – Ophthalmologic	08/2022
7 Warnings and Precautions – Carcinogenesis and Mutagenesis	08/2022
7 Warnings and Precautions – Skin	08/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TEVA-LISINOPRIL/HCTZ (TYPE Z) (lisinopril and hydrochlorothiazide tablets) is indicated for:

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

TEVA-LISINOPRIL/HCTZ (TYPE Z) is not indicated for initial therapy (see 4 DOSAGE AND ADMINISTRATION). Patients in whom lisinopril and diuretic are initiated simultaneously can develop symptomatic hypotension (see 9 DRUG INTERACTIONS).

TEVA-LISINOPRIL/HCTZ (TYPE Z) is not indicated for the treatment of renovascular hypertension (see Hypotension).

Patients should be titrated on the individual drugs. If the fixed combination represents the dosage determined by this titration, the use of TEVA-LISINOPRIL/HCTZ (TYPE Z) may be more convenient in the management of patients. If during maintenance therapy dosage adjustment is necessary, it is advisable to use individual drugs.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (> 65 years of age): In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of lisinopril (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

TEVA-LISINOPRIL/HCTZ (TYPE Z) is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING;
- Patients with a known allergy to angiotensin converting enzyme (ACE) inhibitors;
- Patients with a history of hereditary/idiopathic angioedema or angioedema related to previous treatment with an ACE inhibitor (see 7 WARNINGS AND PRECAUTIONS Angioedema);
- Women who are pregnant, intend to become pregnant, or of childbearing potential who are not using adequate contraception (see 7.1.1 Pregnant Women and 8 ADVERSE REACTIONS);
- Nursing women (see 7.1.2 Breast-feeding);

- Patients who have anuria because of the hydrochlorothiazide component;
- Patients who are hypersensitive to other sulfonamide-derived drugs;
- Combination with sacubitril/valsartan due to an increased risk of angioedema;
- Combination with aliskiren-containing drugs in patients with:
    - diabetes mellitus (type 1 or type 2)
    - moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2)
    - hyperkalemia (>5mMol/L) or,
    - congestive heart failure who are hypotensive (see Dual blockade of the Renin-Angiotensin System (RAS), Renal, 9.4 Drug-Drug Interactions
- Combination with angiotensin receptor blockers (ARBs) or other ACE inhibitors in patients with:
    - diabetes with end organ damage,
    - moderate to severe kidney insufficiency (GFR < 60 mL/min/1.73m^2),
    - hyperkalemia (> 5mMol/L) or,
    - congestive heart failure who are hypotensive (see 9.4 Drug-Drug Interactions)

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- When used in pregnancy, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected, TEVA-LISINOPRIL/HCTZ (TYPE Z) should be discontinued as soon as possible (see 7.1.1 Pregnant Women).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Dosage must be individualized. The fixed combination is not for initial therapy. The dose of TEVA-LISINOPRIL/HCTZ (TYPE Z) should be determined by the titration of the individual components.
- Patients usually do not require doses in excess of 50 mg of hydrochlorothiazide daily, particularly when combined with antihypertensive agents.

4.2 Recommended Dose and Dosage Adjustment

Once the patient has been successfully titrated with the individual components as described below, either one TEVA-LISINOPRIL/HCTZ (TYPE Z) 10/12.5 mg or one or two 20/12.5 mg or 20/25 mg tablets once daily may be substituted if the titrated doses are the same as those in the fixed combination (see 1 INDICATIONS and 7 WARNINGS AND PRECAUTIONS).

Lisinopril monotherapy

For lisinopril monotherapy the recommended initial dose in patients not on diuretics is 10 mg of lisinopril once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range of lisinopril is 10 to 40 mg administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. The maximum dose used in long-term controlled clinical trials was 80 mg/day.

If blood pressure is not controlled with lisinopril alone, a low dose of a diuretic may be added. Hydrochlorothiazide 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of lisinopril.

Diuretic Treated Patients
In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of lisinopril. The diuretic should if possible, be discontinued for two to three days before beginning therapy with lisinopril to reduce the likelihood of hypotension (see Cardiovascular). The dosage of lisinopril should be adjusted according to blood pressure response.

If the patient's blood pressure is not controlled with lisinopril alone, diuretic therapy may be resumed as described above.

If the diuretic cannot be discontinued, an initial dose of 5 mg of lisinopril alone should be administered and the patient remain under medical supervision for at least two hours, and until blood pressure has stabilized for at least an additional hour (see Cardiovascular and 9 DRUG INTERACTIONS).

As a rule, concomitant diuretic therapy is not necessary when TEVA-LISINOPRIL/HCTZ (TYPE Z) is used.

Dosage Adjustment in the Presence of Pathologies

Renal Impairment: In patients with creatinine clearance greater than 30 mL/min the usual dose titration of the individual components is required.

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g.: polyacrylonitrile [PAN] and during low density lipoproteins (LDL) apheresis with dextran sulphate and treated concomitantly with an ACE inhibitor (see Immune).

For patients with creatinine clearance between 10 and 30 mL/min the starting dose of lisinopril is 2.5 - 5.0 mg/day. The dosage may then be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

When concomitant diuretic therapy is required in patients with severe renal impairment (creatinine clearance < 10 mL/min), a loop diuretic, rather than a thiazide diuretic is preferred for use with lisinopril. Therefore, for patients with severe renal dysfunction the lisinopril-hydrochlorothiazide combination tablet is not recommended.

Dosage Adjustments in Special Populations

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

Geriatrics (> 65 years of age): In clinical studies the efficacy and tolerability of lisinopril and hydrochlorothiazide, administered concomitantly, were similar in both elderly and younger hypertensive patients. Based on pharmacokinetic studies, additional dosage adjustments may need to be considered (see 7.1.4 Geriatrics, 10.3 Pharmacokinetics).

4.4 Administration

The tablet should be swallowed whole with water. The tablet should not be crushed, split or chewed.

TEVA-LISINOPRIL/HCTZ (TYPE Z) should be taken at the same time each day.

4.5 Missed Dose

If the patient misses a dose, they should be advised not to take an extra dose to make up for the missed dose and just resume their usual schedule.

5 OVERDOSAGE

No specific information is available on the treatment of overdosage with lisinopril and hydrochlorothiazide tablets. Treatment is symptomatic and supportive. Therapy with TEVA-LISINOPRIL/HCTZ (TYPE Z) should be discontinued and the patient observed closely. Suggested measures include induction of emesis and/or gastric lavage, if ingestion is recent, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

Lisinopril
Overdose symptoms include severe hypotension, electrolyte disturbances and renal failure. Overdosed patients should be kept under very close observation. Therapeutic measures depend on the nature and severity of symptoms. Measures to prevent absorption and methods to speed elimination should be employed. If severe hypotension occurs, place the patient in the shock position and infuse intravenous normal saline immediately. Vasopressors including angiotensin II may be considered if fluid replacement is inadequate or contraindicated. Circulating lisinopril may be removed by hemodialysis. Avoid high-flux polyacrylonitrile dialysis membranes (see Immune). Serum electrolytes and creatinine should be monitored frequently.

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/Composition	Non-medicinal Ingredients
Oral	Tablet: 10 mg / 12.5 mg, 20 mg / 12.5 mg and 20 mg / 25 mg	Corn starch, dibasic calcium phosphate, magnesium stearate, mannitol, pregelatinized corn starch, red iron oxide and yellow iron oxide (10 mg / 12.5 mg tablet and 20 mg / 25 mg tablet).

TEVA-LISINOPRIL/HCTZ (TYPE Z) 10 mg / 12.5 mg are peach, round, biconvex tablets, engraved with **N** on one side and **10/12.5** on the other side. Each tablet contains 10 mg of lisinopril (as lisinopril dihydrate) and 12.5 mg of hydrochlorothiazide. Available in bottles of 100 and blister pack boxes of 30.

TEVA-LISINOPRIL/HCTZ (TYPE Z) 20 mg / 12.5 mg are white to off-white, round, biconvex tablets, engraved with **N** on one side and **20/12.5** on the other side. Each tablet contains 20 mg of lisinopril (as lisinopril dihydrate) and 12.5 mg of hydrochlorothiazide. Available in bottles of 100 and blister pack boxes of 30.

TEVA-LISINOPRIL/HCTZ (TYPE Z) 20 mg / 25 mg are peach, round, biconvex tablets, engraved with **N** on one side and **20/25** on the other side. Each tablet contains 20 mg of lisinopril (as lisinopril dihydrate) and 25 mg of hydrochlorothiazide. Available in bottles of 100 and blister pack boxes of 30.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Carcinogenesis and Mutagenesis

Non-melanoma skin cancer: 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, Hydrochlorothiazide).

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 Drug Reactions).

Cardiovascular

Dual blockade of the Renin-Angiotensin System (RAS): There is evidence that co-administration of angiotensin converting enzyme (ACE) inhibitors, such as the Lisinopril component in lisinopril and hydrochlorothiazide tablets, or of angiotensin receptor antagonists (ARBs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR < 60 mL/min/1.73m^2). Therefore, the use of TEVA-LISINOPRIL/HCTZ (TYPE Z) in combination with aliskiren-containing drugs is contraindicated in these patients (see 2 CONTRAINDICATIONS).

Further, co-administration of ACE inhibitors, including the Lisinopril component of TEVA-LISINOPRIL/HCTZ (TYPE Z), 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, decreased renal function (including acute renal failure) and hyperkalemia.

Avoid the concomitant use of ACE inhibitors and ARBs in patients with diabetic nephropathy.

If dual blockade therapy is considered necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

Hypotension:
Symptomatic hypotension has occurred after administration of lisinopril, 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-LISINOPRIL/HCTZ (TYPE Z) should not be used to start therapy or when a dose change is needed. Severe hypotension is also a risk in renin-dependant renovascular hypertension; TEVA-LISINOPRIL/HCTZ (TYPE Z) is not indicated for this condition (see 1 INDICATIONS). 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 ADVERSE REACTIONS). Because blood pressure could potentially fall, patients at risk for hypotension should start lisinopril therapy 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 lisinopril and/or hydrochlorothiazide is increased. 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.

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 may not be a contraindication to further doses. These can usually be given to hypertensive patients without difficulty once the blood pressure has increased after volume expansion. Re-institution of therapy at reduced dosages, or re-institution with either component alone, should be considered.

Valvular Stenosis, Hypertrophic Cardiomyopathy: 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 after load reduction.

TEVA-LISINOPRIL/HCTZ (TYPE Z) should be given with caution to patients with aortic or hypertrophic cardiomyopathy.

Driving and Operating Machinery
Dizziness or tiredness may occur during treatment with TEVA-LISINOPRIL/HCTZ (TYPE Z). 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 lisinopril and hydrochlorothiazide tablets has been reported.

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

Endocrine and Metabolism

Metabolism: Thiazide therapy may impair glucose tolerance. Dosage adjustment of hypoglycemic agents may be required (see 9 DRUG INTERACTIONS).

Increases in cholesterol, triglyceride and glucose levels may be associated with thiazide diuretic therapy.

Hyperuricemia: Hyperuricemia may occur, or acute gout may be precipitated, in certain patients receiving thiazide therapy.

Serum protein-bound iodine (PBI) levels: Thiazides may decrease serum PBI levels without signs of thyroid disturbance.
Thiazides should be discontinued before carrying out tests for parathyroid function.

Hypomagnesemia: Thiazides have been shown to increase excretion of magnesium; this may result in hypomagnesemia.

Hypercalcemia: 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.

Hyperkalemia: In clinical trials hyperkalemia (serum potassium >5.7 mEq/L) occurred in approximately 1.4% of hypertensive patients. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was not a cause of discontinuation of therapy. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene or amiloride), potassium supplements, other drugs that may increase potassium levels (e.g., heparin, co-trimoxazole) and/or potassium-containing salt substitutes (see 9.4 Drug-Drug Interactions).

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 lisinopril 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 (with very rare progression to hepatic failure), jaundice (hepatocellular and/or cholestatic), marked elevations of liver enzymes and/or serum

bilirubin have occurred during therapy with lisinopril in patients with or without pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug, and appropriate medical follow up.

Should the patient receiving TEVA-LISINOPRIL/HCTZ (TYPE Z) experience any unexplained symptoms, 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-LISINOPRIL/HCTZ (TYPE Z) should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. TEVA-LISINOPRIL/HCTZ (TYPE Z) 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 (see 4.1 Dosing Considerations).

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.

Immune

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

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

Angioedema: Angioedema has been uncommonly reported in patients treated with lisinopril and hydrochlorothiazide tablets and may occur at any time during therapy. Angioedema associated with laryngeal or tongue edema and/or shock may be fatal. If angioedema occurs, TEVA-LISINOPRIL/HCTZ (TYPE Z) should be promptly discontinued and the patient should be treated, and observed until the swelling subsides. Where swelling is confined only to the tongue, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

However, where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, and especially in cases where there has been a history of airway surgery, emergency therapy should be administered promptly when indicated. This includes giving subcutaneous adrenaline/epinephrine (0.5 mL 1:1000) and/or maintaining a patent airway. The patient should be under close medical supervision until the complete and sustained symptom resolution has occurred.

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 co-administration of ACE inhibitor with a mTOR (mammalian target of rapamycin) inhibitor (e.g., temsirolimus, sirolimus, everolimus), neutral endopeptidase (NEP) inhibitor, or tissue plasminogen activator may be at increased risk for angioedema. Caution should be used when either initiating ACE inhibitor therapy in patients already taking a mTOR inhibitor, or a NEP inhibitor or vice versa. Monitor patients for potential development of angioedema after initiation of tissue plasminogen activator infusion (see 9 DRUG INTERACTIONS).

Anaphylactoid Reactions during membrane exposure: Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g.: polyacrylonitrile [PAN] and during low density lipoproteins (LDL) apheresis with dextran sulphate) 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, wasps) 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.

Nitritoid Reactions – Gold: Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness and hypotension, which can be very severe) following injectable gold (for example, sodium aurothiomalate) have been reported more frequently in patients receiving ACE inhibitor therapy (see 9 DRUG INTERACTIONS).

Ophthalmologic

Choroidal Effusion, Acute Myopia and Secondary Angle-Closure Glaucoma related to Hydrochlorothiazide: Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion, acute transient myopia and/or 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 TEVA-LISINOPRIL/HCTZ (TYPE Z) 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 sulfonamide or penicillin allergy.

Peri-Operative Considerations

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, lisinopril 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 (see 9 DRUG INTERACTIONS).

Thiazides may increase the responsiveness to tubocurarine (see 9.4 Drug-Drug Interactions).

Renal

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

The use of ACE inhibitors, including the lisinopril, component of TEVA-LISINOPRIL/HCTZ (TYPE Z) or ARBs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 mL/min/1.73m^2) (see 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions).

Use of TEVA-LISINOPRIL/HCTZ (TYPE Z) 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 (see 4.1 Dosing Considerations).

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.

Skin

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

If photosensitivity reactions occur during treatment with hydrochlorothiazide-containing drugs, treatment should be stopped.

7.1 Special Populations

7.1.1 Pregnant Women

ACE inhibitors must be avoided during pregnancy because these agents can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, TEVA-LISINOPRIL/HCTZ (TYPE Z) should be discontinued as soon as possible. The use of TEVA-LISINOPRIL/HCTZ is contraindicated during pregnancy (see 2 CONTRAINDICATIONS).

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 towards 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.

Lisinopril has been removed from the neonatal circulation by peritoneal dialysis.

Animal Data: Lisinopril was not teratogenic in mice treated on days 6 - 15 of gestation with up to ≤1000 mg/kg/day (625x the maximum recommended human dose). There was an increase in fetal resorptions at doses ≥100 mg/kg; at doses of 1000 mg/kg, this was prevented by saline supplementation. There was no fetotoxicity or teratogenicity in rats treated with ≤300 mg/kg/day (188x the maximum recommended dose) of lisinopril at days 6 - 17 of gestation. In rats receiving lisinopril from day 15 of gestation through day 21 postpartum, there was an increased incidence in pup deaths on days 2 - 7 postpartum and a lower average body weight of

pups on day 21 postpartum. The increase in pup deaths and decrease in pup weight did not occur with maternal saline supplementation.

Lisinopril, at doses ≤1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotoxic effects and enable evaluation of the teratogenic potential at the highest possible dosage level.

Fetotoxicity was demonstrated in rabbits by an increase incidence of fetal resorptions at an oral dose of lisinopril of 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). A single intravenous dose of 15 mg/kg of lisinopril administered to pregnant rabbits on gestation days 16, 21 or 26 resulted in 88 - 100% fetal death.

By whole body autoradiography, radioactivity was found in the placenta following administration of labelled lisinopril to pregnant rats, but none was found in the fetuses.

7.1.2 Breast-feeding

The presence of concentrations of ACE inhibitor have been reported in human milk. Thiazides also appear in human milk. The use of TEVA-LISINOPRIL/HCTZ (TYPE Z) is contraindicated during breast-feeding (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

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

7.1.4 Geriatrics

Geriatrics (> 65 years of age): In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of lisinopril. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution.

Ethnic Origin
ACE inhibitors cause a higher rate of angioedema in black patients than in non black patients.

The antihypertensive effect of ACE inhibitors is generally lower in black patients (usually a low-renin hypertensive population) than in non-black patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of lisinopril and hydrochlorothiazide tablets in the treatment of hypertension has been evaluated in controlled clinical trials including 930 patients. Side effects have usually been mild and transient. The most common adverse reaction observed was dizziness (7.5%), but also headache (5.2%), cough (3.9%), fatigue (3.7%) and hypotension, including orthostatic hypotension (3.2%). The most severe adverse reactions were syncope (0.8%), and hypotension (1.9%) (see Table 2).

Marketing experience also informs on the safety profile of lisinopril and hydrochlorothiazide tablets (see 8.5 Post-Market Adverse Reactions). Symptomatic hypotension may occur (see Hypotension). In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be monitored under close medical supervision.

Particular consideration should be given when therapy is administered to patients with ischaemic heart or cerebrovascular disease because an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.
Hepato-biliary disorder (hepatis, jaundice, hepatic failure) have very rarely been observed. However, as thiazide drugs may cause electrolyte imbalance, additional cautious should be taken with patients with hepatic impairments (see Hepatic/Biliary/Pancreatic).

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been uncommonly reported in patients treated with ACE inhibitors, including lisinopril and hydrochlorothiazide tablets. This may occur at any time during therapy. In such cases, TEVA-LISINOPRIL/HCTZ (TYPE Z) should be discontinued promptly and appropriate treatment and 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 treatment with anti-histamines and corticosteroids may not be sufficient (see Immune – Angioedema).

8.2 Clinical Trial Adverse Reactions

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

In clinical trials involving 930 patients, including 100 patients treated for 50 weeks or more, the most severe clinical adverse reactions were syncope (0.8%), and hypotension (1.9%). The most frequent clinical adverse reactions were: dizziness (7.5%), headache (5.2%), cough (3.9%), fatigue (3.7%) and orthostatic effects (3.2%).

Discontinuation of treatment due to adverse reactions occurred in 4.4% of patients, mainly because of dizziness, cough, fatigue or muscle cramps.

Adverse reactions that have occurred in clinical trials or in marketing experience are those which have been previously reported with lisinopril and hydrochlorothiazide when used separately for the treatment of hypertension.

Adverse reactions occurring in hypertensive patients treated with lisinopril and hydrochlorothiazide in controlled trials are shown in Table 2.

Table 2: Incidence of Adverse Reactions Occurring in Patients Treated with Lisinopril and Hydrochlorothiazide in Controlled Clinical Trials

	LISINOPRIL PLUS HYDROCHLOROTHIAZIDE n = 930 %	LISINOPRIL n = 2633 %
Body as a whole		
fatigue	3.7	-
asthenia	1.8	2.7
impotence	1.2	0.7
decreased libido	1.0	0.2
fever	0.5	0.3
gout	0.2	0.2
Cardiovascular		
orthostatic effects	3.2	0.9
hypotension	1.9	0.8
chest pain	1.0	1.1
palpitation	0.9	0.8
syncope	0.8	0.2
chest discomfort	0.6	-
edema	0.1	0.6
rhythm disturbances	0.1	0.5
angina	0.1	0.3
Digestive		
diarrhea	2.5	1.8
nausea	2.2	1.9
vomiting	1.4	1.1
dyspepsia	1.3	0.5
abdominal pain	0.9	1.4
constipation	0.3	0.2
dry mouth	0.2	0.5
anorexia	0.2	0.4
flatulence	0.2	0.3

	LISINOPRIL PLUS HYDROCHLOROTHIAZIDE n = 930 %	LISINOPRIL n = 2633 %
Dermatologic		
rash	1.2	1.0
flushing	0.8	0.3
pruritus	0.4	0.5
angioedema	-*	0.1
Musculosketal		
muscle cramps	2.0	0.5
back pain	0.8	0.5
shoulder pain	0.5	0.2
Nervous /Psychiatric		
dizziness	7.5	4.4
headache	5.2	5.6
paresthesia	1.5	0.5
vertigo	0.9	0.2
depression	0.5	0.7
somnolence	0.4	0.8
insomnia	0.2	0.3
Respiratory		
cough	3.9	3.0
upper respiratory infection	2.2	2.1
dyspnea	0.4	0.4

*See lisinopril and hydrochlorothiazide (Marketing Experience Only)

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

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) (3.8%) and serum creatinine (4.2%) were observed in patients with essential hypertension treated with lisinopril and hydrochlorothiazide tablets. More marked increases have also been reported and were more likely to occur in patients with bilateral renal artery stenosis (see Renal).

Increases in BUN and serum creatinine, usually reversible upon discontinuation of therapy, were observed in 1.1 and 1.6% of patients respectively with essential hypertension treated with lisinopril alone.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.5 g percent and 1.5 vol percent, respectively) occurred frequently in hypertensive patients treated with lisinopril and hydrochlorothiazide tablets but were rarely of clinical importance unless another cause of anemia coexisted. In clinical trials, 0.4% of patients discontinued therapy due to anemia. Rarely, hemolytic anemia has been reported.

Agranulocytosis and bone marrow depression, manifested as anemia, cytopenia or leukopenia, have been caused by ACE inhibitors, including lisinopril. Several cases of agranulocytosis and neutropenia have been reported in which a causal relationship to lisinopril cannot be excluded (see Hematologic).

Hypokalemia, Hyperkalemia: (see Endocrine and Metabolism, and 9 DRUG INTERACTIONS).

Serum Uric Acid, Glucose, Magnesium, Cholesterol, Triglycerides and Calcium: (see Endocrine and Metabolism).

8.5 Post-Market Adverse Reactions

The following undesirable effects have been observed and reported during treatment with lisinopril and hydrochlorothiazide tablets with the following frequencies: Very common (≥ 10%), common (≥ 1%, < 10%), uncommon (≥ 0.1%, < 1%), rare (≥ 0.01%, < 0.1%), very rare (< 0.01%) including isolated reports.

Blood and lymphatic system disorders

Rare: anemia.
Very rare: agranulocytosis, bone marrow depression, hemolytic anemia, leucopenia, thrombocytopenia (see Hematologic).

Cardiac and vascular disorders

Common: orthostatic effects (including hypotension), syncope.
Uncommon: palpitations.

Endocrine disorders

Rare: inappropriate antidiuretic hormone secretion.

Gastrointestinal disorders

Common: diarrhea, nausea, vomiting.
Uncommon: dry mouth.
Rare: pancreatitis.
Very rare: intestinal angioedema.

General disorders and administration site conditions

Common: asthenia, fatigue.
Uncommon: chest discomfort.

Hepato-biliary disorders

Very rare: hepatitis-either hepatocellular or cholestatic, jaundice, hepatic failure. Very rarely, it has been reported that in some patients the undesirable development of hepatitis has progressed to hepatic failure. Patients receiving TEVA-LISINOPRIL/HCTZ (TYPE Z) who develop jaundice or marked elevation of hepatic

enzymes should discontinue lisinopril and hydrochlorothiazide tablets and receive appropriate medical follow up (see Hepatic/Biliary/Pancreatic).

Immune system disorders

Not known: anaphylactic/anaphylactoid reaction.

Investigations

Common: decreases in hemoglobin, increases in blood urea, increases in liver enzymes (see Hepatic/Biliary/Pancreatic), increases in serum creatinine (see Renal).

Uncommon: decreases in hematocrit.

Rare: increases in serum bilirubin (see Hepatic/Biliary/Pancreatic).

Metabolism and nutrition disorders

Uncommon: gout.

Rare: hyperkalemia (see Endocrine and Metabolism), hyperglycemia (see Endocrine and Metabolism), hyperuricemia, hypokalemia.

Musculoskeletal, connective tissue and bone disorders

Common: muscle cramps.

Rare: muscle weakness.

Nervous system and psychiatric disorders

Common: dizziness, headache, paresthesia.

Uncommon: depressive symptoms.

Rare: olfactory disturbance.

Reproductive system and breast disorders

Common: impotence.

Respiratory, thoracic and mediastinal disorders

Common: cough (see Ear/Nose/Throat).

Skin and subcutaneous tissue disorders

Common: rash.

Uncommon: hypersensitivity/angioedema: angioedema of the face, extremities, lips, tongue, glottis and/or larynx (see Immune).

Very rare: cutaneous pseudolymphoma.

A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestation may occur.

Other side effects reported with the individual components alone, and which may be potential side effects of lisinopril and hydrochlorothiazide tablets are:

Lisinopril

Blood and lymphatic system disorders: rarely, hemolytic anemia has been reported.
Cardiac disorders: Myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients; tachycardia.
Gastrointestinal disorders: abdominal pain and indigestion; pancreatitis.
General disorders and administration site conditions: diaphoresis.
Infections and infestations: sinusitis.
Metabolism and nutrition disorders: hyponatremia.
Psychiatric disorders: mood alterations; mental confusion and vertigo have occurred; as with other ACE inhibitors, taste disturbance, sleep disturbance and hallucinations have been reported.
Renal and urinary disorders: acute renal failure; oliguria/anuria; renal dysfunction; uremia.
Respiratory, thoracic and mediastinal disorders: bronchospasm; rhinitis.
Skin and subcutaneous tissue disorders: alopecia; pruritis; psoriasis and severe skin disorders (including pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme) have been reported; urticaria.

Hydrochlorothiazide

Blood and lymphatic system disorders: agranulocytosis; aplastic anemia; hemolytic anemia; leucopenia; thrombocytopenia.
Ear and labyrinth disorders: vertigo.
Eye disorders: acute angle-closure glaucoma; acute myopia; choroidal effusion; transient blurred vision; xanthopsia.
Gastrointestinal disorders: constipation; gastric irritation; pancreatitis; sialadenitis.
General disorders and administration site conditions: fever.
Hepatobiliary disorders: jaundice (intrahepatic cholestatic jaundice).
Immune system disorders: anaphylactic reactions.
Metabolism and nutrition disorders: anorexia; electrolyte imbalance including hyponatremia; glycosuria; hyperglycemia; hyperuricemia.
Musculoskeletal and connective tissue disorders: muscle spasm; systemic lupus erythematosus.
Psychiatric disorders: restlessness.
Respiratory, thoracic and mediastinal disorders: respiratory distress (including pneumonitis and pulmonary edema).
Renal and urinary disorders: renal dysfunction and interstitial nephritis; renal failure.
Skin and subcutaneous tissue disorders: cutaneous lupus erythematosus; photosensitivity; purpura; urticaria.
Vascular disorders: necrotizing angiitis (vasculitis) (cutaneous vasculitis).

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).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Combination with sacubitril/valsartan; see 2 CONTRAINDICATIONS;
- Combination with aliskiren-containing drugs; see 2 CONTRAINDICATIONS, Dual Blockade of the Renin-Angiotensin System (RAS), Renal and 9.4 Drug-Drug Interactions;
- Combination with angiotensin receptor blockers (ARBs) or other ACE inhibitors; see 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions.

9.2 Drug Interactions Overview

Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney.

Use of TEVA-LISINOPRIL/HCTZ (TYPE Z) and alcohol may increase the risk of orthostatic hypotension (see 9.4 Drug-Drug Interactions).

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 expected 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 Affecting Sympathetic Activity	CT	Beta-adrenergic blocking drugs add some further antihypertensive effect to lisinopril.	Agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) may be used with caution.
Agents Causing Renin Release	CT	The antihypertensive effect of lisinopril is augmented by antihypertensive agents that cause renin release (e.g. diuretics).	
Agents Decreasing Serum Potassium	T	The potassium depleting effect of hydrochlorothiazide could be expected to be potentiated by drugs associated with potassium loss and hypokalemia (e.g., laxatives, carbenoxolone, salicylic acid derivatives).	Monitor serum potassium level.
Agents Increasing Serum Potassium	T, C, CS	Since lisinopril decreases aldosterone production, elevation of serum potassium may occur.	Potassium-sparing diuretics such as spironolactone, triamterene or amiloride, and potassium supplements should be given only for documented hypokalemia with caution and frequent monitoring of serum potassium since they may lead to a significant increase in serum potassium. Other drugs that may increase potassium levels (e.g., heparin, co-trimoxazole, salt substitutes which contain potassium) should also 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.

Proper Name	Source of Evidence	Effect	Clinical Comment
Amantadine	C	Amantadine toxicity symptoms (ataxia, myoclonus confusion) occurred in a patient with parkinsonism previously stabilized on amantadine (300 mg daily), 7 days after starting treatment with triamterene and hydrochlorothiazide. Amantadine toxicity is thought to be due to reduction of the tubular secretion. Thiazides may increase the risk of adverse effects caused by amantadine.	Monitor the patient closely and adjust the dosage of either medication as required.
Amphotericin B	T	Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics.	Monitor serum potassium level.
Antacids	CT	Co-administration with antacids may decrease the oral bioavailability of ACE inhibitors due to delayed gastric emptying and/or elevated gastric pH.	The clinical significance of this interaction appears to be minor. As a precaution, patients may want to take ACE inhibitors and antacids or oral medications that contain antacids 1 to 2 hours apart.
Anticholinergic Agents, including atropine, biperiden, domperidone and metoclopramide.	T, CT	Anticholinergic agents may increase the absorption and oral bioavailability of thiazide diuretics. Pretreatment with propantheline prolonged Tmax for hydrochlorothiazide from 2.4h to 4.8h and increased its total 48-hour urinary recovery by 36%. This may be	Blood pressure monitoring is recommended if concomitant administration is considered. Dose adjustment of TEVA-LISINOPRIL/HCTZ (TYPE Z) may be required.

Proper Name	Source of Evidence	Effect	Clinical Comment
		associated with increased and prolonged antihypertensive effect of hydrochlorothiazide. Similar results were reported for chlorothiazide in another study. Conversely, prokinetic drugs may decrease the bioavailability of thiazide diuretics. The proposed mechanism involves increased gastrointestinal transit time due to reduction of stomach and intestinal motility by anticholinergic agents.	
Antidiabetic Agents (e.g. 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 appropriate serum potassium levels, and adjust diabetes medications as required.
Antiepileptic Agents: Topiramate	CT	Thiazide diuretics such as chlorothiazide may enhance the hypokalemic effect of topiramate. Thiazide diuretics may increase the serum concentration of topiramate.	Monitor for increased topiramate concentrations/adverse effects (e.g., hypokalemia) with initiation/dose increase of a thiazide diuretic. Closely monitor serum potassium concentrations with concomitant therapy. Topiramate dose reductions may be necessary.
Carbamazepine	C	There may be an increased risk of symptomatic hyponatremia.	The patient's mental status and serum sodium concentrations should be monitored periodically.

Proper Name	Source of Evidence	Effect	Clinical Comment
		Concomitant use with thiazide diuretics may potentiate hyponatremia.	
Antihypertensive Therapy	CT	When lisinopril is given to patients already treated with other antihypertensive agents, further falls in blood pressure may occur. Hydrochlorothiazide may potentiate the action of other antihypertensive drugs (e.g. guanethidine, methyldopa, calcium channel blockers, ACEI, ARB, and direct renin inhibitors).	Dose adjustment of other concomitantly taken antihypertensive may be required.
Antineoplastic drugs, including cyclophosphamide and methotrexate	C	Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects. Increased myelosuppression was reported when thiazides were co-administered with 5-Fluorouracil. Significant augmentation of granulocytopenia during thiazide chemotherapy combination, as compared with chemotherapy without thiazides, was observed. The most consistent changes in the neutrophil count were observed during the period of maximal	Alternative antihypertensive therapy may be advisable. Hematological status should be closely monitored in patients receiving this combination. Dose adjustment of cytotoxic agents may be required.

Proper Name	Source of Evidence	Effect	Clinical Comment
		myelosuppression from the antitumor drugs. Antineoplastic-induced bone marrow suppression may be prolonged with concomitant thiazide administration. Thiazides have been associated with blood dyscrasias. Hydrochlorothiazide was frequently part of drug interactions with anticancer drugs. The mechanism is unknown.	
Bile acid sequestrants, (e.g. cholestyramine and colestipol resins)	CT	Bile acid sequestrants bind hydrochlorothiazide in the gut and reduce its absorption from the gastrointestinal tract by 43-85%. Administration of thiazide 4 hours after a bile acid sequestrant reduced absorption of hydrochlorothiazide by 30-35%.	TEVA-LISINOPRIL/HCTZ (TYPE Z)should be given at least 4h before or 4-6h after the administration of 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. Co-administration with high doses of calcium and vitamin D supplements may potentiate the rise in serum calcium.	Particularly susceptible patients include those with hyperparathyroidism, those treated for osteoporosis, and those receiving high dosages of vitamin D for hypoparathyroidism. Serum calcium should be monitored if thiazide diuretics are co-administered with high dosages of calcium and/or vitamin D. Dose reduction or withdrawal of calcium and/or vitamin D supplements may be necessary.

Proper Name	Source of Evidence	Effect	Clinical Comment
Capsaicin	CT	Capsaicin may worsen ACE inhibitor-induced cough.	
Corticosteroids and adrenocorticotropic hormone (ACTH)	T	Intensified electrolyte depletion, particularly hypokalemia may occur.	Monitor serum potassium and adjust medications, as required.
Cyclosporin	T	Co-administration may potentially result in hypermagnesemia, hyperuricemia, and increase risk of nephrotoxicity and gout-type complications.	Renal function, serum electrolytes, uric acid levels, and cyclosporine blood concentrations should be monitored. The clinical significance is unknown.
Diazoxide	C	Co-administration of thiazide diuretics enhances the hyperglycemic effect of diazoxide.	Blood glucose levels should be monitored and dose adjustment of insulin or antidiabetics may be required in diabetic patients.
Digoxin	CT	Thiazide-induced electrolyte disturbances, i.e. hypokalemia, hypomagnesemia, increase the risk of digoxin and other digitalis glycosides toxicity, which may lead to fatal arrhythmic events.	Caution should be used with concomitant administration of TEVA-LISINOPRIL/HCTZ (TYPE Z)and digoxin. Monitor electrolytes and digoxin levels closely. Supplement potassium or adjust doses of digoxin or TEVA-LISINOPRIL/HCTZ (Type Z), as required.
Dual blockade of the Renin-Angiotensin System (RAS) with ACE inhibitors, ARBs or aliskiren-containing drugs	CT	When combined with other antihypertensive agents, additive falls in blood pressure may occur. Clinical trial data has shown that dual blockade of the RAS through the combined use of ACE-inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension,	Dual blockade of the RAS with ARBs or ACEIs and aliskiren-containing drugs is contraindicated in patients with diabetes and/or renal impairment (see **2 CONTRAINDICTIONS**). The combined use of ARBs, ACEIs or aliskiren-containing drugs is generally not recommended (see cardiovascular, Dual Blockade of the Renin-Angiotensin-System (RAS)).

Proper Name	Source of Evidence	Effect	Clinical Comment
		hyperkalemia and decreased renal function (including acute renal failure) compared to the use of a single RAS-acting agent.	
Gold	C	Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness and hypotension, which can be very severe) following injectable gold (for example, sodium aurothiomalate) have been reported more frequently in patients receiving ACE inhibitor therapy.	
Gout medications (allopurinol, uricosurics, xanthine oxidase inhibitors)	T, RCS	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.	Dosage adjustment of gout medications may be required.
Lithium	CT	Diuretic agents and ACE inhibitors reduce the renal clearance of lithium and add a high risk of lithium toxicity.	Concomitant use of TEVA-LISINOPRIL/HCTZ (TYPE Z) 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.,	C, RCS	Patients taking concomitant mTOR inhibitor therapy may be	Caution should be used when these drugs are used concomitantly when either

Proper Name	Source of Evidence	Effect	Clinical Comment
temsirolimus, sirolimus, everolimus)		at increased risk for angioedema.	initiating ACE inhibitor therapy in patients already taking a mTOR inhibitor or vice versa (see 7 WARNINGS AND PRECAUTIONS, Angioedema).
Neutral endopeptidase (NEP) inhibitors	T	Concomitant treatment of ACE inhibitors with neutral endopeptidase (NEP) inhibitors may increase the risk of angioedema.	Caution should be used when these drugs are used concomitantly and when either initiating ACE inhibitor therapy in patients already taking a neutral endopeptidase inhibitor or vice versa (see 7 WARNINGS AND PRECAUTIONS, Angioedema).
Non-steroidal anti-inflammatory drugs (NSAIDs)	CT	In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. In some patients with compromised renal function, lisinopril co-administration with non-steroidal anti-inflammatory drugs (NSAIDs) may produce further renal function deterioration. Indomethacin may diminish the antihypertensive efficacy of concomitantly administered lisinopril and hydrochlorothiazide.	When lisinopril 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. If combination use is necessary, monitor renal function, serum potassium, and blood pressure closely. Dose adjustments may be required. Patients with heart failure may be at particular risk.
Pressor Amines (e.g., norepinephrine)	CT	Possible decreased response to pressor	

Proper Name	Source of Evidence	Effect	Clinical Comment
		amines but not sufficient to preclude their use.	
Rituximab used to treat cancer, transplant rejection, and some autoimmune diseases	T, C	Antihypertensives such as chlorothiazides may enhance the hypotensive effect of rituximab.	Consider temporarily withholding antihypertensive medications for 12 hours prior to rituximab infusion to avoid excessive hypotension during or immediately after infusion.
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., tubocurarine	C	Thiazide drugs may increase the responsiveness of some nondepolarizing skeletal muscle relaxants, such as curare derivatives.	
Tetracycline antibiotics	T, C	The co-administration of diuretics and tetracyclines may result in decreased renal function manifested by increases in serum creatinine and blood urea nitrogen (BUN).	Usually, no clinical intervention is necessary, unless decreases in renal function occur. If renal function deteriorates, discontinuation of one or both agents may be necessary.
Tissue plasminogen activators	CS	Concomitant treatment with tissue plasminogen activators may increase the risk of angioedema.	Monitor patients for potential development of angioedema after initiation of tissue plasminogen activator infusion.

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

9.5 Drug-Food Interactions

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

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Lisinopril and hydrochlorothiazide tablets combines the action of an angiotensin converting enzyme inhibitor, lisinopril, and a diuretic, hydrochlorothiazide.

Lisinopril
Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyzes the conversion of angiotensin I to the pressor substance, angiotensin II. 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 lisinopril plus a thiazide diuretic, there was essentially no change in serum potassium (see 7 WARNINGS AND PRECAUTIONS). ACE is identical to kininase II. Thus, lisinopril may also block the degradation of bradykinin, a potent vasodilator peptide. However, the role that this plays in the therapeutic effects of lisinopril is unknown.

While the mechanism through which lisinopril lowers blood pressure is believed to be primarily the suppression of the renin-angiotensin-aldosterone system, lisinopril also lowers blood pressure in patients with low-renin hypertension. However, black hypertensive patients (usually a low-renin hypertensive population) have a smaller average response to lisinopril monotherapy than non-black patients.

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

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.

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. The mechanism of its antihypertensive action is not known. Lowering of the sodium content of arteriolar smooth muscle cells and diminished response to norepinephrine have been postulated.

10.2 Pharmacodynamics

Lisinopril
Administration of lisinopril to patients with hypertension results in a reduction of both supine and standing blood pressure. Abrupt withdrawal of lisinopril has not been associated with a rapid increase in blood pressure. In most patients studied, after oral administration of an individual dose of lisinopril, the onset of antihypertensive activity is seen at one hour with peak reduction of blood pressure achieved by 6 hours. Although an antihypertensive effect was observed 24 hours after dosing with recommended single daily doses, the effect was more consistent and the mean effect was considerably larger in some studies with doses of 20 mg or more than with lower doses. However, at all doses studied, the mean antihypertensive effect was substantially smaller 24 hours after dosing than it was 6 hours after dosing. On occasion, achievement of optimal blood pressure reduction may require 2 to 4 weeks of therapy.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with little or no change in cardiac output and in heart rate. In a study in nine hypertensive patients, following administration of lisinopril, there was an increase in mean renal blood flow that was not significant. Data from several small studies are inconsistent with respect to the effect of lisinopril on glomerular filtration rate in hypertensive patients with normal renal function, but suggest that changes, if any, are not large.

	Species/strain	Number of animals/group	Route	Dose	Results
MECHANISM OF ACTION					
In vitro ACE inhibitory activity*	Hog plasma		*In vitro*		IC_{50} = 1.7 ± 0.5 M
Augmentation of contractile response to bradykinin	Guinea pig ileum	7 segments	*In vitro*		AC_{50} = 1.6 nM
In vivo ACE inhibition in the rat**	Male Sprague/Dawley	8	I.V.		ID_{50} = 2.3 (1.7-3.1) µg/kg
Duration of ACE Inhibitory activity of lisinopril in rats**	Male Sprague/Dawley	4	I.V.	3 & 10 µg/kg	Duration approx. 110 min.
In vivo ACE Inhibitory activity of lisinopril in conscious rats**	Sprague/Dawley	3 - 5	P.O.	0.03-3.0 mg/kg (single dose)	Duration of at least 360 min.
In vivo ACE inhibition in anesthetized dogs**	Mongrel	6	I.V.	1-30 µg/kg	ID_{50} = 6.5 µg/kg
In vivo ACE inhibitory activity of lisinopril in conscious dogs**	Mongrel	3	P.O.	0.05-1.0 mg/kg (single dose)	Duration of action of between 6-24 hrs
EFFECTS ON BLOOD PRESSURE					
Antihypertensive activity in renal hypertensive dogs (single doses)	Mongrel	3	P.O.	0.3 mg/kg with and without hydro-chlorothiazide	After 2 hours: Lisinopril alone: 5% reduction in mean systolic pressure vs pretreatment. Lisinopril + HCTZ = 11% reduction in mean systolic pressure vs. pretreatment.
Antihypertensive activity in rats on a sodium-deficient diet (single doses)	Male Sprague/Dawley	5	P.O.	0.3 - 3.0 mg/kg daily for 4 days	After 2 hours: 11% reduction in mean systolic pressure vs pretreatment at 1 mg/kg. 22% reduction in mean systolic pressure vs. pretreatment at 3 mg/kg. Consistent response over 4 days.

	Species/strain	Number of animals/group	Route	Dose	Results
Antihypertensive in 2 kidney Grollman hypertensive rats (single doses)	Male Sprague/Dawley	6 - 7	P.O.	1 & 3 mg/kg	At 2 hours: approx. 6% reduction in mean systolic pressure vs pretreatment with the antihypertensive effect lasting up to 24 hours.
Antihypertensive activity in spontaneously hypertensive rats with and without hydroclorothiazide	SH rats	3 - 6	P.O.	1.25 mg/kg HCTZ = 50 mg/kg daily for 3 days	Enhancement of hypotensive activity over 3 - 5 days. 2 hours after drug administration lisinopril alone reduced the average mean arterial pressure from 198 to 161 mmHg. In combination with HCTZ the average mean arterial pressure was reduced from 202 to 132 mmHg.
Antihypertensive activity in spontaneously hypertensive rats (single doses)	SH rats	3 - 9	P.O. & I.V.	0.1 - 20 mg/kg	Slight fall in blood pressure at 0.312 – 5 mg/kg p.o. Pronounced fall at 20 mg/kg p.o. and 0.1 mg/kg I.V. with statistically significant reductions being observed for the majority of time points between ½ - 18 hours

*Inhibition of enzymatic activity of hog plasma ACE using 14C labeled substrate
**Blockage of functional (pressor) response to AI challenge

Hydrochlorothiazide
Hydrochlorothiazide increases the excretion of sodium and chloride in approximately equivalent amounts and causes a simultaneous, usually minimal loss of bicarbonate. The excretion of ammonia is reduced slightly by hydrochlorothiazide and the blood ammonia concentration may be increased. The excretion of potassium is increased slightly. Calcium excretion is decreased by hydrochlorothiazide and magnesium excretion is increased.

Hydrochlorothiazide is eliminated rapidly by the kidney. Its rate of elimination is decreased somewhat by the co-administration of probenecid without, however, an accompanying reduction in diuresis.

Lisinopril and Hydrochlorothiazide
In spontaneously hypertensive rats (SHR) lisinopril was studied in an oral dose of 1.25 mg/kg daily, given alone or concomitantly with hydrochlorothiazide 50 mg/kg orally, for 3 days. Reductions in blood pressure were recorded (tail cuff method) on each of the 3 treatment days, reaching normotensive levels (113-116 mmHg) on Day 3 at 4-8 hours after the concomitant therapy.

10.3 Pharmacokinetics

Lisinopril

Absorption: Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours. Declining serum concentrations exhibit a prolonged terminal phase which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose.

Based on urinary recovery, the extent of absorption of lisinopril is approximately 25%, with large inter-subject variability (6 - 60%) at all doses tested (5 - 80 mg).

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

Distribution: Lisinopril does not bind to plasma proteins other than ACE.

Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly.

Metabolism: Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine.

Elimination: Upon multiple dosing, lisinopril exhibits an effective half-life of accumulation of 12 hours.

Lisinopril can be removed by dialysis.

Hydrochlorothiazide

Absorption: 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.

Metabolism: Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney.

Elimination: 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.

Lisinopril - Hydrochlorothiazide

Distribution: Concomitant administration of lisinopril 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

- **Geriatrics:** In a study in elderly healthy subjects (65 years and above), a single dose of lisinopril 20 mg produced higher serum concentrations and higher values for the area under the plasma curve than those seen in young healthy adults given a similar dose. In another study, single daily doses of lisinopril 5 mg were given for 7 consecutive days to young and elderly healthy volunteers. Maximum serum concentrations of lisinopril on Day 7 were higher in the elderly volunteers than in the young.

- **Pregnancy and Breast-feeding:** Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Renal Insufficiency: Impaired renal function decreases elimination of lisinopril. This decrease becomes clinically important when the glomerular filtration rate is below 30 mL/min (see **Renal**, and **4 DOSAGE AND ADMINISTRATION**).

11 STORAGE, STABILITY AND DISPOSAL

Store between 15°C - 30°C. Protect from light and moisture.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II : SCIENTIFIC INFORMATION

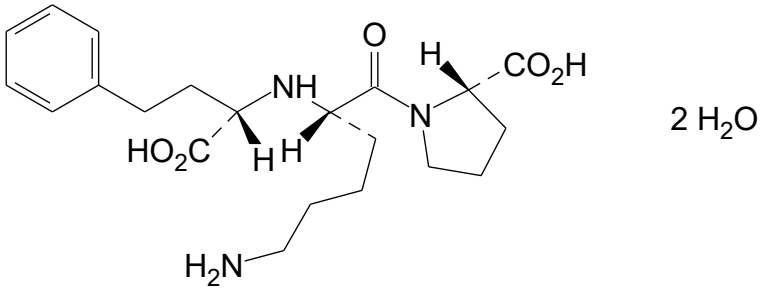
13 PHARMACEUTICAL INFORMATION

Drug Substance: Lisinopril

Proper name: Lisinopril

Chemical Name: 1-[N^2-[(S)-1-Carboxy-3-phenylpropyl]-L-lysyl]-L-proline dihydrate

Structural Formula:



Molecular Formula: $C_{21}H_{31}N_3O_5 \cdot 2H_2O$

Molecular Weight: 441.52

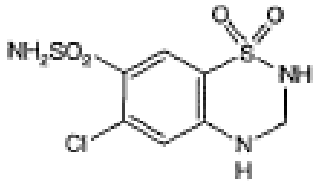
Description: Lisinopril is a white to off-white, crystalline powder. It is soluble in water, sparingly soluble in methanol and practically insoluble in acetone and in ethanol.

Drug Substance: Hydrochlorothiazide

Proper name: Hydrochlorothiazide

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

Structural Formula:



Molecular Formula: $C_7H_8ClN_3O_4S_2$

Molecular Weight: 297.74

Description: Hydrochlorothiazide is a white to off-white, crystalline powder. It practically insoluble in water, but freely soluble in sodium hydroxide solution.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Essential Hypertension

The clinical trial data on which the original indication was authorized is not available.

14.3 Comparative Bioavailability Studies

A blinded, single dose, randomized, three-period, six-sequence, three-treatment, crossover study between TEVA-LISINOPRIL/HCTZ 20 mg / 12.5 mg Tablets (Teva Canada Limited, Canada) and ZESTORETIC® 20 mg / 12.5 mg Tablets (AstraZeneca Canada Inc.) and PRINZIDE® 20 mg / 12.5 mg Tablets (Merck Frosst Canada Ltd.) in 35 healthy subjects (male and female) under fasting conditions. A summary of the bioavailability data comparing TEVA-LISINOPRIL/HCTZ 20 mg / 12.5 mg Tablets (Teva Canada Limited) and ZESTORETIC® 20 mg / 12.5 mg Tablets (AstraZeneca Canada Inc.) is presented in the following table:

Lisinopril (1 x 20 mg lisinopril /12.5 mg hydrochlorothiazide) Geometric Mean Arithmetic Mean (CV %)				
Parameter[1]	Test[2]	Reference[3]	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72} (ng·h/mL)	1351.09 1443.99 (38)	1334.84 1410.77 (33)	101.2	95.2 – 107.6
C_{max} (ng/mL)	92.70 100.30 (40)	90.16 96.59 (37)	102.8	95.9 – 110.2
T_{max}[4] (h)	6.01 (20)	6.13 (18)		

[1] Due to the design of the study, meaningful AUC_I and $T_{½}$ parameters could not be calculated.
[2] TEVA-LISINOPRIL/HCTZ (lisinopril and hydrochlorothiazide) 20 mg / 12.5 mg Tablets (Teva Canada Limited)
[3] ZESTORETIC® (lisinopril and hydrochlorothiazide) 20 mg/ 12.5 mg Tablets (AstraZeneca Canada Inc.)
[4] Expressed as the arithmetic mean (CV%) only

Hydrochlorothiazide (1 x 20 mg lisinopril /12.5 mg hydrochlorothiazide) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	752.046 776.753 (27)	745.815 771.059 (27)	100.8	97.5 – 104.2
AUC_{inf} (ng·h/mL)	768.009 793.508 (27)	762.089 787.838 (27)	100.8	97.5 – 104.2
C_{max} (ng/mL)	113.190 118.611 (31)	114.292 120.297 (32)	99.0	92.8 – 105.7
T_{max}[3] (h)	1.83 (32)	1.98 (39)		
$T_{½}$[3] (h)	9.26 (12)	9.17 (13)		

[1] TEVA-LISINOPRIL/HCTZ (lisinopril and hydrochlorothiazide) 20 mg / 12.5 mg Tablets (Teva Canada Limited)
[2] ZESTORETIC® (lisinopril and hydrochlorothiazide) 20 mg / 12.5 mg Tablets (AstraZeneca Canada Inc.)
[3] Expressed as the arithmetic mean (CV%) only

A blinded, single dose, randomized, three-period, six-sequence, three-treatment, crossover study between TEVA-LISINOPRIL/HCTZ 20 mg / 25 mg Tablets (Teva Canada Limited, Canada) and ZESTORETIC® 20 mg / 25 mg Tablets (AstraZeneca Canada Inc.) and PRINZIDE® 20 mg / 25 mg Tablets (Merck Frosst Canada Ltd.) in 36 healthy subjects (male and female) under fasting conditions. A summary of the bioavailability data comparing TEVA-LISINOPRIL/HCTZ 20 mg / 25 mg Tablets (Teva Canada Limited) and ZESTORETIC® 20 mg / 25 mg Tablets (AstraZeneca Canada Inc.) is presented in the following table.

Lisinopril (1 x 20 mg lisinopril / 25 mg hydrochlorothiazide) Geometric Mean Arithmetic Mean (CV %)				
Parameter[1]	Test[2]	Reference[3]	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72} (ng·h/mL)	1350.48 1382.20 (21)	1321.26 1400.75 (32)	102.2	95.0 - 109.9
C_{max} (ng/mL)	93.89 96.73 (24)	88.74 95.61 (35)	105.8	96.9 - 115.5
T_{max}[4] (h)	6.13 (17)	6.14 (15)		

[1] Due to the design of the study, meaningful AUC_I and $T_{½}$ parameters could not be calculated.
[2] TEVA-LISINOPRIL/HCTZ (lisinopril and hydrochlorothiazide) 20 mg / 25 mg Tablets (Teva Canada Limited)
[3] ZESTORETIC® (lisinopril and hydrochlorothiazide) 20 mg / 25 mg Tablets (AstraZeneca Canada Inc.)
[4] Expressed as the arithmetic mean (CV%) only

Hydrochlorothiazide (1 x 20 mg lisinopril / 25 mg hydrochlorothiazide) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	1493.462 1523.506 (20)	1505.126 1541.004 (22)	99.2	95.7 - 102.9
AUC_{inf} (ng·h/mL)	1524.107 1554.848 (20)	1536.497 1573.082 (22)	99.2	95.7 - 102.8
C_{max} (ng/mL)	233.350 241.694 (28)	230.172 240.861 (32)	101.4	94.7 - 108.6
T_{max}[3] (h)	1.92 (50)	2.05 (42)		

$T_{½}$[3] (h)	9.13 (10)	9.19 (14)		

[1] TEVA-LISINOPRIL/HCTZ (lisinopril and hydrochlorothiazide) 20 mg / 25 mg Tablets (Teva Canada Limited)
[2] ZESTORETIC® (lisinopril and hydrochlorothiazide) 20 mg / 25 mg Tablets (AstraZeneca Canada Inc.)
[3] Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Acute Toxicity Lisinopril: LD_{50} Values

Route	Species	Sex	LD_{50} (g/kg)
Oral	Mouse	Male	>20
	Mouse	Female	>20
	Rat	Male	>20
	Rat	Female	>20
	Dog	Male	>6
	Dog	Female	>6
Intravenous	Mouse	Male	>10
	Mouse	Female	>10
Intraperitoneal	Rat	Male	>10
	Rat	Female	>10

Signs of toxicity: Following oral administration to mice decreased activity and one male death (1/10) occurred. No signs of toxicity occurred in rats after oral administration. Dogs given 6 g/kg had transient diarrhea and increases in serum urea nitrogen. Intravenous administration to mice produced bradypnea, ataxia, clonic convulsions, exophthalmia, and tremors. After intraperitoneal administration in rats, ataxia and one female death (1/10) occurred. No signs of toxicity or death occurred in the males.

Subacute/Chronic Toxicology (Lisinopril)

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Results
Rat	2 Week	10 F + 10 M	Oral	3, 10, 30	At all doses, decrease of 2 to 16% in weight gain and 12 to 14% in heart weights were observed in female rats.
Rat	3-Months with 1-Month Interim	25 F + 25 M	Oral	3, 10, 30	At all doses, increased serum urea nitrogen values (up to approximately 2-fold) and decreased heart weights (7 to 10%) were observed in female rats. At 10 and 30 mg, respectively, weight gain decreased 11 to 14% in males. An increased incidence of focal erosions of the gastric mucosa and focal renal tubular basophilia were also seen.
Rat	1 Year with 6 Months Interim	25 F + 25 M	Oral	2, 5, 10, 30, 90[a]	At all doses, a decrease in weight gain (up to 16%) was observed. Serum urea nitrogen increased up to 4-fold; serum sodium decreased (average down to 3 mEq/L) and serum potassium increased (average up to 0.5 mEq/L). At 2, 5, 10 and 30 mg, heart weight decreased; at 5, 10 and 30 mg, kidney weight increased; and at 5, 10, 30 and 90 mg, renal tubular basophilia increased. At 10, 30 and 90 mg, focal interstitial nephritis was observed.
Rat	3 Month with a 1 Month Interim and a 1 Month Recovery	30 F + 30 M	Oral	3, 30, 300, 3000	At all doses, weight gain decreased by 5 to 11% and increases were observed in serum urea nitrogen (up to approximately 3-fold) and serum potassium (average up to 0.4 mEq/L). At 30, 300 and 3000 mg there was an increased incidence of focal renal tubular basophilia and focal necrosis of the glandular mucosa of the stomach. An increased incidence of focal tubular basophilia persisted in rats given 300 or 3000 mg/kg/day.
Rat	1 Month	15 F + 15 M	Oral	30, 60 30, 60 (with saline)	Saline supplementation prevented decreased weight gain and elevations in serum urea nitrogen at 30 and 60 mg. Decreases in cardiac weight at 30 and 60 mg were suppressed by saline supplementation in males at 30 mg. At 30 and 60 mg, renal changes produced due to a low salt diet (renal tubular degeneration and renal tubular basophilia) were prevented by saline supplementation. Mild gastric erosions or necrotic changes were seen in 1 or 2 of 30 rats given 30 or 60 mg. These gastric changes were not seen in saline supplemented animals given these doses; however, the relationship of amelioration due to saline is uncertain because of the low incidence of this change, which is also occasionally seen in untreated animals.
Rat	5 Days 6 Days recovery	8 M	Oral	5, 300	Consumption of 2% saline increased during treatment at 5 mg and on Days 2 to 4 post-treatment at 300 mg.
Dog	2 Week	3 F + 3 M	Oral	3, 10, 30	At 30 mg, slight mineralization of the papilla muscle of the heart was seen in 1 of 6 dogs.

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Results
Dog	3 Month with 1 Month Interim	5 F + 5 M	Oral	3, 10, 30	At 10 mg, hemoglobin concentration, hematocrit, and erythrocyte count decreased in 2 dogs. Marked increases in serum urea nitrogen and creatinine were observed in 2 of 10 dogs. One of these dogs had marked renal tubular degeneration and ulcers of the tongue, gums and gastric pyloric mucosa related to uremia. At 30 mg, there was an increase in serum urea nitrogen (average up to 2-fold) and a decrease in serum sodium (down to 4 mEq/L) and serum chloride (down to 3 mEq/L). At 10 and 30 mg, average cardiac weight was decreased (13 to 15%).
Dog	1 Year with 6 Month Interim	5 F + 5 M	Oral	3, 5, 15	At 15 mg, increases were observed in serum urea nitrogen (less than 2-fold). Decreases in serum sodium (average down to 2 mEq/L) and increases in serum potassium (average up to 0.5 mEq/L) occurred at all doses.
Dog	18-Day	3 F + 3 M	Oral	60, 90 with and without saline	Saline supplementation prevented increases in serum urea nitrogen in dogs given 60 mg for 6 days followed by 90 mg for 8 or 9 days.
Dog	7-Day	4 F + 4 M	I.V.	60, 90	Decreases in blood pressure and increases in serum urea nitrogen occurred in dogs given 60 or 90 mg/kg/day. Supplementation with physiologic saline (25 mL/kg one hour prior to dosing and 4 hours after dosing) prevented these changes. Increased serum potassium (average up to 0.6 mEq/L) and decreased serum chloride (average down to 0.4 mEq/L) values were seen in both supplemented and unsupplemented animals.
Dog	1-Month	2 F + 2 M	Oral	3, 30, 300 and 1000	At 30 mg or greater, BUN increased and specific gravity of the urine decreased. Hyperplasia of renal epithelial cells were observed and deaths occurred. Dogs that died had dilation of distal renal tubules and fatty degeneration of renal tubular epithelium. No drug-related effects were observed at 3 mg.
Dog	3-Month with 1-Month Recovery (high dose)	Control 5 M + 5 F 3, 10, 30 mg/kg/day 3 M + 3 F 100 mg/kg/day 8 M + 8 F Recovery Control 2 M + 2 F	Oral	3, 10, 30 and 100	Eight of 16 dogs given 100 mg died or were killed because of poor physical condition. One of 6 dogs given 30 mg was killed because of poor physical condition. At 10 mg or greater increased BUN and dilation of renal tubules was seen. Fatty degeneration of renal tubular epithelium occurred at the 2 highest dosage levels. The changes are reversible as only slight dilation of renal tubules was present in some animals given 100 mg after 4 weeks of recovery.

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Results
		100 mg/kg/day 5 M + 5 F			
Rabbit	2 Weeks	6 F	Oral	15 (1, 6 and 13 doses) with and without saline	Renal tubular basophilia and renal tubular dilation (considered sequela to necrosis) were seen after 6 and 13 doses in unsupplemented rabbits. Two supplemented rabbits (6 doses) also had the same renal lesion. One rabbit drank very little saline and had increases in BUN, creatinine and potassium. Increases in these parameters were seen in unsupplemented animals after 1, 6, and 13 doses.

[a] Dosing terminated week 11, rats killed week 27.

Hydrochlorothiazide: Hydrochlorothiazide was found to have relatively low toxicity in acute and chronic toxicity studies. In acute animal toxicity studies in mice the LD50 was >10,000 mg/kg suspension orally and was 884 mg/kg intravenously. In rats the acute LD50 was >10,000 mg/kg suspension orally and 3,130 mg/kg suspension intraperitoneally. In the rabbit the acute intravenous LD50 was 461 mg/kg and in the dog it was approximately 1000 mg/kg. Dogs tolerated ≥2000 mg/kg orally without signs of toxicity.

Subacute oral toxicity studies in the rat at 500, 1000 and 2000 mg/kg/day of suspension 5 days/week for 3 weeks displayed no sign of drug effect. Three of the rats given 2000 mg/kg/day hydrochlorothiazide sodium salt died after the 5th day. These deaths were attributed to pneumonia. No sign of drug effect was observed among the other animals. In dogs given doses of 250, 500 and 1000 mg/kg 7 days/week for 8 weeks, no gross signs of drug effect were noted except for electrolyte imbalance.

Chronic oral toxicity studies in the rat using doses of ≤ 2000 mg/kg/day 5 days/week for 26 weeks showed no signs of drug effect and no drug related changes on post mortem examination. In dogs oral doses of 0, 125, 250 mg/kg/day 5 days/week for 26 weeks; 500 mg/kg/day for 7 weeks; 11 weeks without drug then 500 mg/kg/day 7 days/week for 8 weeks, were given. Slight depression of plasma potassium, small amounts of yellow crystalline precipitate in the bladder in 2/12 dogs were found on gross examination. Histomorphologic studies did not show drug related changes.

Lisinopril and Hydrochlorothiazide:

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Effects
Rat	2-weeks	10 M + 10 F	Oral	Lisinopril 0, 3, 10, 30 mg/kg/day; Lisinopril/HCTZ* 3/10, 10/10, 30/10 mg/kg/day	Decreased body weight gain was seen in all the drug-treated groups. A decrease in serum chloride occurred in all groups given the combination. Increased serum urea nitrogen occurred in the 2 highest groups given the combination. Renal tubular degeneration and gastritis or gastric ulcer occurred in one rat each at 10/10 and 30/10 mg/kg/day. An additional rat at 30/10 mg/kg/day also had a gastric ulcer without renal lesions. Decreased average heart weight (females) was seen in all the groups given the combination.
Rat	14-weeks	25 M + 25 F	Oral	Toxicity study with one month interim necropsy Lisinopril/HCTZ 0/0, 3/10, 10/10, 30/10 mg/kg/day	Decreased body weight gain, increased serum urea nitrogen, decreased serum sodium and chloride, and decreased average heart weights occurred at all dosage levels. Very slight focal necrosis of the fundic mucosa of the stomach occurred in the 2 highest dosage groups. Focal renal tubular basophilia occurred at a higher incidence in drug-treated animals compared to control animals.
Rat	27-weeks	15 M + 15 F	Oral	Lisinopril/HCTZ 0/0, 3/10, 10/10, 30/10 mg/kg/day	All animals had average body weight gains approximately 5 to 25% below the controls throughout the study. Average serum nitrogen values were generally two to three times greater in drug-treated animals compared to controls. Other serum biochemical parameters changed very slightly. Decreases in erythrocyte parameters were seen at all dosage levels. Decreases in heart weight occurred at all dosage levels and increase in kidney weight occurred at the 2 highest dosage levels. Mineralization of the renal cortico-medullary junction occurred in 2 to 5 rats in each of the drug-treated groups. Very small or small necrotic foci of gastric mucosa occurred in 5 rats in the high dose group. Chronic nephritis and its early stage of renal tubular basophilia occurred among treated and control rats, but occurred at a greater incidence in treated rats.
Dog	2-weeks	3 M + 3 F	Oral	Lisinopril 0, 3, 10, 30 mg/kg/day; Lisinopril/HCTZ 3/10, 10/10, 30/10	Average body weight losses in dogs given lisinopril 30 mg/kg/day or lisinopril 10 or 30 mg/kg/day with hydrochlorothiazide were probably related to treatment. Increases in serum urea nitrogen, creatinine and phosphorus occurred at the 2 highest dosage levels of the combination. At these doses renal tubular degeneration and secondary lymphoid depletion and gastrointestinal lesions were seen. At the highest dose

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Effects
				mg/kg/day	increases in SGPT, alkaline phosphatase, potassium, and calcium and decreases in serum chloride, necrosis of hepatocytes, and mineralization of the papillary muscle of the heart were seen.
Dog	14-weeks	5 M + 5 F	Oral	Toxicity study with one month interim necropsy Lisinopril/HCTZ 0/0, 1/10, 3/10, 10/10 mg/kg/day	3 dogs given 10/10 mg/kg/day of lisinopril/hydrochlorothiazide showed physical signs that were attributable to drug treatment; these included decreased activity, dehydration and anorexia. Marked increases in the serum concentrations of urea nitrogen (128.4 to 271.5 mg/100 mL), creatinine (5.1 to 11.5 mg/100 mL), and phosphorus (9.2 to >16.0 mg/100 mL) in terminal samples of 3 dogs given 10/10 mg/kg/day of lisinopril/hydrochlorothiazide that were sacrificed due to their poor physical condition after 11 or 18 doses. These dogs had renal tubular necrosis and secondary lymphoid depletion, and gastrointestinal lesions. At 3/10 mg/kg/day, an increase in serum urea nitrogen was seen. At all doses decreases in serum sodium, potassium, and chloride occurred probably due to hydrochlorothiazide.
Dog	27-weeks	3 M + 3 F	Oral	Lisinopril/HCTZ 0/0, 0.3/1, 1/3, 3/10 mg/kg/day	All dogs given 3/10 mg/kg/day had elevations in serum urea nitrogen and some had increases in serum creatinine. One dog at this level was markedly affected with increases in serum urea nitrogen, creatinine, glucose, GOT, and GPT and decreases in serum sodium, chloride, and potassium. This dog was killed in the fifth week and had renal tubular degeneration and secondary lymphoid depletion and gastro-intestinal lesions. A transient decrease in blood erythroid parameters were seen at the highest dosage level and a decrease in serum sodium and at necropsy males in this group had a mild hypertrophy of the renal proximal tubules probably due to hypokalemia. The only changes seen at 0.3/1 and 1/3 mg/kg/day were decreases in serum potassium and chloride, and elevation in serum urea nitrogen at 1/3 mg/kg/day.

*Hydrochlorothiazide

Carcinogenicity

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 repair deficient 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.

Lisinopril:

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Results
Mice Cri:CD-1(ICR)BR	92 weeks	50 F & 50 M	Oral	15, 45, 135 mg/kg/day	No evidence of carcinogenic effect was observed. Decreased weight gain (7 to 15%) was seen in females at 135 mg. A greater incidence and severity of chronic nephritis in females and males given 45 and 135 mg was also seen.
Rats Cri:CD(SD)BR	105 weeks	50 F & 50 M	Oral	10, 30, 90 mg/kg/day	No evidence of carcinogenic effect was observed. Decreased weight gain (5 to 14%) in male drug-treated rats during the first 67 weeks of the study was observed. Focal sacculations of the retinal vessels was more prevalent in rats given 30 or 90 mg than in controls in Drug Week 100. An increased incidence of renal tubular hypertrophy in drug-treated males was seen at termination of study (1 mg was considered the no-effect dose for this change in males based on an additional 105 week study at 1, 3, and 10 mg/kg/day). An increased incidence of chronic nephritis in drug-treated females (10 mg is the no-effect dose based on an additional 105-week study at 1, 3, and 10 mg/kg/day) was observed.

Genotoxicity

Lisinopril:

Study	Test System	Dose	Results
Mutagenesis			
Microbial mutagen with and without metabolic activation	*Salmonella typhimurium* TA1535, TA1537, TA98, TA100	≤2000 µg/plate	Negative for mutagenic potential
	Escherichia coli WP2, WP2 uvrA	≤10 mg/plate	
In vitro V-79 mammalian cell mutagenesis with and without metabolic activation	Chinese Hamster Lung Cell	≤10 mM (4.42 mg/mL)	Negative for mutagenic potential
DNA Damage			
In vitro alkaline elution	Rat Hepatocyte	≤30 mM (13.25 mg/mL)	Negative for induction of DNA single strand breaks
Chromosomal Evaluation			
In vitro chromosomal aberration assay	Chinese Hamster Ovary	≤30 mM	Negative for induction of chromosomal

with and without metabolic activation		(13.25 mg/mL)	aberration
In vivo chromosomal aberration assay	Bone Marrow Cells of Male Mice	≤5000 mg/kg	Negative for increases in chromosomal aberrations

Lisinopril and Hydrochlorothiazide: The results of a battery of mutagenic and chromosomal aberration studies (Ames test, mammalian cell mutagenesis assay, an *in vitro* alkaline elution test for single strand DNA breaks, an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, and *in vivo* mouse bone marrow chromosome aberration) failed to reveal a genotoxic potential for the combination of lisinopril and hydrochlorothiazide.

Reproductive and Developmental Toxicology

Teratology Studies (Lisinopril)

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Results
Mice	25	100, 300, 1000, 1000 with saline	Oral	Day 6 through Day 15 of gestation	No teratogenic effect was observed. There was an increased incidence of resorptions in all unsupplemented groups (no increase in serum urea nitrogen).
Rat	35	30, 100, 300 300 with saline	Oral	Day 6 through Day 17 of gestation	No teratogenic effect was observed. Maternal weight gain decreased in all unsupplemented groups. The open field behavioral test (measure of spontaneous activity) showed increased activity in Week 5 postpartum F1 females at 300 mg with and without saline, but only in 300 mg with saline females in Week 6. When the open field test was repeated in males and females given 300 mg with and without saline in Week 11, no increase in activity was seen.
Rabbit (New Zealand)	18	0.1, 0.3, 1.0 all groups with saline	Oral	Day 6 through Day 18 of gestation	No teratogenic effect was observed. At all doses there was an increased incidence of incomplete ossification (sternebrae, metacarpals, forefoot phalanges, pelvic bones, and tali and/or calcanea) which was considered to represent a fetotoxic effect. At 1 mg one rabbit had a high incidence of resorptions.
Rabbit (New Zealand)	18	0.031, 0.125, 0.5	Oral	Day 6 through Day 18 of gestation	No fetotoxicity or embryotoxicity was observed at maternotoxic doses. At 0.125 and 0.5 mg maternal deaths, decreased maternal weight gain and food consumption, as well as increases in BUN, creatinine and potassium were seen. In addition, doses of 0.5 mg produced decreases in serum sodium and chloride, diffuse distention of the renal distal tubules and degeneration of renal tubules.

Fertility and Late Gestation and Lactation with Postnatal Evaluation Studies - Lisinopril

Species	No of Animals/Group	Route	Dose mg/kg/day	Duration of Dosing	Results
Rat	24 F & 24 M	Oral	30, 100, 300 300 with saline	Males were dosed for 78 days prior to mating and females from 15 days prior to mating until sacrifice on Day 20 of gestation	Weight gain was reduced in unsupplemented males at all doses and during gestation in unsupplemented females. No effects on fertility and no signs of teratogenicity were observed. There was an increase in F1 pup deaths (3 to 8% vs. control 1%) Day 1 to 7 postpartum in 100 and 300 mg (saline and nonsaline) groups. Decreased mean F1 pup weight (3 to 7% less than controls) on Day 0 postpartum was seen in all unsupplemented groups.
Rat	20 F	Oral	30, 100, 300 300 with saline	Day 15 of gestation through Day 21 post-partum	On Days 2 to 7 postpartum, there was an increased number of dead pups (8 to 10% vs. control 0%). On Day 21 postpartum, a decrease in pup weights (8% less than controls) was observed in the unsupplemented 100 and 300 mg groups. There was no effect in the supplemented group. Pup development was not altered.

Hydrochlorothiazide: Hydrochlorothiazide has been administered to rats in a 2 litter study, to mice in a 2 generation study, and to rabbits in an established pregnancy test. None of these studies showed any evidence of teratogenic effects of hydrochlorothiazide. Offspring carried on to weaning or maturity did not show evidence of effects related to treatment.

Teratology (lisinopril and hydrochlorothiazide)

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Effects
Mouse	4-weeks	25 F	Oral	Lisinopril/HCTZ 0/0, 10/10, 30/10, 90/10 mg/kg, 90/10 mg/kg + 0.9% saline – Days 6 - 15 of gestation	There were no maternal deaths and no treatment-related abortions. In all drug-treated groups there were no treatment-related effects on mean live fetal weights and numbers of implants and live and dead fetuses. There was a dose-response increase in incidence of skeletal malformations. In addition, there was an increase in the incidence of lumbar ribs, a skeletal-variation, among drug-treated groups. All of the skeletal malformations, with the exception of the fetus with the extra vertebra, were among mice not given saline supplementation and have occurred at comparable incidences in control groups of other studies, and some were observed in the control group of this study. A repeat of

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Effects
					this study did not produce any evidence of treatment-related fetal skeletal malformations.
Rat	4-weeks	25 F	Oral	Lisinopril/HCTZ 0/0, 10/10, 30/10, 90/10 mg/kg + 0.9% saline – Days 6 - 17 of gestation	In the lisinopril/hydrochlorothiazide 90/10 mg/kg/day group, there was a significant (P≤0.05) decrease in the number of live fetuses per pregnant female. Maternotoxicity was evident in all unsupplemented drug-treated groups. There were significant (P≤0.05) treatment-related decreases in live fetal weight in all drug-treated groups not supplemented with saline. Fetal weight in the 90/10 mg/kg/day group supplemented with saline was comparable to control. There was an increased incidence of fetuses with incompletely ossified sternebrae in the 30/10 and 90/10 mg/kg/day groups without saline supplementation which were considered to represent an embryotoxic effect. Ossification was not delayed in the 10/10 mg/kg/day group or the 90/10 mg/kg/day group supplemented with saline.
Rat	4-weeks	20 or 22 F	Oral	Lisinopril/HCTZ 0/0, 3/10, 30/10, 90/10 mg/kg + 0.9% saline – Days 6 - 17 of gestation	Fetotoxicity was apparent as treatment-related decreases in live fetal weight at all dosage levels without saline supplementation which were statistically significant (P≤0.05) in the 30/10 and 90/10 mg/kg/day groups. Results from this study confirmed those of the previous study. There was a delay in ossification, consistent with decreased live weights, at all dosage levels without saline supplementation. Maternotoxicity was evident in all unsupplemented drug-treated groups.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrZESTORETIC® (Tablets, 10 mg / 12.5 mg, 20 mg / 12.5 mg and 20 mg / 25 mg), submission control #250625, Product Monograph, Searchlight Pharma Inc. (March 17, 2022)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]TEVA-LISINOPRIL/HCTZ (TYPE Z)
Lisinopril and hydrochlorothiazide tablets

Read this carefully before you start taking **TEVA-LISINOPRIL/HCTZ (TYPE Z)** 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 **TEVA-LISINOPRIL/HCTZ (TYPE Z).**

Serious Warnings and Precautions

- TEVA-LISINOPRIL/HCTZ (TYPE Z) should not be used during pregnancy. Taking TEVA-LISINOPRIL/HCTZ (TYPE Z) during pregnancy can cause injury or even death to your baby. If you discover that you are pregnant while taking TEVA-LISINOPRIL/HCTZ (TYPE Z), stop the medication and contact your healthcare professional as soon as possible.

What is TEVA-LISINOPRIL/HCTZ (TYPE Z) used for?
- TEVA-LISINOPRIL/HCTZ (TYPE Z) is used in adults to lower high blood pressure.

How does TEVA-LISINOPRIL/HCTZ (TYPE Z) work?
TEVA-LISINOPRIL/HCTZ (TYPE Z) is a combination of 2 drugs, lisinopril and hydrochlorothiazide:
- Lisinopril is an angiotensin converting enzyme (ACE) inhibitor. It lowers blood pressure.
- Hydrochlorothiazide is a diuretic or 'water pill' that increases urination. This also helps to lower blood pressure.

This medicine does not cure high blood pressure. It helps to control it. Therefore, it is important to continue taking TEVA-LISINOPRIL/HCTZ (TYPE Z) regularly even if you feel fine.

What are the ingredients in TEVA-LISINOPRIL/HCTZ (TYPE Z)?
Medicinal ingredients: Lisinopril and hydrochlorothiazide.
Non-medicinal ingredients: Corn starch, dibasic calcium phosphate, magnesium stearate, mannitol, pregelatinized corn starch, red iron oxide and yellow iron oxide (10 mg / 12.5 mg tablet and 20 mg / 25 mg tablet).

TEVA-LISINOPRIL/HCTZ (TYPE Z) comes in following dosage forms:
Lisinopril and hydrochlorothiazde tablets: 10 mg / 12.5 mg, 20 mg / 12.5 mg and 20 mg / 25 mg.

Do not use TEVA-LISINOPRIL/HCTZ (TYPE Z) if:
- You are allergic to lisinopril, hydrochlorothiazide, or to any non-medicinal ingredient in the formulation.
- You are allergic to any sulfonamide-derived drugs (sulfa drugs); most of them have a medicinal ingredient that ends in "-MIDE".
- You have a family history of angioedema (allergic reaction) or have ever had angioedema to any ACE inhibitor. Be sure to tell your healthcare professional that this has happened to you.
- You are already taking a blood pressure-lowering medicine that contains aliskiren and you have one of the following conditions:
  - diabetes
  - kidney disease
  - high potassium levels

- heart failure combined with low blood pressure

- You are taking an angiotensin receptor blocker (ARB), another medicine to treat your high blood pressure, or another ACE inhibitor and have one of the following conditions:
  - diabetes with end organ damage
  - kidney disease
  - high potassium levels
  - heart failure combined with low blood pressure

  You can recognize ARBs because their medicinal ingredient ends in "-SARTAN".
- You are taking sacubitril/valsartan, due to the increased risk of serious allergic reaction, which causes swelling of the face or throat (angioedema) when taken with TEVA-LISINOPRIL/HCTZ (TYPE Z).
- You have difficulty urinating or produce no urine.
- You are pregnant or intend to become pregnant. Taking TEVA-LISINOPRIL/HCTZ (TYPE Z) during pregnancy can cause injury and even death to your baby.
- You are breastfeeding. TEVA-LISINOPRIL/HCTZ (TYPE Z) passes into breast milk.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-LISINOPRIL/HCTZ (TYPE Z). Talk about any health conditions or problems you may have, including if you:

- Have experienced an allergic reaction to any drug used to lower blood pressure or penicillin.
- Have recently received or are planning to get allergy shots for bee or wasp stings.
- Have a history of allergic reactions or asthma.
- Have narrowing of an artery or a heart valve.
- Have had a heart attack or stroke.
- Have heart failure.
- Have a liver or kidney disorder.
- Have diabetes, liver, heart or kidney disease.
- Have lupus or gout.
- Are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- Are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill").
- Are taking an angiotensin receptor blocker (ARB).
- Are on a low-salt diet.
- Are on dialysis.
- Are receiving gold (sodium aurothiomalate) injections.
- Are on LDL Apheresis (a treatment to lower the LDL cholesterol in the blood).
- Have had skin cancer or have a family history of skin cancer.
- Have a greater chance of developing skin cancer because you have light-coloured skin, get sunburned easily, or are taking drugs to suppress your immune system.

Other warnings you should know about:

Use of anesthesia: If you are going to have a surgery or dental procedure with anesthesia, be sure to tell your healthcare professional that you are taking TEVA-LISINOPRIL/HCTZ (TYPE Z).

Risk of skin cancer: TEVA-LISINOPRIL/HCTZ (TYPE Z) contains hydrochlorothiazide. Treatment with hydrochlorothiazide may increase the risk of developing non-melanoma skin cancer. The risk is higher if you have been taking TEVA-LISINOPRIL/HCTZ (TYPE Z) for many years (more than 3) or at a high dose.
While taking TEVA-LISINOPRIL/HCTZ (TYPE Z):

- Make sure to regularly check your skin for any new lesions. Check areas that are most exposed to the sun, such as the face, ears, hands, shoulders, upper chest and back.
- Limit your exposure to the sun and to indoor tanning. Always use sunscreen (SPF-30 or higher) and wear protective clothing when going outside.

- Talk to your doctor immediately if you get more sensitive to the sun or UV light or if you develop an unexpected skin lesion (such as a lump, bump, sore, or patch) during the treatment.

Sudden eye disorders: Treatment with Hydrochlorothiazide in TEVA-LISINOPRIL/HCTZ (TYPE Z) can cause sudden eye problems such as:
- **Myopia:** sudden near-sightedness or blurred vision.
- **Glaucoma:** an increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss.
- **Choroidal effusion:** an abnormal buildup of liquid in your eye that may result in vision changes.

These eye disorders are related and can develop within hours to weeks of starting TEVA-LISINOPRIL/HCTZ (TYPE Z). If you earlier have had a penicillin or sulfonamide allergy, you can be at higher risk of developing this. If you experience the above symptoms, stop taking TEVA-LISINOPRIL/HCTZ (TYPE Z) and seek immediate medical help.

Monitoring: During your treatment with TEVA-LISINOPRIL/HCTZ (TYPE Z), your healthcare professional may monitor:
- Your kidney function.
- Your blood pressure.
- The amount of electrolytes in your blood (such as potassium).

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to TEVA-LISINOPRIL/HCTZ (TYPE Z). Dizziness, light-headedness, or fainting can occur, especially after the first dose and when the dose is increased.

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 TEVA-LISINOPRIL/HCTZ (TYPE Z):

Serious Drug Interactions

- Medicines containing aliskiren, ARBs or other ACE inhibitors if you also have:
  - Diabetes (with or without end organ damage),
  - Kidney disease,
  - High potassium levels, or
  - Heart failure with low blood pressure.
- Sacubitril/valsartan.

- Adrenocorticotropic hormone (ACTH), which may be used to treat diseases such as nephrotic syndrome or collagen diseases, and in diagnostic tests.
- Alcohol, barbiturates (sleeping pills), or narcotics (strong pain medications). They may cause low blood pressure and dizziness when you go from lying or sitting to standing up.
- Amantadine used to treat the flu and reduce symptoms of Parkinson's disease.
- Amphotericin B, an antifungal drug.
- Antacids.
- Drugs used to treat cancer such as cyclophosphamide, methotrexate, temsirolimus and everolimus.
- Antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), such as citalopram, escitalopram, and sertraline.
- Drugs to treat diabetes such as insulin and oral medications (such as sulphonylureas).
- Bile acid resins used to lower cholesterol such as cholestyramine.
- Other blood pressure-lowering drugs such as:
  - Diuretics ("water pills").
  - Guanethidine.

  - Diazoxide.
  - Methyldopa.
  - Beta-blockers such as atenolol, metoprolol, propranolol.
  - Vasodilators.
  - Calcium channel blockers such as felodipine, amlodipine, nifedipine.
  - Angiotensin converting enzyme inhibitors (ACEIs).
  - Angiotensin II receptor blockers (ARBs) such as candesartan, valsartan, losartan.
  - Direct renin inhibitors.
- Calcium or vitamin D supplements.
- Capsaicin, an ingredient in some creams used to relieve arthritis pain.
- Corticosteroids used to treat joint pain and swelling.
- Cyclosporine used to treat autoimmune diseases.
- Digoxin, a heart medication.
- Drugs that slow down or speed up bowel function such as atropine, biperiden, domperidone and metoclopramide.
- Drugs used to treat epilepsy such as carbamazepine and topiramate.
- Gold (sodium aurothiomalate), used to treat autoimmune conditions such as rheumatoid arthritis and psoriatic arthritis.
- Gout medications such as allopurinol, probenecid, uricosurics and xanthine oxidase inhibitors.
- A type of drug called a "neutral endopeptidase inhibitor".
- Lithium, a medicine to treat bipolar disease.
- Drugs that can cause low blood potassium levels (hypokalemia) such as Laxatives, Corticosteroids (such as prednisone) and Salicylic acid derivatives.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include ibuprofen, naproxen, and celecoxib.
- Drugs that can increase blood potassium levels (hyperkalemia) such as potassium supplements or potassium containing salt substitutes.
- Rituximab used to treat cancer, transplant rejection, and some autoimmune diseases.
- Mammalian target of rapamycin (mTOR) inhibitors such as sirolimus, a drug used to prevent organ rejection after a transplant.
- Skeletal muscle relaxants used to relieve muscle spasms, including tubocurarine.
- Tetracycline antibiotics.
- Tissue plasminogen activator (TPA) that is used to dissolve blood clots that have formed in blood vessels.
- Pressor amines such as norepinephrine.

How to Take TEVA-LISINOPRIL/HCTZ (TYPE Z):
- Take TEVA-LISINOPRIL/HCTZ (TYPE Z) exactly as prescribed.
- It is recommended to take your dose at about the same time every day.
- Swallow TEVA-LISINOPRIL/HCTZ (TYPE Z) whole, with water. Do NOT crush, split or chew the tablet.
- TEVA-LISINOPRIL/HCTZ (TYPE Z) can be taken with or without food. If TEVA-LISINOPRIL/HCTZ (TYPE Z) causes upset stomach, take it with food or milk.

Usual Dose:
Your healthcare professional has decided the best dose for you. Take your dose once daily, exactly as your healthcare professional has told you to.

Overdose:

If you think you, or a person you are caring for, have taken too much TEVA-LISINOPRIL/HCTZ (TYPE Z), contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

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

What are possible side effects from using TEVA-LISINOPRIL/HCTZ (TYPE Z)?
These are not all the possible side effects you may have when taking TEVA-LISINOPRIL/HCTZ (TYPE Z). If you experience any side effects not listed here, tell your healthcare professional.

- dizziness
- headache
- cough
- drowsiness, fatigue, weakness
- diarrhea, nausea, vomiting, indigestion
- cold or flu-like symptoms
- muscle pain or cramps
- pins and needles in hands or feet
- rash
- impotence, low sex drive
- abdominal pain, upset stomach, decreased appetite, constipation
- muscle pain or cramps

TEVA-LISINOPRIL/HCTZ (TYPE Z) can cause abnormal blood test results. Your healthcare professional 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			
Decreased or increased levels of potassium in the blood: irregular heartbeats, muscle weakness and generally feeling unwell.		✓	
Low Blood Pressure: dizziness, fainting, lightheadedness. May occur when you go from lying or sitting to standing up.	✓		
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.		✓	

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	
UNCOMMON			
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.			✓
Electrolyte Imbalance: weakness, drowsiness, muscle pain or cramps, irregular heartbeat.		✓	
High blood sugar: frequent urination, thirst, and hunger.	✓		
Kidney Disorder: decreased urination, nausea, vomiting, swelling of extremities, fatigue.		✓	
Liver Disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite.		✓	
Tachycardia (abnormally fast heartbeat): dizziness, lightheadedness, shortness of breath, racing heart.		✓	
RARE			
Decreased Platelets: bruising, bleeding, fatigue, weakness, small purple or red dots under the skin.		✓	
Decreased White Blood Cells: infections, fatigue, fever, aches, pains, and flu-like symptoms.		✓	
Edema: unusual swelling of the arms, hands, legs, ankles or feet.		✓	
VERY RARE			
Serious Skin Reactions: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine.			✓
UNKNOWN			
Anemia (decreased number of red blood cells): fatigue, loss of energy, weakness, shortness of breath.		✓	
Eye disorders: **- Myopia**: sudden near-sightedness or blurred vision. **- Glaucoma:** increased pressure in your eyes, eye pain decrease in vision. **- Choroidal effusion** (buildup of liquid in			✓

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	
your eye): blind spots, eye pain, blurred vision.			
Hallucinations: sensation of seeing or hearing things.		✓	
Lupus (an autoimmune disease that occurs when your body's immune system attack your own tissues and organs): fever, malaise, joint or muscle pain, fatigues. Conditions may be activated, or made worse.		✓	
Pancreatitis (inflammation of the pancreas): abdominal pain that lasts and gets worse when you lie down, nausea, vomiting.		✓	

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 between 15°C - 30°C. Protect from light and moisture.
- When you first open the package, if you find any damage to the plastic seal or foil which exposes the tablet, ask your pharmacist to check the package.
- Do not transfer TEVA-LISINOPRIL/HCTZ (TYPE Z) to other pill containers.
- **Keep out of reach and sight of children.** Never take medicine in front of small children as they will want to copy you.
- Do not keep or use TEVA-LISINOPRIL/HCTZ (TYPE Z) after the expiry date indicated on the package. Unused medicines, which you know you will no longer need, should be carefully discarded. You may wish to seek advice from your pharmacist.
- **Remember** to get a new prescription from your doctor or a refill from your pharmacy a few days before all your tablets are taken.

If you want more information about TEVA-LISINOPRIL/HCTZ (TYPE Z):

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient

Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website: http://www.tevacanada.com, or by calling 1-800-268-4127 ext. 3.

This leaflet was prepared by Teva Canada Limited, Toronto, Ontario M1B 2K9.

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