PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]APO-LOSARTAN/HCTZ

Losartan Potassium and Hydrochlorothiazide Tablets

Tablets, 50 mg / 12.5 mg, 100 mg / 12.5 mg and 100 mg / 25 mg, Oral

USP

Angiotensin II Receptor Antagonist and Diuretic

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Respiratory	02/2023

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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

Hypertension:

APO-LOSARTAN/HCTZ (Losartan Potassium and Hydrochlorothiazide Tablets) is indicated for:

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

APO-LOSARTAN/HCTZ is not indicated as the initial therapy for essential hypertension, except in patients with severe essential hypertension (Sitting DBP ≥110 mmHg) for whom the benefit of a prompt blood pressure reduction exceeds the risk of initiating combination therapy in these patients (see 4 DOSAGE AND ADMINISTRATION and 14 CLINICAL TRIALS)

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.

1.2 Geriatrics

Geriatrics (>65 years of age): No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see 4 DOSAGE AND ADMINISTRATION).

2 CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- Because of the hydrochlorothiazide component, APO-LOSARTAN/HCTZ is also contraindicated in patients with anuria, and in patients who are hypersensitive to other sulfonamide-derived drugs.

- Concomitant use of angiotensin receptor antagonists (ARBs) –including APO-LOSARTAN/HCTZ or of angiotensin-converting-enzyme inhibitors (ACEIs) with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR < 60 mL/min/1.73m^2) is contraindicated (see 7 WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal, and 9 DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ACEIs, ARBs or aliskiren-containing drugs).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

When used in pregnancy, angiotensin receptor (AT_1) blockers (ARB) can cause injury or even death of the developing fetus. When pregnancy is detected, APO-LOSARTAN/HCTZ should be discontinued as soon as possible (see 7 WARNINGS AND PRECAUTIONS, Special Populations).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Dosage must be individualized.
- The fixed combination is not for initial therapy, except for severe hypertension.
- The dose of APO-LOSARTAN/HCTZ should be determined by the titration of the individual components.

4.2 Recommended Dose and Dosage Adjustment

Hypertension: Once the patient has been stabilized on the individual components as described below, either one tablet APO-LOSARTAN/HCTZ 50 mg/12.5 mg or 100 mg/12.5 mg, or one tablet 100 mg/25 mg once daily may be substituted if the doses on which the patient was stabilized are the same as those in the fixed combination. The maximum dose is one tablet APO-LOSARTAN/HCTZ 100 mg/25 mg once daily.

Severe Hypertension (Sitting DBP ≥110 mmHg): The starting dose of APO-LOSARTAN/HCTZ for initial treatment of severe hypertension is one tablet of APO-LOSARTAN/HCTZ 50 mg/12.5 mg once daily. For patients who do not respond adequately to APO-LOSARTAN/HCTZ 50 mg/12.5 mg after 2 to 4 weeks of therapy, the dosage may be increased to one tablet of APO-LOSARTAN/HCTZ 100 mg/25 mg once daily. The maximum dose is one tablet of APO-LOSARTAN/HCTZ 100 mg/25 mg once daily.

Losartan Monotherapy: The usual starting dose of losartan monotherapy is 50 mg once daily.

Dosage should be adjusted according to blood pressure response. The maximal antihypertensive effect is attained 3 to 6 weeks after initiation of therapy.

The usual dose range for losartan is 50 to 100 mg once daily. A dose of 100 mg daily should not be exceeded, as no additional antihypertensive effect is obtained with higher doses.

In most patients taking losartan 50 mg once daily, the antihypertensive effect is maintained. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. This can be evaluated by measuring the blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either

twice daily administration with the same total daily dosage, or an increase in the dose should be considered. If blood pressure is not adequately controlled with losartan alone, a non-potassium sparing diuretic may be administered concomitantly.

For patients with volume-depletion, a starting dose of 25 mg once daily should be considered (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular-Hypotension and 9 DRUG INTERACTIONS).

Diuretic Treated Patients: In patients receiving diuretics, losartan therapy should be initiated with caution, since these patients may be volume-depleted and thus more likely to experience hypotension following initiation of additional antihypertensive therapy. Whenever possible, all diuretics should be discontinued two to three days prior to the administration of losartan, to reduce the likelihood of hypotension (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular - Hypotension and 9 DRUG INTERACTIONS, Diuretics). If this is not possible because of the patient's condition, losartan should be administered with caution and the blood pressure monitored closely. Thereafter, the dosage should be adjusted according to the individual response of the patient.

Dosage Adjustment in Renal Impairment: No initial dosage adjustment in losartan is usually necessary for patients with renal impairment, including those requiring hemodialysis. However, appropriate monitoring of these patients is recommended.

The usual regimens of therapy with APO-LOSARTAN/HCTZ may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so APO-LOSARTAN/HCTZ is not recommended.

Patients with Liver Impairment: Since dosage adjustment of losartan is required in patients with liver impairment, and thiazide diuretics may precipitate hepatic coma, a fixed combination product such as APO-LOSARTAN/HCTZ is not advisable (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic -Patients with Liver Impairment).

Geriatrics (>65 years of age): No initial dosage adjustment is necessary for most elderly patients. Appropriate caution should nevertheless be used when prescribing to the elderly, as increased vulnerability to drug effect is possible in this patient population (see 7 WARNINGS AND PRECAUTIONS, 7.1.4 Geriatrics).

4.4 Administration

APO-LOSARTAN/HCTZ tablet is for oral administration.

APO-LOSARTAN/HCTZ may be administered with or without food, however it should be taken consistently with respect to food intake at about the same time every day.

4.5 Missed Dose

If a dose is missed, an extra dose should not be taken. The usual schedule must be resumed.

5 OVERDOSAGE

No specific information is available on the treatment of overdosage with APO-LOSARTAN/HCTZ. Treatment is symptomatic and supportive.

Losartan: Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia.

If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor its active metabolite can be removed by hemodialysis.

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.

The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

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	Tablets 50 mg/12.5 mg, 100 mg/12.5 mg, 100 mg/25 mg	Hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch and titanium dioxide. APO-LOSARTAN/HCTZ 50 mg/12.5 mg and 100 mg/25 mg also contain the carnauba wax and quinoline yellow aluminum lake

APO-LOSARTAN/HCTZ 50 mg/12.5 mg tablets are Light yellow to yellow coloured, film coated, oval shaped, biconvex tablets, debossed 'APO' on one side and '50 12.5' on the other side. Each

tablet contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide, as the active ingredients. Available in blisters of 30 tablets and bottles of 100 tablets.

APO-LOSARTAN/HCTZ 100 mg/12.5 mg tablets are White to off white coloured, oval shaped, biconvex film coated tablets, with 'APO' debossed on one side and '100 12.5' on the other side. Each tablet contains 100 mg of losartan potassium and 12.5 mg of hydrochlorothiazide, as the active ingredients. Available in blisters of 30 tablets and bottles of 100 tablets.

APO-LOSARTAN/HCTZ 100 mg/25 mg tablets are Light yellow to yellow coloured, film coated, oval shaped, biconvex tablets, debossed 'APO' on one side and '100 25' on the other side. Each tablet contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide, as the active ingredients. Available in blisters of 30 tablets and bottles of 100 tablets.

APO-LOSARTAN/HCTZ 50 mg/12.5 mg tablets contain 4.24 mg (<1 mmol) of potassium and APO-LOSARTAN/HCTZ 100 mg/12.5 mg and APO-LOSARTAN/HCTZ 100 mg/25 mg contain 8.48 mg (<1 mmol) of potassium as losartan potassium.

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 ADVERSE REACTIONS, 8.5 Post Market Adverse Reactions). The photosensitizing action of hydrochlorothiazide may be a possible mechanism for NMSC (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity – 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 ADVERSE REACTIONS, 8.5 Post Market Adverse Reactions).

Cardiovascular

Hypotension: Occasionally, symptomatic hypotension has occurred after administration of losartan, in some cases after the first dose. It is more likely to occur in patients who are volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In these patients, because of the potential fall in blood pressure, therapy should be started under close medical supervision. Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident.

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

Dual blockade of the Renin-Angiotensin System (RAS): There is evidence that co-administration of angiotensin receptor antagonists (ARBs), such as APO-LOSARTAN/HCTZ, or of angiotensin-converting-enzyme inhibitors (ACEIs) 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 APO-LOSARTAN/HCTZ in combination with aliskiren-containing drugs is contraindicated in these patients. Co-administration of ARBs, including APO-LOSARTAN/HCTZ, with other agents blocking the RAS, such as ACEIs or aliskiren-containing drugs, is not recommended in any patients, as adverse outcomes cannot be excluded.

Endocrine and Metabolism

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

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

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

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

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

Hepatic/Biliary/Pancreatic

Patients with Liver Impairment: Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan and its active metabolite in cirrhotic patients after administration of losartan potassium tablets, a lower dose should be considered for patients with hepatic impairment, or a history of hepatic impairment (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY).

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

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

Anaphylactic reactions, angioedema (involving swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, and/or tongue and pharynx, requiring intubation/tracheotomy in some cases) have been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with ACE inhibitors. Vasculitis, including Henoch-Schoenlein purpura, has been reported rarely.

Ophthalmologic

Choroidal Effusion, Acute Myopia and Secondary Angle-Closure Glaucoma:
Hydrochlorothiazide, a sulphonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion, acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity, blurred vision or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

Renal

Renal Impairment: As a consequence of inhibiting the renin-angiotensin-aldosterone system,

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

Increases in Serum Potassium: Concomitant use of other drugs that may increase serum potassium may lead to hyperkalemia (see 9 DRUG INTERACTIONS).

The use of ARBs – including APO-LOSARTAN/HCTZ – or of ACEIs 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 DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs, or aliskiren-containing drugs).

Use of losartan should include appropriate assessment of renal function.

Thiazides should be used with caution.

Because of the hydrochlorothiazide component, APO-LOSARTAN/HCTZ is not recommended in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min).

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.

Respiratory

Acute respiratory distress: Very rare severe cases of acute respiratory distress including pneumonitis and pulmonary edema have been reported after taking hydrochlorothiazide. In such cases, pulmonary edema typically develops within minutes to hours after hydrochlorothiazide intake. At onset, symptoms can include dyspnea, fever, pulmonary deterioration and hypotension. APO-LOSARTAN/HCTZ should be discontinued, and appropriate treatment should be given if the patient presents with acute respiratory distress. APO-LOSARTAN/HCTZ should not be administered to patients who previously experienced acute respiratory distress following hydrochlorothiazide intake.

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

Drugs that act directly on the renin-angiotensin-aldosterone-system (RAAS) can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, APO-LOSARTAN/HCTZ should be discontinued as soon as possible.

The use of ARB is not recommended during pregnancy. Epidemiological evidence regarding the risk of teratogenicity following exposure to angiotensin converting enzyme inhibitors (another class of therapeutic products interfering with the RAAS) during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Given the current evidence available on the risk with ARB, similar risks may exist for this class of drugs. Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

The use of ARBs during the second and third trimesters is known to induce human fetotoxicity (decreased renal function; oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia).

Infants with a history of *in utero* exposure to ARBs should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as 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. Neither losartan nor the active metabolite can be removed by hemodialysis.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and fetus to unnecessary hazard including fetal or neonatal jaundice, thrombocytopenia and possibly other adverse experiences which have occurred in the adult. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

<u>Animal data</u>
Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, which include decreased body weight, mortality and/or renal toxicity. Significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on pharmacokinetic assessments, these findings are attributed to drug exposure in late gestation and during lactation.

7.1.2 Breast-feeding

It is not known whether losartan or its active metabolite are excreted in human milk, but significant levels of both of these compounds have been found in the milk of lactating rats. Thiazides appear in human milk. Because many drugs are excreted in human milk and because of their potential for affecting the nursing infant adversely, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7.1.3 Pediatrics

Pediatrics (<18 years of age): Losartan Potassium and Hydrochlorothiazide Tablets have not been studied in children, therefore use in this age group is not recommended.

7.1.4 Geriatrics

Geriatrics (>65 years of age): No overall differences in safety were observed between elderly patients and younger patients, but appropriate caution should nevertheless be used when prescribing to the elderly, as increased vulnerability to drug effect is possible in this patient population. (see 8 ADVERSE REACTIONS).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Losartan Potassium and Hydrochlorothiazide Tablets have been evaluated for safety in 2498 patients treated for essential hypertension. Of these, 1088 were treated with Losartan Potassium and Hydrochlorothiazide Tablets monotherapy in controlled clinical trials. In open studies, 926 patients were treated with Losartan Potassium and Hydrochlorothiazide Tablets for a year or more.

The following potentially serious adverse reactions have been reported rarely with Losartan Potassium and Hydrochlorothiazide Tablets in controlled clinical trials: syncope, hypotension.

In controlled clinical trials, discontinuations of therapy due to clinical adverse experiences occurred in 2.4% and 2.1% of patients treated with Losartan Potassium and Hydrochlorothiazide Tablets and placebo, respectively.

8.2 Clinical Trial Adverse Reactions

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

In these double-blind controlled clinical trials, the following adverse reactions reported with losartan potassium - hydrochlorothiazide in ≥1% of patients, regardless of drug relationship:

Table 2 - Adverse Reactions Reported with Losartan Potassium-Hydrochlorothiazide Occurring in ≥1% of Patients

	Losartan Potassium – Hydrochlorothiazide (n=1088)	Losartan Alone (n=655)	Hydrochlorothiazide (n=272)	Placebo (n=187)
Body as a Whole				
Abdominal pain	1.3	0.9	1.8	1.1
Asthenia/fatigue	3.1	2.9	5.1	3.7
Edema/swelling	1.2	0.6	2.9	1.6
Cardiovascular				
Palpitation	1.6	1.5	1.1	0
Digestive				
Diarrhea	1.6	1.8	0.4	2.1
Nausea	1.5	1.2	0	2.1
Musculoskeletal				
Back pain	2.9	1.1	0	0.5
Nervous/Psychiatric				
Dizziness	5.8	3.7	3.7	3.2
Headache	8.0	10.5	14.0	15.0
Respiratory				
Bronchitis	1.1	1.2	0.4	1.6
Cough	2.2	2.1	1.1	2.1
Influenza	1.2	0.2	0.7	0.5
Pharyngitis	1.2	0.8	1.8	1.6
Sinusitis	1.0	0.9	2.2	0.5
Upper respiratory infection	5.8	4.6	5.5	4.8
Skin				
Rash	1.3	0.5	1.5	0.5

In these controlled clinical trials for essential hypertension, dizziness was the only adverse experience, occurring in more than 1% of cases, that was reported as drug-related, and that occurred at a greater incidence in losartan potassium - hydrochlorothiazide-treated (3.3%) than placebo-treated (2.1%) patients.

Severe Hypertension (SiDBP ≥110 mmHg): The adverse experience profile for patients with severe hypertension (SiDBP ≥110 mmHg) treated with losartan/hydrochlorothiazide as initial therapy was similar to the adverse experience profile in patients treated with losartan

monotherapy at the time of first dose, at 4 weeks of therapy, and at 6 weeks of therapy. Additionally, the adverse experience rates for hypotension, syncope, dizziness, and increased serum creatinine (all of which are signs and symptoms of hypoperfusion) did not differ between the treatment groups.

Hypertensive patients with a history of cough: In an 8-week controlled study of the incidence of cough in hypertensive patients with a history of cough during ACE inhibitor therapy, the incidence of cough reported by patients receiving losartan potassium or hydrochlorothiazide was similar and was significantly less than in patients rechallenged with an ACE inhibitor. In addition, an overall analysis of double-blind clinical trials in 4131 patients revealed that the incidence of spontaneously reported cough in patients treated with losartan potassium monotherapy (n=2085; 3.1%) or losartan potassium and hydrochlorothiazide (n=858; 2.6%) was similar to that of patients treated with placebo (n=535; 2.6%) or hydrochlorothiazide alone (n=271; 4.1%), whereas the incidence with ACE inhibitors (n=239) was 8.8%.

8.3 Less Common Clinical Trial Adverse Reactions

In double-blind, controlled clinical trials with losartan potassium alone, the following adverse experiences were reported at an occurrence rate of less than 1%, regardless of drug relationship:

Cardiovascular: orthostatic effects

Ear/Nose/Throat: epistaxis, tinnitus

Gastrointestinal: constipation

General: malaise

Neurologic: somnolence, vertigo

Skin: rash

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

Clinical Trial Findings

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Hyperkalemia: In controlled hypertensive trials with losartan monotherapy and Losartan Potassium and Hydrochlorothiazide Tablets, a serum potassium >5.5 mEq/L occurred in 1.5% and 0.7% of patients, respectively. However, no patient discontinued losartan or Losartan Potassium and Hydrochlorothiazide Tablets therapy due to hyperkalemia.

Serum Creatinine, Blood Urea Nitrogen (BUN): Minor increases in blood urea nitrogen (1.0%) and serum creatinine (1.0%) were observed in patients with essential hypertension treated with Losartan Potassium and Hydrochlorothiazide Tablets. More marked increases have also been reported and were more likely to occur in patients with bilateral renal artery stenosis (see 7

WARNINGS AND PRECAUTIONS).

Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1 percent of patients with essential hypertension treated with losartan potassium alone. In clinical studies, no patient discontinued taking losartan potassium alone due to increased BUN or serum creatinine.

No other adverse experiences have been reported with Losartan Potassium and Hydrochlorothiazide Tablets, which have not been reported with losartan or hydrochlorothiazide individually.

8.5 Post-Market Adverse Reactions

The following additional adverse reactions have been reported in post-marketing experience with Losartan Potassium and Hydrochlorothiazide Tablets and/or in clinical trials or post-marketing use with the individual components:

Blood and Lymphatic System Disorders: Thrombocytopenia, anemia, aplastic anemia, hemolytic anemia, leukopenia, and agranulocytosis.

Cardiac Disorders: Palpitation, tachycardia.

Eye Disorders: Xanthopsia, transient blurred vision.

Gastrointestinal Disorders: Dyspepsia, abdominal pain, gastric irritation, cramping, diarrhea, constipation, nausea, vomiting, pancreatitis, sialoadenitis.

General Disorders and Administration Site Conditions: Chest pain, edema/swelling, malaise, fever, weakness.

Hepatobiliary Disorders: Hepatitis, jaundice (intrahepatic cholestatic jaundice).

Immune System Disorders: Anaphylactic reactions, angioedema (including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, and/or tongue and pharynx, requiring therapeutic intervention in some cases) has been reported rarely in patients treated with losartan. Some patients previously experienced angioedema with ACE inhibitors.

Investigations: Liver function abnormalities.

Metabolism and Nutrition Disorders: Anorexia, hyperglycemia, hyperuricemia, electrolyte imbalance including hyponatremia and hypokalemia.

Musculoskeletal and Connective Tissue Disorders: Back pain, muscle cramps, muscle spasm,

myalgia, arthralgia.

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

- 122 additional cases (95% CI, from 112 to 133 additional cases) of SCC per 1000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 3 observational studies);
- 31 additional cases (95% CI, from 24 to 37 additional cases) of BCC per 1000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 2 observational studies).

Nervous System Disorders: Dysgeusia, headache, migraine, paraesthesias.

Psychiatric Disorders: Insomnia, restlessness.

Renal and Urinary Disorders: Glycosuria, renal dysfunction, interstitial nephritis, renal failure.

Reproductive System and Breast Disorders: Erectile dysfunction/impotence.

Respiratory, Thoracic and Mediastinal Disorders: Cough, nasal congestion, pharyngitis, sinus disorder, upper respiratory infection, respiratory distress, including pneumonitis, pulmonary edema and Adult Respiratory Distress Syndrome have been reported rarely in post-marketing experience. Acute respiratory distress has been reported in very rare instances (see 7 WARNINGS AND PRECAUTIONS, Respiratory).

Skin and Subcutaneous Tissue Disorders: Rash, pruritus, purpura (including Henoch-Schoenlein purpura), toxic epidermal necrolysis, urticaria, erythroderma, photosensitivity, cutaneous lupus erythematosus.

Vascular Disorders: Dose-related orthostatic effects, necrotizing angiitis (vasculitis) (cutaneous vasculitis).

Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Concomitant use of angiotensin receptor antagonists (ARBs) –including APO-LOSARTAN/HCTZ - or of angiotensin-converting-enzyme inhibitors (ACEIs) with aliskiren-containing drugs in

patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR <60 mL/min/1.73m^2) is contraindicated (see 7 WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal).

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/Common name	Source of Evidence	Effect	Clinical comment
Agents Increasing Serum Potassium	T	Concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium, or other drugs that may increase serum potassium (e.g., trimethoprim- containing products) may lead to increases in serum potassium.	Since losartan decreases the production of aldosterone, potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium when losartan therapy is instituted. Potassium-containing salt substitutes or other drugs that may increase serum potassium should also be used with caution. Concomitant thiazide diuretic use may attenuate any effect that losartan may have on serum potassium.
Alcohol, barbiturates, or narcotics	C	Potentiation of orthostatic hypotension may occur.	Avoid alcohol, barbiturates or narcotics, especially with initiation of therapy.
Amphotericin B	T	Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics	Monitor serum potassium level.
Antidiabetic agents	CT	Thiazide-induced	Monitor glycemic control,

Proper/Common name	Source of Evidence	Effect	Clinical comment
e.g.: • CT insulin • oral hypoglycemic		hyperglycemia may compromise blood sugar control. Depletion of serum potassium augments glucose intolerance	supplement potassium if necessary, to maintain potassium levels, and adjust diabetes medications as required.
Antihypertensive drugs	CT	Hydrochlorothiazide may potentiate the action of other antihypertensive drugs (e.g., guanethidine, methyldopa, betablockers, vasodilators, calcium channel blockers, ACEI, ARB, and direct renin inhibitors).	
Antineoplastic drugs, including • cyclophosphamide • methotrexate	C	Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.	Hematological status should be closely monitored in patients receiving this combination. Dose adjustment of cytotoxic agents may be required.
Bile acid sequestrants, e.g.: • cholestyramine • Colestipol Resins	CT	Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.	Give thiazide 2-4 hours before or 6 hours after the bile acid sequestrant. Maintain a consistent sequence of administration. Monitor blood pressure, and increase dose of thiazide, if necessary.
Calcium and vitamin D supplements	C	Thiazides decrease renal excretion of calcium and increase calcium release from bone.	Monitor serum calcium, especially with concomitant use of high doses of calcium supplements. Dose reduction or withdrawal of calcium and/or vitamin D

Proper/Common name	Source of Evidence	Effect	Clinical comment
			supplements may be necessary.
Carbamazepine	C	Carbamazepine may cause clinically significant hyponatremia. Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Corticosteroids, and adrenocorticotropic hormone (ACTH) or Glycyrrhizin (found in liquorice)	T	Intensified electrolyte depletion, particularly hypokalemia, may occur	Monitor serum potassium, and adjust medications, as required.
Digoxin	CT	Thiazide-induced electrolyte disturbances may predispose to digitalis-induced arrhythmias.	In 9 healthy volunteers, when a single oral dose of 0.5 mg digoxin was administered to patients receiving losartan for 11 days, digoxin AUC and digoxin C_{max} ratios, relative to placebo, were found to be 1.06 (90% C.I. 0.98–1.14) and 1.12 (90% C.I. 0.97–1.28), respectively. The effect of losartan on steady-state pharmacokinetics of cardiac glycosides is not known.
Drugs that alter GI motility, i.e.: • anti- cholinergic agents, such as atropine and; • prokinetic agents, such as metoclopramide, domperidone	CT, T	Bioavailability of thiazide diuretics may be increased by anticholinergic agents due to a decrease in gastrointestinal motility and gastric emptying. Conversely, prokinetic drugs may decrease the bioavailability of thiazide diuretics.	Dose adjustment of thiazide may be required.
Diuretics	CT	Patients on diuretics, and	The possibility of

Proper/Common name	Source of Evidence	Effect	Clinical comment
		especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with losartan potassium.	symptomatic hypotension with losartan potassium can be minimized by discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with losartan potassium.
Dual blockage of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs or aliskiren-containing drugs	T	Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs or aliskiren-containing drugs is contraindicated in patients with diabetes and/or renal impairment, and is not recommended in any other patients, as adverse outcomes cannot be excluded.	See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS).
Drugs Affecting Cytochrome P450 System	CT	Rifampin, an inducer of drug metabolism, decreases the concentrations of the active metabolite of losartan. In humans, two inhibitors of P450 3A4 have been studied. Ketoconazole did not affect the conversion of losartan to the active metabolite after intravenous administration of losartan, and erythromycin had no clinically significant effect after oral losartan administration. Fluconazole, an inhibitor of P450 2C9, decreased active metabolite concentration. The pharmacodynamic consequences of	

Proper/Common name	Source of Evidence	Effect	Clinical comment
		concomitant use of losartan and inhibitors of P450 2C9 have not been examined. When losartan was administered to 10 healthy male volunteers as a single dose in steady-state conditions of phenobarbital, a cytochrome P450 inducer, losartan AUC, relative to baseline, was 0.80 (90% C.I. 0.72–0.88), while AUC of the active metabolite, E-3174, was 0.80 (90% C.I. 0.78–0.82). When losartan was administered to 8 healthy male volunteers as a single dose in steady-state conditions of cimetidine, a cytochrome P450 inhibitor, losartan AUC, relative to baseline, was 1.18 (90% C.I. 1.10–1.27), while AUC of the active metabolite, E-3174, was 1.00 (90% C.I. 0.92–1.08).	
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 Salts	CT	As with other drugs which	Lithium generally should

Proper/Common name	Source of Evidence	Effect	Clinical comment
		eliminate sodium, lithium clearance may be reduced in the presence of losartan. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be administered with losartan.	not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.
Nonsteroidal anti-inflammatory drugs (NSAID) Including • Cyclooxygenase-2 Inhibitors	CT	In some patients, the administration of a non-steroidal anti-inflammatory agent including a selective cyclooxygenase-2 inhibitor can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when APO-LOSARTAN/HCTZ and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained. Non-steroidal anti-inflammatory drugs (NSAIDs) including indomethacin and selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs. Therefore, the antihypertensive effect of angiotensin II receptor antagonists or ACE inhibitors may be	If combination use is necessary, monitor renal function, serum potassium, and blood pressure closely. Dose adjustments may be required.

Proper/Common name	Source of Evidence	Effect	Clinical comment
		attenuated by NSAIDs including selective COX-2 inhibitors. In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with NSAIDS, including selective COX-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function. Cases of acute renal failure, usually reversible, have been reported. Therefore, this combination should be administered with caution in this patient population.	
Pressor Amines, e.g.: • norepinephrine	T	In the presence of diuretics possible decreased response to pressor amines may be seen but not sufficient to preclude their use.	
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	C	Thiazide drugs may increase the responsiveness of some	

Proper/Common name	Source of Evidence	Effect	Clinical comment
curare family, e.g.: • d-tubocurare		skeletal muscle relaxants, such as curare derivatives	
Topiramate	CT	Additive hypokalemia. Possible thiazide-induced increase in topiramate serum concentrations.	Monitor serum potassium and topiramate levels.
Warfarin	T	Losartan administered for 7 days did not affect the pharmacokinetics or pharmacodynamic activity of a single dose of warfarin.	The effect of losartan on steady-state pharmacokinetics of warfarin is not known.

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

9.5 Drug-Food Interactions

Grapefruit juice contains components that inhibit CYP 450 enzymes and may lower the concentration of the active metabolite of losartan which may reduce the therapeutic effect of of Losartan Potassium and Hydrochlorothiazide.Tablets Consumption of grapefruit juice should be avoided while taking Losartan Potassium and Hydrochlorothiazide Tablets.

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

APO-LOSARTAN/HCTZ combines the actions of losartan potassium, an angiotensin II receptor antagonist, and that of a thiazide diuretic, hydrochlorothiazide.

Losartan: Losartan potassium antagonizes angiotensin II by blocking the angiotensin type one (AT_1) receptor.

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin system. Its effects include vasoconstriction and the stimulation of aldosterone secretion by the adrenal cortex.

Losartan, and its active metabolite, E-3174, block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to AT_1 receptors found in many tissues, including vascular smooth muscle. A second type of angiotensin II receptor has been identified as the AT_2 receptor, but it plays no known role in cardiovascular homeostasis to date. Both losartan and its active metabolite do not exhibit any agonist activity at the AT_1 receptor, and have much greater affinity, in the order of 1000-fold, for the AT_1 receptor than for the AT_2 receptor. *In vitro* binding studies indicate that losartan itself is a reversible, competitive antagonist at the AT_1 receptor, while the active metabolite is 10 to 40 times more potent than losartan, and is a reversible, non-competitive antagonist of the AT_1 receptor.

Neither losartan nor its active metabolite inhibits angiotensin converting enzyme (ACE), also known as kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

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.

10.2 Pharmacodynamics

Losartan: Losartan inhibits the pressor effect of angiotensin II. A dose of 100 mg inhibits this effect by about 85% at peak, with 25 to 40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2 to 3 fold rise in plasma renin activity, and a consequent rise in angiotensin II plasma concentration, in hypertensive patients.

Maximum blood pressure lowering, following oral administration of a single dose of losartan, as seen in hypertensive patients, occurs at about 6 hours.

In losartan-treated patients during controlled trials, there was no meaningful change in heart rate.

There is no apparent rebound effect after abrupt withdrawal of losartan therapy.

Black hypertensive patients show a smaller average blood pressure response to losartan monotherapy than other hypertensive patients.

Hydrochlorothiazide: 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.

Losartan – Hydrochlorothiazide: The components of Losartan Potassium and Hydrochlorothiazide Tablets have been shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone.

The antihypertensive effect of Losartan Potassium and Hydrochlorothiazide Tablets are sustained for a 24-hour period. In clinical studies of at least one year's duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of Losartan Potassium and Hydrochlorothiazide Tablets had no clinically significant effect on heart rate.

10.3 Pharmacokinetics

Absorption:

Losartan
Following oral administration, losartan is well absorbed, with systemic bioavailability of losartan approximately 33%. About 14% of an orally-administered dose of losartan is converted to the active metabolite, although about 1% of subjects did not convert losartan efficiently to the active metabolite.

Mean peak concentrations of losartan occur at about one hour, and that of its active metabolite at about 3 to 4 hours. Although maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times greater than that of losartan.

Hydrochlorothiazide

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

Distribution:

Losartan
Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2% respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

The volume of distribution of losartan is about 34 liters, and that of the active metabolite is about 12 liters.

Hydrochlorothiazide
Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Metabolism:

Losartan
Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite, E-3174, that is responsible for most of the angiotensin II receptor antagonism that follows oral losartan administration.

Various losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, E-3174, several inactive metabolites are formed. *In vitro* studies indicate that the cytochrome P450 isoenzymes 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites.

Hydrochlorothiazide
Hydrochlorothiazide is not metabolized.

Elimination:
Losartan
The terminal half-life of losartan itself is about 2 hours, and that of the active metabolite, about 6 to 9 hours. The pharmacokinetics of losartan and this metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily administration.

Total plasma clearance of losartan is about 600 mL/min, with about 75 mL/min accounted for by renal clearance. Total plasma clearance of the active metabolite is about 50 mL/min, with about 25 mL/min accounted for by renal clearance. Both biliary and urinary excretion contribute substantially to the elimination of losartan and its metabolites.

Following oral ^{14}C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of ^{14}C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

Hydrochlorothiazide

Hydrochlorothiazide is eliminated rapidly by the kidney. The plasma half-life is 5.6 to 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.

Special Populations and Conditions

- **Patients with mild to moderate alcoholic cirrhosis**

Following oral administration of losartan potassium to patients with mild to moderate alcoholic cirrhosis, AUC of losartan and its active metabolite, E-3174, were about 5-times and 1.7-times greater, respectively, than in young healthy male volunteers. Compared to these normal subjects, the total plasma clearance of losartan in patients with hepatic insufficiency was about 50% lower and the oral bioavailability was about 2-times higher.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 30°C). Keep container tightly closed. Protect from light.

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special requirements for use or handling of this product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

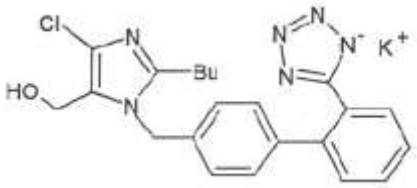
Drug Substance

Proper name: losartan potassium

Chemical name: 2-butyl-4-chloro-1-[[2'-(1H¬ -tetrazol-5-yl) [1,1'-biphenyl]-4¬-yl]methyl]-1H-imidazole-5--methanol monopotassium salt.

Molecular formula and Molecular mass: $C_{22}H_{22}ClKN_6O$ 461.01 g/mol

Structural formula:



Physicochemical properties: Losartan potassium is a white to off-white free-flowing crystalline powder. It is freely soluble in water, soluble in alcohol, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.

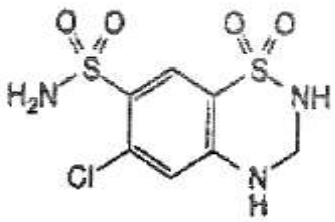
Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

Proper name: hydrochlorothiazide

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

Molecular formula and Molecular mass: $C_7H_8ClN_3O_4S_2$ 297.74 g/mol

Structural formula:



Physicochemical properties: Hydrochlorothiazide is a white, or practically white, crystalline powder. It is slightly soluble in water, but freely soluble in sodium hydroxide solution.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Hypertension

Table 4 - Summary of Patient Demographics for Double-Blind Clinical Trial in Adult Patients with Severe Hypertension

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age in years (Range)	Sex
P232	A randomized, double-blind, multicenter, clinical study in patients with severe hypertension	Oral administration Treatment groups: <u>At 4 weeks:</u> Patients on losartan/hydrochlorothiazide 50 mg/12.5 mg Patients on losartan 50 mg titrated to 100 mg <u>At 6 weeks</u> Patients on losartan/hydrochlorothiazide 50 mg/12.5 mg titrated to losartan/hydrochlorothiazide 100 mg/25 mg Patients on losartan 50 mg titrated to 100 mg and then to 150 mg	585	53 (22-87)	Male: 321 Female: 264

The safety and efficacy of Losartan Potassium and Hydrochlorothiazide Tablets as initial therapy for severe hypertension (baseline mean SiDBP ≥110 mmHg confirmed on 2 separate occasions) was demonstrated in a six-week double-blind, randomized, multicenter study of 585 patients with severe hypertension. The primary endpoint was a comparison at 4 weeks of patients who

achieved goal diastolic blood pressure (trough SiDBP <90 mmHg) on losartan/hydrochlorothiazide 50 mg/12.5 mg versus patients on losartan 50 mg titrated to 100 mg as needed to reach goal diastolic blood pressure. The secondary endpoint was a comparison at 6 weeks of patients who achieved goal diastolic blood pressure on losartan/hydrochlorothiazide 50 mg/12.5 mg titrated as needed to losartan/hydrochlorothiazide 100 mg/25 mg versus patients on losartan 50 mg titrated to 100 mg and then to 150 mg. In a post-hoc analysis, patients who achieved goal systolic blood pressure (trough SiSBP <140 mmHg) were compared for the 2 treatment groups at 4 and 6 weeks.

Table 5 - Results of Losartan/Hydrochlorothiazide Efficacy Compared to Losartan in Double-Blind, Multicenter Study in Patients with Severe Hypertension

Primary Endpoints	Patients who received losartan/hydrochlorothiazide 50 mg/12.5 mg combination therapy	Patients on losartan 50 mg titrated to 100 mg as needed	p-value
Comparison at 4 weeks of patients who achieved goal diastolic blood pressure (trough SiDBP <90 mmHg)	17.6%	9.4%	0.007

After 4 weeks of therapy, more patients who received losartan/hydrochlorothiazide 50 mg/12.5 mg combination therapy reached target diastolic blood pressure than those who received losartan 50 or 100 mg monotherapy (17.6% versus 9.4%, respectively; p=0.007). Similarly, after 6 weeks of therapy, more patients who received the combination regimen reached target diastolic blood pressure than those who received the monotherapy regimen (29.8% versus 12.5%, respectively; p<0.001). Additionally, more patients achieved goal systolic blood pressure on combination therapy versus monotherapy at each time point (week 4: 24.5% versus 11.9%, respectively, p<0.001; week 6: 36.9% versus 14.1%, respectively, p<0.001). The safety and tolerability of losartan/hydrochlorothiazide for patients with severe hypertension were comparable to losartan monotherapy at the time of first dose, at 4 weeks of therapy, and at 6 weeks of therapy.

14.2 Comparative Bioavailability Studies

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study of APO-LOSRATAN/HCTZ Tablets, 100 mg/25 mg (APOTEX INC.) and HYZAAR® DS Tablets, 100 mg/25 mg (Merck Frosst Canada Ltd.) was conducted in 24 healthy, Asian male subjects under fasting conditions. Comparative bioavailability data from 23 subjects that were included in the statistical analysis are presented in the following tables:

Summary Tables of the Comparative Bioavailability Data

Losartan (1 x 100 mg losartan potassium /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)	1158.24 1224.30 (37)	1178.42 1250.76 (36)	98.3	92.5 – 104.4
AUC_I (ng·h/mL)	1179.42 1244.74 (36)	1201.03 1272.71 (36)	98.2	92.5 – 104.2
C_{max} (ng/mL)	782.55 876.85 (57)	744.10 848.05 (59)	105.2	89.7 – 123.4
T_{max} [3] (h)	1.00 (0.50 – 2.00)	1.17 (0.67 – 2.66)		
$T_{1/2}$ [4] (h)	1.99 (25)	1.98 (21)		

[1] APO-LOSARTAN/HCTZ (losartan potassium and hydrochlorothiazide) Tablets, 100mg/25mg (APOTEX INC.)
[2] HYZAAR® DS (losartan potassium and hydrochlorothiazide) Tablets, 100mg/25mg (Merck Frosst Canada Ltd.)
[3] Expressed as median (range) only
[4] Expressed as mean (CV %) only

Hydrochlorothiazide (1 x 100 mg losartan potassium /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)	1067.30 1092.05 (24)	1085.86 1129.08 (30)	98.3	92.8 – 104.1

Hydrochlorothiazide (1 x 100 mg losartan potassium /25 mg hydrochlorothiazide) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_I (ng·h/mL)	1139.47 1168.85 (25)	1156.71 1205.40 (31)	98.5	93.1 – 104.2
C_{max} (ng/mL)	150.17 153.14 (20)	150.20 155.22 (27)	100.0	92.3 – 108.3
T_{max} [3] (h)	2.33 (1.00 – 3.00)	2.33 (1.33 – 4.00)		
$T_{1/2}$ [4] (h)	10.01 (14)	9.62 (12)		

[1] APO-LOSARTAN/HCTZ (losartan potassium and hydrochlorothiazide) Tablets, 100mg/25mg (APOTEX INC.)
[2] HYZAAR® DS (losartan potassium and hydrochlorothiazide) Tablets, 100mg/25mg (Merck Frosst Canada Ltd.)
[3] Expressed as median (range) only
[4] Expressed as mean (CV %) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

The oral LD_{50} of losartan potassium in male mice is 2248 mg/kg (6744 mg/m^2). Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg (3000 mg/m^2) and 2000 mg/kg (11,800 mg/m^2), respectively (see Table 6).

Table 6 - Acute Toxicity (Losartan)

Route	Species	Sex	LD_{50} Values	Maximum Tolerated Dose
Intraperitoneal	Mouse	Female Male	- -	>160 mg/kg - <400 mg/kg

	Rat	Female Male	- -	>100 mg/kg - <200 mg/kg
Intraperitoneal study with active metabolite, E-3174 (L-158,641) Oral	Mice	Female	441.3 mg/kg	-
	Mouse	Female Male	2248 mg/kg -	500 mg/kg - 1000 mg/kg
	Rat	Female Male	- -	~1000 mg/kg
	Dog	Female Male	- -	>160 mg/kg - <320 mg/kg

Chronic Toxicity

The toxic potential of losartan potassium was evaluated in a series of repeated-dose oral toxicity studies of up to three months in monkeys and up to one year in rats and dogs. The toxic potential of losartan potassium -hydrochlorothiazide was evaluated in repeated-dose oral toxicity studies for up to six months in rats and dogs (see Table 7).

Table 7 - Chronic Toxicity

a) Oral Administration (Losartan)

Species	Duration	No. of Animals/Group	Dose mg/kg/day	Effects
Rat (Sprague-Dawley Crl:CD (SD) BR)	5 weeks	12 M + 12 F	0, 15, 45, 135	**Mid- and high-dose males:** slight decrease in body weight gain. **High-dose males:** slight decrease in red blood cell count. **Males all dosage levels:** decrease in heart weight. **High-dose groups:** slight increases in BUN; focal gastric lesions. **Mid- and high-dose groups:**

Species	Duration	No. of Animals/Group	Dose mg/kg/day	Effects
				slight increase in serum chloride. **All dosage levels:** slight increases in serum glucose.
Rat (Sprague-Dawley Crl:CD (SD) BR)	14 weeks	17 M + 17 F	0, 15, 45, 135	**Mid- and high-dose males:** slight decreases in the rate of body weight gain; increase in BUN; grossly evident focal lesions in the gastric mucosa. **High-dose males:** slight decreases in RBC parameters; increase in cholesterol; alkalinization of the urine. **Males all dosage levels:** decrease in heart weight. **High-dose females:** increase in BUN. **High-dose groups:** increase in sodium, chloride, and/or potassium.
Rat (Sprague-Dawley Crl:CD (SD) BR)	53 weeks	30 M + 30 F	0, 15, 45, 135	**High-dose males:** slight decrease in erythrocyte parameters (week 25); slight increase in serum phosphorus (week 25); focal erosions of the glandular mucosa of the stomach (also noted in one low-dose male). **Mid- and high-dose males:** increases in BUN; decreased heart weight and heart weight relative to brain weight (at terminal necropsy); very slight hyperplasia of juxtaglomerular

Species	Duration	No. of Animals/Group	Dose mg/kg/day	Effects
				cells (at interim necropsy). **High-dose females:** increases in BUN; decreased absolute heart weight and heart weight relative to brain weight (at interim necropsy). **Mid- and high-dose females:** slight decreases in food consumption; slight decrease in erythrocyte parameters (high-dose week 39, mid-dose weeks 39 and 51). **All females:** decreases in serum triglycerides. **All groups:** decreases in urinary protein; very slight juxtaglomerular cell hyperplasia; lower incidence and severity of spontaneous chronic nephritis. **Mid- and high-dose groups:** postdose salivation (weeks 11 and 20). **High-dose groups:** decrease in body weight gain.
Dog (Beagle)	5 weeks	4 M + 4 F	0, 15, 45, 135	**All groups:** adverse gastrointestinal effects (emesis, abnormal stools, positive fecal occult blood). No treatment-related mortality or change in body weight, food consumption, urinalysis, serum biochemistry, or hematology parameters. No treatment-

Species	Duration	No. of Animals/Group	Dose mg/kg/day	Effects
				related postmortem findings.
Dog (Beagle)	14 weeks	5 M + 5 F	0, 5, 25, 125	**High-dose males:** slight decrease in erythroid parameters. **High-dose groups:** gastrointestinal toxicity (emesis, abnormal stool colour and consistency, fecal occult blood); slight decrease in heart weight. **Mid-dose groups:** excessive salivation and emesis. No treatment-related effects on body weight, food consumption, clinical pathology, electrocardiography, physical exams, ophthalmoscopic exams, or gross and microscopic postmortem findings.
Dog (Beagle)	53 weeks	8 M + 8 F	0, 5, 25, 125	**High-dose groups:** predose and/or postdose hypersalivation; occasional emesis and change in stool consistency and colour. **Mid- and high-dose groups:** sporadic, isolated increases in serum ALT. No treatment-related alteration in body weight or food consumption, ophthalmologic findings or changes in electrocardiographic, hematologic, or urinalysis parameters. No treatment-related mortality.

Species	Duration	No. of Animals/Group	Dose mg/kg/day	Effects
Monkey [Rhesus (Macaca mulatta)]	14 weeks	4 M + 4 F	0, 20, 100, 300	**High-dose group:** slight decrease in erythrocyte parameters (weeks 8 and 11); slight decrease in BUN (week 11); increase in angiotensin II levels (24 hours postdose); tarry intestinal contents and small depressed, reddened foci in the stomach and/or small intestine (at necropsy). No treatment-related physical signs, mortality, or changes in food consumption, body weight, ophthalmic exams, or urinalysis. No treatment-related changes in organ weights.

b) Oral Administration (Losartan – Hydrochlorothiazide)

Species	Duration	No. of Animals/Group	Dose mg/kg/day	Effects
Rat	27 weeks	20 M + 20 F	0 and 135 losartan; 33.75 HCTZ; 15/3.75, 45/11.25, 135/33.75 losartan/ HCTZ.	No treatment-related deaths. Slightly decreased body weight gain in losartan and high and mid-dose combination groups. Mildly decreased red cell count sometimes associated with decreased hemoglobin and hematocrit. Increased serum urea concentration. Slight variations in serum electrolytes attributed to the pharmacodynamics of the compounds. Mild increase in juxtaglomerular apparatus hyperplasia at high dose. Coadministration of losartan and

Species	Duration	No. of Animals/Group	Dose mg/kg/day	Effects
				hydrochlorothiazide did not alter systemic exposure to losartan or E-3174†.
Dog	27 weeks	4 M + 4 F	0 and 135 losartan; 31.25 HCTZ; 5/1.25, 25/6.25, 125/31.25 losartan/ HCTZ.	Adverse, clinically evident, effects limited to occasional emesis, excessive salivation and/or stool abnormalities. No gross or histological evidence of gastrointestinal toxicity. Slight alterations in serum and urine electrolytes attributed to the pharmacodynamic properties of the compounds. Coadministration of losartan and hydrochlorothiazide did not alter systemic exposure to losartan or E-3174†.

† E-3174 (L-158,641): Primary pharmacologically active metabolite of losartan.
HCTZ = hydrochlorothiazide

c) I.V. Administration (Losartan)

Species	Duration	No. of Animals/Group	Dose mg/kg/day	Effects
Rats (Sprague-Dawley Crl:CD (SD) BR)	16 days	15 M + 15 F	0, 0.92, 4.59, 9.17	**High-dose males:** slight decreases in erythrocyte count and hematocrit. No treatment-related deaths, clinical signs, or changes in body weight gain, food consumption, ophthalmology, serum biochemistry, or urinalysis.

Species	Duration	No. of Animals/Group	Dose mg/kg/day	Effects
Rats (Sprague-Dawley Crl:CD (SD) BR)	15 days	15 M + 15 F	0, 1, 5, 10†	**Mid- and high-dose males:** slight decrements in body weight. **All groups:** slight decrease in heart weight; slight decrease in mean terminal body weight. No treatment-related effects on food consumption, ophthalmologic exams, hematology, serum biochemical determinations, or urinalysis.
Dogs (Beagle)	17 days	4 M + 4 F	0, 0.92, 4.59, 9.17	No drug-related deaths, no drug-related clinical signs, and no drug-related changes in body weight gain, food consumption, ophthalmology, electrocardiography, hematology, serum biochemistry and urinalysis. No treatment-related changes in organ weight or gross microscopic changes.
Dogs (Beagle)	15 days	4 M + 4 F	0, 1, 5, 10†	No drug-related deaths, no drug-related clinical signs, and no drug- related changes in body weight gain, food consumption, ophthalmology, electrocardiography, hematology, serum biochemistry and urinalysis. No treatment-related changes in organ weight or gross microscopic changes.

† E-3174 (L-158,641): Primary pharmacologically active metabolite of losartan

Carcinogenicity:

Losartan: Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 weeks (maximum dose of 270 mg/kg/day) and 92 weeks (maximum dose of 200 mg/kg/day), respectively.

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.

Genotoxicity:

Losartan: Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays. In addition, there was no evidence of direct genotoxicity in the *in vitro* alkaline elution and *in vitro* chromosomal aberration assays. Similarly, there was no induction of chromosomal aberrations in bone marrow cells of male or female mice after the administration of toxic oral doses of up to 1500 mg/kg (4500 mg/m^2). In addition, the active metabolite E-3174 showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Losartan – Hydrochlorothiazide: Losartan potassium - hydrochlorothiazide was negative in the Ames microbial mutagenesis assay and the V-79 Chinese hamster lung cell mutagenesis assay. In addition, there was no evidence of direct genotoxicity in the *in vitro* alkaline elution assay in rat hepatocytes and *in vitro* chromosomal aberration assay in Chinese hamster ovary cells at noncytotoxic concentrations.

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

Reproductive and Developmental Toxicology:

Losartan: Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium up to approximately 150 and 300 mg/kg/day, respectively.

Losartan – Hydrochlorothiazide: Losartan potassium - hydrochlorothiazide administration had

no effect on the reproductive performance or fertility in male rats at dosage levels of up to 135 mg/kg/day of losartan in combination with 33.75 mg/kg/day of hydrochlorothiazide. These dosage levels provided respective plasma concentrations (AUC) for losartan, the active metabolite E-3174, and hydrochlorothiazide that were approximately 260-, 120-, and 50-fold greater than those achieved in man with 50 mg of losartan potassium in combination with 12.5 mg hydrochlorothiazide. In female rats, however, the coadministration of losartan potassium - hydrochlorothiazide (10 mg/2.5 mg/kg/day) induced a slight but statistically significant decrease in fecundity and fertility indices. Compared to plasma concentrations in man (see above) these dosage levels provided respective increases in plasma concentration (AUC) for losartan, the active metabolite E-3174, and hydrochlorothiazide of approximately 15-, 4-, and 5-fold.

Teratology

Losartan: Losartan potassium has been shown to produce adverse reactions in rat fetuses and neonates. The reactions include decreased body weight, mortality and/or renal toxicity. Pharmacokinetic evaluation of fetal plasma showed significant levels of losartan and its active metabolite, E-3174 (L-158,641), on Gestation Day 20 compared to negligible value on Gestation Day 15. In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on these findings, the fetal and neonatal effects of losartan potassium in rats are attributed to drug exposure in late gestation and during lactation.

Losartan – Hydrochlorothiazide: There was no evidence of teratogenicity in rats or rabbits treated with losartan potassium - hydrochlorothiazide. Fetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs in the F_1 generation, was observed when females were treated prior to and throughout gestation. As observed in studies with losartan alone, adverse fetal and neonatal effects, including decreased body weight and renal toxicity, also occurred when pregnant rats were treated with losartan potassium - hydrochlorothiazide during late gestation and/or lactation.

17 SUPPORTING PRODUCT MONOGRAPHS

1. HYZAAR® (losartan potassium and hydrochlorothiazide tablets, 50 mg / 12.5 mg and 100 mg / 12.5 mg) and HYZAAR® DS (losartan potassium and hydrochlorothiazide tablets, 100 mg / 25 mg), submission control 265018, Product Monograph, Organon Canada Inc. (November 2, 2022)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrAPO-LOSARTAN/HCTZ

Losartan Potassium and Hydrochlorothiazide Tablets

Read this carefully before you start taking **APO-LOSARTAN/HCTZ** 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 **APO-LOSARTAN/HCTZ**.

Serious Warnings and Precautions

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

What is APO-LOSARTAN/HCTZ used for?

APO-LOSARTAN/HCTZ is used in adults to lower high blood pressure.

How does APO-LOSARTAN/HCTZ work?

APO-LOSARTAN/HCTZ contains a combination of 2 drugs, losartan and hydrochlorothiazide:

- losartan is an angiotensin receptor blocker (ARB). 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 APO-LOSARTAN/HCTZ regularly even if you feel fine.

What are the ingredients in APO-LOSARTAN/HCTZ?

Medicinal ingredients: losartan potassium and hydrochlorothiazide.

Non-medicinal ingredients: Hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch and titanium dioxide. APO-LOSARTAN/HCTZ 50 mg/12.5 mg and 100 mg/25 mg also contain the carnauba wax and quinoline yellow aluminum lake.

Although APO-LOSARTAN/HCTZ contains potassium, this amount is too small to replace potassium supplements. If your doctor has prescribed potassium supplements, continue to follow their advice.

APO-LOSARTAN/HCTZ comes in the following dosage forms:

Tablets; 50 mg / 12.5 mg, 100 mg / 12.5 mg and 100 mg / 25 mg

Do not use APO-LOSARTAN/HCTZ if:

- you are allergic to losartan potassium and hydrochlorothiazide or any of the non-medicinal ingredients 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 difficulty urinating or produce no urine.
- you are already taking a blood pressure-lowering medicine that contains aliskiren (such as Rasilez) and you have diabetes or kidney disease.

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

- are allergic to any drug used to lower blood pressure, including angiotensin converting enzyme (ACE) inhibitors, or penicillin.
- are taking an ACE inhibitor.
- have narrowing of an artery or a heart valve.
- have had a heart attack or stroke.
- have recently received or are planning to get allergy shots for bee or wasp stings.
- have heart failure.
- have diabetes, liver or kidney disease.
- have lupus or gout.
- are on dialysis.
- 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"), or other drugs that may increase potassium levels (such as trimethoprim-containing products).
- are on a low-salt diet.
- 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.

- are pregnant, planning to become pregnant or think you are pregnant.
- are breastfeeding or plan to breastfeed.
- have had breathing or lung problems (including inflammation or fluid in the lungs) in the past following the use of medication containing hydrochlorothiazide. If you experience any severe shortness of breath or difficulty breathing after taking APO-LOSARTAN/HCTZ, stop the medication and seek medical attention immediately.

Other warnings you should know about:

Use of anesthesia: If you are about to have a surgery or dental procedure with anesthesia, be sure to tell your healthcare professional that you are taking APO-LOSARTAN/HCTZ.

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

While taking APO-LOSARTAN/HCTZ

- 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 of skin to sun and avoid indoor tanning. Always use sunscreen (SPF 30 or higher) and wear protective clothing when going outside.
- Talk to your healthcare professional 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.

Eye problems: Hydrochlorothiazide in APO-LOSARTAN/HCTZ can cause sudden eye disorders:
- **Choroidal effusion:** an abnormal building of liquid in your eye that may result in vision changes.
- **Myopia:** sudden nearsightedness or blurred vision.
- **Glaucoma:** an increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss.

If your vision changes, stop taking APO-LOSARTAN/HCTZ and seek immediate medical help. These eye disorders are related and can develop within hours to weeks of starting APO-LOSARTAN/HCTZ.

Testing and check-ups: During your treatment with APO-LOSARTAN/HCTZ, your healthcare professional may monitor:
- Your kidney function.
- Your blood pressure.
- The amount of electrolytes in your blood (such as potassium, sodium, calcium).

- Your liver function

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to APO-LOSARTAN/HCTZ. Dizziness, lightheadedness, 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.

Serious Drug Interactions
• Aliskiren-containing drugs if you have diabetes or kidney disease.

The following may also interact with APO-LOSARTAN/HCTZ:

- Other medications used to lower blood pressure, such as diuretics ("water pills").
- 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.
- Amphotericin B, an antifungal drug.
- Anticancer medications, such as cyclophosphamide and methotrexate.
- Antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), including citalopram, escitalopram, and sertraline.
- Antidiabetic medications, such as insulin and oral medicines.
- Bile acid resins used to lower cholesterol such as cholestyramine.
- Calcium or vitamin D supplements.
- Corticosteroids used to treat joint pain and swelling.
- Digoxin, a heart medication.
- Medications that slow down or speed up bowel function, such as atropine, metoclopramide, and domperidone.
- Medications used to treat epilepsy, such as carbamazepine and topiramate.
- Glycyrrhizin (found in liquorice).
- Gout medications, such as allopurinol and probenecid.
- Grapefruit juice (which should be avoided while taking APO-LOSARTAN/HCTZ).
- Lithium used to treat bipolar disease.
- Medicines may cause high blood pressure (adrenaline).
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling such as ibuprofen, naproxen, acetylsalicylic acid and celecoxib.
- Skeletal muscle relaxants used to relieve muscle spasms, such as tubocurare.
- Sympathomimetics which may be found in some decongestants, cough/cold, hay fever, sinus medicines.
- Potassium supplements, salt substitutes containing potassium or other drugs that may

increase serum potassium (e.g., trimethoprim-containing products).

How to take APO-LOSARTAN/HCTZ:

- Take APO-LOSARTAN/HCTZ exactly as prescribed.
- It is recommended to take your dose at about the same time everyday.
- APO-LOSARTAN/HCTZ can be taken with or without food, but it should be taken the same way each day. If APO-LOSARTAN/HCTZ causes upset stomach, take it with food or milk.

Usual dose:

Your healthcare professional has decided the best dose for you. The usual dose is 1 tablet of APO-LOSARTAN/HCTZ once daily.

The maximum dose is 1 tablet of APO-LOSARTAN/HCTZ (100 mg/25 mg) once daily.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-LOSARTAN/HCTZ, 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 the dose.

What are possible side effects from using APO-LOSARTAN/HCTZ?

These are not all the possible side effects you may have when taking APO-LOSARTAN/HCTZ. If you experience any side effects not listed here, tell your healthcare professional.
Side effects may include:

- constipation
- decreased appetite
- diarrhea
- enlargement of the glands in your mouth
- nausea
- upset stomach
- vomiting
- cramping
- seeing more of the colour yellow in your vision
- temporary blurred vision
- fatigue

- fever
- back or leg pain
- joint pain
- muscle cramps
- restlessness
- spasms and pain
- weakness
- dizziness
- headache
- pins and needles in your fingers
- change in taste
- erectile dysfunction/impotence
- reduced libido
- dry cough
- nasal congestion
- upper respiratory infections
- bleeding under the skin
- rash
- red patches on the skin
- hives
- itch
- bruising
- increased sensitivity to the sun
- a feeling of dizziness or lightheadedness due to a sudden drop in blood pressure when standing up quickly

APO-LOSARTAN/HCTZ can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Chest pain		√	
Edema: swelling of the hands or ankles	√		
Electrolyte imbalance: confusion, drowsiness, generally feeling unwell, irregular heartbeats, lack of energy, muscle pain or cramps, muscle		√	

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**	
twitching, muscle weakness			
Gout: red, tender, hot, swollen joints, fever, generally feeling unwell, fast heart rate		√	
Kidney Disorder: change in frequency of urination, fatigue, nausea, swelling of extremities, vomiting		√	
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.		√	
UNCOMMON			
Allergic Reaction: difficulty breathing or swallowing, hives, skin rash and swelling of the face, lips, throat or tongue			√
Anemia (decreased number of red blood cells): fatigue, loss of energy, shortness of breath, weakness		√	
High blood sugar: frequent urination, thirst, and hunger, sugar in the urine		√	
Liver Disorder: abdominal pain, dark urine, nausea, loss of appetite, vomiting, yellowing of the skin or eyes			√
Low Blood Pressure: dizziness, fainting, light-headedness may occur when you go from lying or sitting to standing up			√
Pancreatitis (inflammation of the pancreas): abdominal pain that lasts and gets worse when you lie down, nausea, vomiting			√
Tachycardia: Racing or irregular heart rate	√		
RARE			
Decreased White Blood Cells: aches, fatigue, fever, flu-like symptoms, infections, pains		√	
Rhabdomyolysis (breakdown of damaged muscle): dark brown urine, muscle pain that you cannot explain, muscle tenderness or weakness		√	
VERY RARE			

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	
Acute respiratory distress (inflammation of lung tissue or excess fluid in the lungs): severe shortness of breath or difficulty breathing, fever, weakness, and confusion			√
UNKNOWN FREQUENCY			
Decreased Platelets: bruising, bleeding, fatigue, weakness, small purple or red dots under the skin		√	
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 your eye): blind spots, eye pain, blurred vision			√
Toxic Epidermal Necrolysis (a severe skin reaction): redness, blistering an/or severe skin peeling, especially in mouth and eyes			√

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 APO-LOSARTAN/HCTZ at room temperature (15°C to 30°C). Keep container tightly closed. Protect from light.

- Keep out of reach and sight of children.

If you want more information about APO-LOSARTAN/HCTZ:

- 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.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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