PRODUCT MONOGRAPH

[Pr] ratio-LOSARTAN HCTZ

100 mg/25 mg
Losartan Potassium and Hydrochlorothiazide Tablets

Angiotensin II Receptor Antagonist and Diuretic

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
M1B 2K9

Date of Preparation:
January 31, 2012

Submission Control No: 152953

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION 3
SUMMARY PRODUCT INFORMATION 3
INDICATIONS AND CLINICAL USE 3
CONTRAINDICATIONS 3
WARNINGS AND PRECAUTIONS 4
ADVERSE REACTIONS 7
DRUG INTERACTIONS 10
DOSAGE AND ADMINISTRATION 12
OVERDOSAGE 13
ACTION AND CLINICAL PHARMACOLOGY 14
STORAGE AND STABILITY 17
DOSAGE FORMS, COMPOSITION AND PACKAGING 17

PART II: SCIENTIFIC INFORMATION 18
PHARMACEUTICAL INFORMATION 18
CLINICAL TRIALS 19
DETAILED PHARMACOLOGY 21
TOXICOLOGY 22
REFERENCES 31

PART III: CONSUMER INFORMATION 33

ratio-LOSARTAN HCTZ

Losartan Potassium and Hydrochlorothiazide Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Oral	Tablet and 100 mg/ 25 mg	D&C yellow 10, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and titanium dioxide. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

ratio-LOSARTAN HCTZ (losartan potassium and hydrochlorothiazide) is indicated for the treatment of essential hypertension in patients for whom combination therapy is appropriate.

ratio-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 CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

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 DOSAGE AND ADMINISTRATION).

Pediatrics (<18 years of age): No data are available.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Because of the hydrochlorothiazide component, ratio-LOSARTAN HCTZ is also contraindicated in patients with anuria, and in patients who are hypersensitive to other sulfonamide-derived drugs.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

When used in pregnancy, angiotensin receptor (AT1) blockers (ARB) can cause injury or even death of the developing fetus. When pregnancy is detected, ratio-LOSARTAN HCTZ should be discontinued as soon as possible (see WARNINGS AND PRECAUTIONS, Special Populations).

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.

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, a lower dose should be considered for

patients with hepatic impairment, or a history of hepatic impairment (see DOSAGE AND ADMINISTRATION and DETAILED 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.

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.

Use of losartan should include appropriate assessment of renal function.

Thiazides should be used with caution.

Because of the hydrochlorothiazide component, losartan and hydrochlorothiazide tablets are 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.

Sensitivity/Resistance

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

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

Special Populations

Pregnant Women: 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, losartan and hydrochlorothiazide tablets 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.

Animal data

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.

Nursing Women: 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.

Pediatrics (<18 years of age): Losartan potassium - hydrochlorothiazide have not been studied in children, therefore use in this age group is not recommended.

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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Losartan potassium - hydrochlorothiazide has been evaluated for safety in 2498 patients treated for essential hypertension. Of these, 1088 were treated with losartan potassium-hydrochlorothiazide monotherapy in controlled clinical trials. In open studies, 926 patients were treated with losartan potassium- hydrochlorothiazide for a year or more.

The following potentially serious adverse reactions have been reported rarely with losartan potassium- hydrochlorothiazide 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 – hydrochlorothiazide and placebo, respectively.

Clinical Trial Adverse Drug Reactions

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

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

	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

	Losartan Potassium - Hydrochlorothiazide (n=1088)	Losartan Alone (n=655)	Hydrochlorothiazide (n=272)	Placebo (n=187)
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.

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

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: orthostatic effects, somnolence, vertigo, epistaxis, tinnitus, constipation, malaise, rash.

Abnormal Hematologic and Clinical Chemistry 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- hydrochlorothiazide 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-hydrochlorothiazide 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- hydrochlorothiazide. More marked increases have also been reported and were more likely to occur in patients with bilateral renal artery stenosis (see 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- hydrochlorothiazide which have not been reported with losartan or hydrochlorothiazide individually.

Post-Market Adverse Drug Reactions

The following additional adverse reactions have been reported in post-marketing experience with Losartan potassium -hydrochorothiazide 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.
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 and pulmonary edema) and Adult Respiratory Distress Syndrome have been reported rarely in post-marketing experience.
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.

DRUG INTERACTIONS

Drug-Drug Interactions

Diuretics: Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with losartan potassium. The possibility of 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 (see WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension and DOSAGE AND ADMINISTRATION).

Agents Increasing Serum Potassium: Concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium 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 should also be used with caution. Concomitant thiazide diuretic use may attenuate any effect that losartan may have on serum potassium.

Lithium Salts: As with other drugs which 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.

Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.

Digitalis: 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.

Thiazide-induced electrolyte disturbances may predispose to digitalis-induced arrhythmias.

Warfarin: 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.

Drugs Affecting Cytochrome P450 System: 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 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).

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

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

Alcohol, Barbiturates, or Narcotics: Diuretic potentiation of orthostatic hypotension may occur.

Corticosteroids, ACTH or Glycyrrhizin (found in liquorice): Intensified electrolyte depletion, particularly hypokalemia, may occur when given concomitantly with diuretics.

Cholestyramine and Colestipol Resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

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

Non-Steroidal Anti-inflammatory Drugs Including Cyclooxygenase-2 Inhibitors: 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 losartan potassium-hydrochlorothiazide 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 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.

Dual blockade of the renin-angiotensin-aldosterone system: It has been reported in the literature that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, dual blockade of the renin-angiotensin-aldosterone system is associated with a higher frequency of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure) as compared to use of a single renin-angiotensin-aldosterone system agent. Dual blockade (e.g., by adding an ACE inhibitor to an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

Recommended Dose and Dosage Adjustment

Hypertension: Once the patient has been stabilized on the individual components as described below, one tablet ratio-LOSARTAN HCTZ 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 ratio-LOSARTAN HCTZ 100 mg/25 mg once daily (see INDICATIONS AND CLINICAL USE).

Severe Hypertension (SiDBP ≥110 mmHg): The maximum dose is one tablet of ratio-LOSARTAN HCTZ 100 mg/25 mg once daily.

ratio-LOSARTAN HCTZ may be administered with or without food, however it should be taken consistently with respect to food intake.

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 3-6 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 WARNINGS AND PRECAUTIONS, Hypotension and 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 WARNINGS AND PRECAUTIONS, Hypotension and 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 ratio-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 ratio-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 ratio-LOSARTAN HCTZ is not advisable (see WARNINGS AND PRECAUTIONS, 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 WARNINGS AND PRECAUTIONS, Geriatrics).

Missed Dose

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

OVERDOSAGE

No specific information is available on the treatment of overdosage with losartan potassium - hydrochlorothiazide. 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 immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Losartan potassium - hydrochlorothiazide 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 (AT1) 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 AT1 receptors found in many tissues, including vascular smooth muscle. A second type of angiotensin II receptor has been identified as the AT2 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 AT1 receptor, and have much greater affinity, in the order of 1000-fold, for the AT1 receptor than for the AT2 receptor. *In vitro* binding studies indicate that losartan itself is a reversible, competitive antagonist at the AT1 receptor, while the active metabolite is 10 to 40 times more potent than losartan, and is a reversible, non-competitive antagonist of the AT1 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.

Pharmacodynamics

Losartan: Losartan inhibits the pressor effect of angiotensin II. A dose of 100 mg inhibits this effect by about 85% at peak, with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2-3 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 - hydrochlorothiazide 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 - hydrochlorothiazide is 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 - hydrochlorothiazide had no clinically significant effect on heart rate.

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 3-4 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.

Excretion:
Losartan
The terminal half-life of losartan itself is about 2 hours, and that of the active metabolite, about 6-9 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 5.6-14.8 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.

STORAGE AND STABILITY

For bottles: Store at room temperature (15°C - 30°C). Keep container tightly closed. Protect from light.
For blisters: Store at room temperature (15°C - 30°C). Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

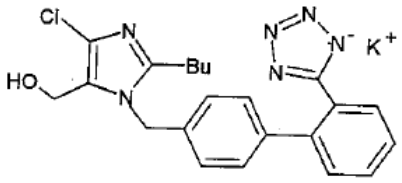
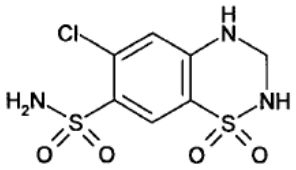
ratio-LOSARTAN HCTZ 100 mg/25 mg tablets are light-yellow, tear drop shaped, film-coated tablets, with “rph” on one side and “L91”on the other. Each tablet contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide, as the active ingredients. Available in blister packages of 30 tablets, bottles of 30 tablets and 500 tablets.

ratio-LOSARTAN HCTZ 100 mg/25 mg contain the following non-medicinal ingredients: D&C yellow 10, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	losartan potassium	hydrochlorothiazide
Chemical name:	2-butyl-4-chloro-1-[[2'-(1*H*-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-1*H*-imidazole-5-methanol monopotassium salt.	6-chloro-3,4-dihydro-2*H*-1,2,4- benzothiadiazine-7-sulfonamide 1,1- dioxide.
Molecular formula:	$C_{22}H_{22}ClKN_6O$	$C_7H_8ClN_3O_4S_2$
Molecular mass:	461.01	297.74
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.	Hydrochlorothiazide is a white, or practically white, crystalline powder. It is slightly soluble in water, but freely soluble in sodium hydroxide solution.

CLINICAL TRIALS

Comparative Bioavailability

A randomized, two period, two treatment crossover bioequivalence study of ratio-LOSARTAN HCTZ 100 mg-25 mg tablets (Teva Canada Limited, Canada) and Hyzaar® DS 100 mg-25 mg tablets (Merck Frosst Canada Ltd., Canada) administered as a single 1 x 100 mg-25 mg dose, was conducted in 24 healthy adult males under fasting conditions. A summary of the bioavailability data is presented below.

Losartan (1x 100mg/25mg losartan potassium and hydrochlorothiazide) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-t} (ng·h/mL)	704.11 761.15 (42.17)	711.80 759.23 (37.59)	98.92%	95.41% to 102.56%
AUC_{0-inf} (ng·h/mL)	731.34 792.88 (43.11)	735.41 785.46 (37.94)	99.45%	95.91% to 103.12%
C_{max} (ng/mL)	364.13 426.02 (63.14)	402.60 450.51 (51.60)	90.44%	77.89% to 105.02%
T_{max}§ (h)	1.43 (57.18)	1.54 (72.39)		
$T_{½\ el}$§ (h)	2.01 (19.39)	1.98 (21.11)		

* ratio-LOSARTAN HCTZ 100 mg-25 mg tablets manufactured by Teva Canada Limited, Canada
† Hyzaar® DS 100 mg-25 mg tablets (Merck Frosst Canada Ltd., Canada) were purchased in Canada
§ Expressed as the arithmetic mean (CV%) only

HCTZ (1 x 100mg/25mg losartan potassium and hydrochlorothiazide) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-t} (ng·h/mL)	797.12 818.44 (23.06)	781.70 797.94 (20.27)	101.97%	96.66% to 107.58%
AUC_{0-inf} (ng·h/mL)	838.48 861.06 (23.35)	818.50 835.99 (20.65)	102.44%	97.50% to 107.63%
C_{max} (ng/mL)	130.17 133.40 (21.43)	130.56 133.55 (21.29)	99.70%	90.60% to 109.70 %
T_{max} § (h)	2.56 (37.84)	2.60 (43.83)		
$T_{½\ el}$ § (h)	9.37 (16.38)	9.30 (13.44)		

* ratio-LOSARTAN HCTZ 100 mg-25 mg tablets manufactured by Teva Canada Limited, Canada
† Hyzaar® DS 100 mg-25 mg tablets (Merck Frosst Canada Ltd., Canada) were purchased in Canada
§ Expressed as the arithmetic mean (CV%) only

The safety and efficacy of losartan potassium – hydrochlorothiazide as initial therapy for severe hypertension (baseline mean SiDBP ≥110 mmHg confirmed on 2 separate occasions) was demonstrated in a six-week doubleblind, 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.

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.

DETAILED PHARMACOLOGY

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.

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%.

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 1).

Table 1 - 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)	Mice	Female	441.3 mg/kg	-
Oral	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 2).

Table 2 - 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:** 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.

Species	Duration	No. of Animals/Group	Dose mg/kg/day	Effects
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 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.**

Species	Duration	No. of Animals/Group	Dose mg/kg/day	Effects
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-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.

Table 2 - Chronic Toxicity (continued)
a) 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 hydrochlorothiazide did not alter systemic exposure to losartan or E-3174[†].

Species	Duration	No. of Animals/Group	Dose mg/kg/day	Effects
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.

Table 2 - Chronic Toxicity (continued)
b) 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.
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.

Reproduction

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.

Carcinogenesis

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.

Mutagenesis

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.

REFERENCES

1. Chan JCN, Critchley JAJH, Lappe JT, Raskin SJ, Snavely D, Goldberg AI, Sweet CS. Randomised, Double-blind, Parallel Study of the Anti-hypertensive Efficacy and Safety of Losartan Potassium Compared with Felodipine ER in Elderly Patients with Mild to Moderate Hypertension. J Human Hypertens 1995;9:765-71.

2. Dahlöf B, Keller SE, Makris L, Goldberg AI, Sweet CS, Lim NY. Efficacy and Tolerability of Losartan Potassium and Atenolol in Patients with Mild to Moderate Essential Hypertension. Am J Hypertens 1995;8:578-83.

3. Eberhardt RT, Kevak RM, Kang PM, Frishman WH. Angiotensin II Receptor Blockade: An Innovative Approach to Cardiovascular Pharmacotherapy. J Clin Pharmacol 1993;33(11):1023-38.

4. Goldberg AI, Dunlay MC, Sweet CS. Safety and Tolerability of Losartan Potassium, an Angiotensin II Receptor Antagonist, Compared with Hydrochlorothiazide, Atenolol, Felodipine ER, and Angiotensin-Converting Enzyme Inhibitors for the Treatment of Systemic Hypertension. Am J Cardiol 1995;75:793-5.

5. Goldberg M, Tanaka W, Barchowsky A, Bradstreet T, McCrea J, Lo MW, McWilliams E, Bjornsson T. Effects of Losartan on Blood Pressure, Plasma Renin Activity, and Angiotensin II in Volunteers. Hypertension 1993;21:704-13.

6. Lacourcière Y, Brunner H, Irwin R, Karlberg BE, Ramsay LE, Snavely DB, Dobbins TW, Faison EP, Nelson EB, the Losartan Cough Study Group. Effects of Modulators of the Renin Angiotensin-Aldosterone System on Cough. J Hypertens 1994;12(12):1387-93.

7. MacKay JH, Arcuri KE, Goldberg AI, Snapinn SM, Sweet CS. Losartan and Low-Dose Hydrochlorothiazide in Patients With Essential Hypertension. A Double-blind, Placebo-Controlled Trial of Concomitant Administration Compared With Individual Components. Arch Intern Med 1996;156:278-85.

8. Ohtawa M, Takayama F, Saitoh K, Yoshinaga T, Nakashima M. Pharmacokinetics and Biochemical Efficacy After Single and Multiple Oral Administration of Losartan, An Orally Active Nonpeptide Angiotensin II Receptor Antagonist, In Humans. Br J Clin Pharmacol 1993;35:290-7.

9. Schoenberger JA. Losartan with Hydrochlorothiazide in the Treatment of Hypertension. J Hypertens 1995;13(suppl. 1):S43-S47.

10. Weber MA, Byyny RL, Pratt JH, Faison EP, Snavely DB, Goldberg AI, Nelson EB. Blood Pressure Effects of the Angiotensin II Receptor Blocker, Losartan. Arch Intern Med 1995;155:405-11.

11. Salerno CM, Demopoulos L, Mukherjee R, Gradman AH. Combination Angiotensin Receptor Blocker/Hydrochlorothiazide as Initial Therapy in the Treatment of Patients with Severe Hypertension. J Clin Hyperten 2004;6:614-20.

12. Product Monograph, HYZAAR® and HYZAAR® DS losartan potassium-hydrochlorothiazide tablets, Merck Frosst Canada Ltd, November 3, 2011, Control # 149406.

PART III: CONSUMER INFORMATION

ratio-LOSARTAN HCTZ

Losartan Potassium and Hydrochlorothiazide Tablets

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

Please read this leaflet carefully before you start to take your medicine, even if you have just refilled your prescription. Some of the information in the previous leaflet may have changed.

ABOUT THIS MEDICATION

What the medication is used for:

- **lowering high blood pressure**

What it does:
The losartan ingredient of ratio-LOSARTAN HCTZ lowers blood pressure by specifically blocking a naturally-occurring substance called angiotensin II. Angiotensin II normally tightens your blood vessels. The losartan ingredient of ratio-LOSARTAN HCTZ allows them to relax. The hydrochlorothiazide ingredient of ratio-LOSARTAN HCTZ works by making your kidneys pass more water and salt. Together, losartan and hydrochlorothiazide lower high blood pressure. Although your physician will be able to tell you that the medicine is working by measuring your blood pressure, you probably will feel no different while you are taking ratio-LOSARTAN HCTZ.

When it should not be used:
Do not take ratio-LOSARTAN HCTZ if you:
• are allergic to losartan potassium and hydrochlorothiazide or any of the non-medicinal ingredients (see the section What the important non-medicinal ingredients are);
• are allergic to any sulfonamide-derived drugs (ask your physician or pharmacist if you are not sure what sulfonamidederived drugs are);
• are not passing urine.

If you are not sure whether you should start taking ratio-LOSARTAN HCTZ, contact your physician or your pharmacist.

What the medicinal ingredients are:
Losartan potassium and hydrochlorothiazide

What the nonmedicinal ingredients are:
ratio-LOSARTAN HCTZ 100 mg/25 mg contain the following non-medicinal ingredients: D&C yellow 10, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and titanium dioxide.

Although ratio-LOSARTAN HCTZ 100 mg/25 mg contain a very mall amount of potassium, they cannot replace potassium supplements. If your doctor has prescribed potassium supplements, continue to follow his advice.

What dosage forms it comes in:
ratio-LOSARTAN HCTZ 100 mg/25 mg is available in tablets.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
ratio-LOSARTAN HCTZ should not be used during pregnancy. If you discover that you are pregnant while taking ratio-LOSARTAN HCTZ, stop the medication and please contact your physician.

BEFORE you use ratio-LOSARTAN HCTZ talk to your doctor or pharmacist if:

- you perform tasks which may require special attention (for example, driving an automobile or operating dangerous machinery). Almost all patients can, but you should not perform these tasks until you know how you tolerate your medicine.
- you have or have had any medical problems, and about any allergies.
- you have liver or kidney disease, gout, diabetes, lupus erythematosus, or if you are being treated with other diuretics (water tablets). In these cases, your physician may need to adjust the dose of your medications.
- you have recently suffered from excess vomiting or diarrhea.
- you have to undergo any kind of surgery and general anesthesia (even at the dentist's office). Tell the physician or dentist that you are taking ratio-LOSARTAN HCTZ, as there may be a sudden fall in blood pressure associated with general anesthesia.
- you are hypersensitive to this drug or to any ingredient in the formulation.

Taking ratio-LOSARTAN HCTZ during pregnancy can cause injury and even death to your baby. This medicine should not be used during pregnancy. If you are planning to become pregnant while taking ratio-LOSARTAN HCTZ, contact immediately your physician.

It is possible that ratio-LOSARTAN HCTZ passes into breast milk. You should discuss with your physician about taking ratio-LOSARTAN HCTZ while breastfeeding.

Remember that your physician has prescribed this medicine only for you. Never give it to anyone else.

INTERACTIONS WITH THIS MEDICATION

Some drugs may have negative effect on ratio-LOSARTAN HCTZ, or ratio-LOSARTAN HCTZ may have negative effect on other drugs. If you are currently taking a medication, whether on prescription or otherwise, inform your physician or pharmacist.

Drugs that may interact with ratio-LOSARTAN HCTZ include:
• Medicines used to lower blood pressure, including diuretics (water pills), and ACE Inhibitors (such as enalapril, captopril)
• Potassium retaining diuretics, potassium supplements, or salt substitutes containing potassium
• Medicines may cause high blood pressure (adrenaline)
• Resins which reduce high cholesterol level
• Lithium salts (a drug to treat a certain kind of depression)
• Antidiabetic agents (insulin)
• Digitalis preparation (digoxin)
• Non-steroidal anti-inflammatory drugs
• Corticosteroids
• Sympathomimetics which may be found in some decongestants, cough/cold, hay fever, sinus medicines
• Analgesic medicines to treat pain, arthritis or muscle relaxants
• Glycyrrhizin (found in liquorice).

Avoid alcoholic beverages until you have discussed their use with your physician. Alcohol consumption may alter your blood pressure and/or increase the possibility of dizziness or fainting.

PROPER USE OF THIS MEDICATION

Usual dose:
•Take ratio-LOSARTAN HCTZ every day exactly as your physician has instructed. It is important to continue taking ratio-LOSARTAN HCTZ for as long as your physician prescribes it in order to maintain smooth control of your blood pressure.
• ratio-LOSARTAN HCTZ may be taken with or without food, but it should be taken consistently with respect to food intake, at the same time every day.
• **r**atio-LOSARTAN HCTZ should not be given to children.

Overdose:

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

Missed Dose:
Try to take ratio-LOSARTAN HCTZ daily as prescribed. However, if you miss a dose, do not take an extra dose. Just resume your usual schedule.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, ratio-LOSARTAN HCTZ may cause unwanted reactions, so-called side effects. Most patients do not experience side effects from ratio-LOSARTAN HCTZ. Examples of common side effects include:
• Nausea, vomiting, cramping, diarrhea, and lack of appetite
• Headache
• Difficulty sleeping
• Dizziness
• Fatigue, unusual tiredness and/or weakness
• Hives, rash, itch and bruising
• Taste alteration, red painful swelling of salivary gland
• Seeing more of the colour yellow in your vision, or temporary blurred vision
• Dry cough, nasal congestion and upper respiratory infections
• Back pain, joint pain, muscle spasms
• Fever
• Inability to develop or maintain an erection of the penis sufficient for satisfactory sexual performance
• Restlessness

Rare side effects include constipation, drowsiness, and increased sensitivity of the skin to the sun. Another side effect may be a feeling of dizziness or lightheadedness due to a sudden drop in blood pressure when standing up quickly.

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

Symptom / effect		Talk with your physician or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Common	Chest pain		✓	
	Swelling of the hands or ankles	✓		
	Red tender, hot, swollen joint (gout), high uric acid levels in the blood (hyperuricemia)	✓ (hyperuricemia)	✓ (gout)	
	Urine and kidney dysfunction decreased urine production	✓	✓ (renal failure)	
Uncommon	Inflammation of the pancreas (pancreatitis) which may cause abdominal pain that can radiate to your back			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
		Talk with your physician or pharmacist		
	A low number of red and white blood cells causing tiredness, weakness, shortness of breath, feeling generally unwell and less resistance to infections		✓	
	Racing or irregular heart rate	✓		
	Low sodium level in blood which may cause lack of energy, confusion, muscular twitching		✓	
	High blood sugar which may cause Excessive thirst, hunger and urination, sugar in the urine		✓	
Uncommon / Rare	*Hypersensitivity reactions:* Skin rash, skin eruption or other effect on the skin or eyes			✓
	Hypotension: Fainting when the blood pressure is too low			✓
	Allergic reactions: Swelling of the lips, face, tongue or throat, accompanied by difficulty in breathing or speaking (signs of angioedema)			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
		Talk with your physician or pharmacist		
	Liver disorder: Symptoms such as nausea, vomiting, dark/brown urine, yellow skin and eyes			✓
	Muscle tenderness or weakness		✓	

This is not a complete list of side effects. For any unexpected effects while taking ratio-LOSARTAN HCTZ contact your physician or pharmacist.

HOW TO STORE IT

For bottles: Store ratio-LOSARTAN HCTZ at room temperature (15°C - 30°C). Keep container tightly closed. Protect from light.
For blisters: Store ratio-LOSARTAN HCTZ at room temperature (15°C - 30°C). Protect from light.

Keep all medicines out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Teva Canada Limited, at:

1-800-268-4127 ext. 5005 (**English**)
1-877-777-9117 (**French**)
or druginfo@tevacanada.com

This leaflet was prepared by Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada, M1B 2K9

Last revised: January 31, 2012