PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]MINT-LOSARTAN

Losartan Potassium Tablets

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

House Standard

Angiotensin II Receptor Antagonist

Mint Pharmaceuticals Inc.
6575 Davand Drive
Mississauga, ON Canada L5T 2M3

Date of Initial Authorization:
May 09, 2013

Date of Revision:
April 18, 2023

Submission Control Number: 269236

RECENT MAJOR LABEL CHANGES

None	

TABLE OF CONTENTS

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Hypertension:

MINT-LOSARTAN (losartan potassium) is indicated for:

- the treatment of essential hypertension
- in patients with essential hypertension and left ventricular hypertrophy (see 14 CLINICAL TRIALS)

MINT-LOSARTAN may be used alone or concomitantly with thiazide diuretics.

A great majority of patients with severe hypertension in controlled clinical trials required combination therapy. Losartan potassium has been used concomitantly with beta-blockers and calcium channel blockers, but the data on such use are limited.

Type 2 Diabetic Patients with Proteinuria and Hypertension:

MINT-LOSARTAN (losartan potassium) is indicated:

- to delay the progression of renal disease as measured by the occurrence of doubling of serum creatinine, and end stage renal disease, and to reduce proteinuria (see 14 CLINICAL TRIALS)

1.1 Pediatrics

Pediatrics (6-16 years of age): Antihypertensive effects of losartan potassium have been demonstrated in hypertensive pediatric patients aged 6 to 16 years. Use of losartan potassium in these age groups is supported by evidence from adequate and well-controlled studies of losartan potassium in pediatric patients (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, 10 CLINICAL PHARMACOLOGY and 14 CLINICAL TRIALS).

1.2 Geriatrics

Geriatrics (≥65 years of age): In clinical studies, there was no age-related difference in the efficacy or safety profile of losartan (see 7 WARNINGS AND PRECAUTIONS).

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.
- Concomitant use of angiotensin receptor antagonists (ARBs) –including MINT-LOSARTAN- 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, MINT-LOSARTAN should be discontinued as soon as possible (see 7 WARNINGS AND PRECAUTIONS, Special Populations).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other pertinent clinical factors. The dosage of other antihypertensive agents used with MINT-LOSARTAN may need to be adjusted.

4.2 Recommended Dose and Dosage Adjustment

Hypertension: The dosage of MINT-LOSARTAN must be individualized.

Monotherapy: The usual starting dose of MINT-LOSARTAN 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 MINT-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 potassium 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 MINT-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).

Concomitant Diuretic Therapy: In patients receiving diuretics, MINT-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 MINT-LOSARTAN, to reduce the likelihood of hypotension (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular - Hypotension and 9 DRUG INTERACTIONS). If this is not possible because of the patient's condition, MINT-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.

Type 2 Diabetic Patients with Proteinuria and Hypertension: The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response. MINT-LOSARTAN may be administered with other antihypertensive agents (e.g., diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).

Geriatrics (≥65 years of age): No initial dosage adjustment is necessary for most elderly patients. However, appropriate monitoring of these patients is recommended.

Pediatrics (6-16 years of age): For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients ≥20 to <50 kg. The dose can be increased to a maximum of 50 mg once daily. In patients >50 kg, the starting dose is 50 mg once daily. The dose can be increased to a maximum of 100 mg once daily.

Dosage should be adjusted to blood pressure response.

In pediatric patients who are intravascularly volume depleted, these conditions should be corrected prior to administration of MINT-LOSARTAN.

MINT-LOSARTAN is not recommended in pediatric patients with glomerular filtration rate <30 mL/min/ 1.73 m^2, in pediatric patients with hepatic impairment, or in neonates as no data are available.

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

Hepatic Impairment: An initial dosage of 25 mg should be considered for patients with hepatic impairment, or a history of hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic - Hepatic Impairment and 10 CLINICAL PHARMACOLOGY).

4.4 Administration

MINT-LOSARTAN tablet is for oral administration.

MINT-LOSARTAN 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

Limited data are available in regard to overdosage with losartan potassium in humans. The most likely manifestation of overdosage would be hypotension and/or tachycardia. If symptomatic hypotension should occur, supportive treatment should be instituted.

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

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 / 25 mg, 50 mg, 100 mg	Cellulose microcrystalline, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, pregelatinised starch and titanium dioxide.

MINT-LOSARTAN tablets 25 mg are white to off white, oval shaped, film-coated tablets debossed with 'J' on one side and '25' on the other. MINT-LOSARTAN 25 mg tablets are available in bottles of 100 tablets.

MINT-LOSARTAN tablets 50 mg, are white to off white, oval shaped, film-coated tablets scored on one side, debossed with "J" on scored side and "50" on the other. MINT-LOSARTAN 50 mg tablets are available in bottles of 100 tablets. The splitting of MINT-LOSARTAN 50 mg tablets is not advised.

MINT-LOSARTAN tablets 100 mg, are white to off white, capsule shaped, film-coated tablets debossed with 'J' on one side and '100' on the other. MINT-LOSARTAN 100 mg tablets are available in bottles of 100 tablets.

MINT-LOSARTAN 25 mg, 50 mg and 100 mg tablets contain the following amounts of potassium: 2.12 mg (<1 mmol), 4.24 mg (<1 mmol), and 8.48 mg (<1 mmol) respectively.

7 WARNINGS AND PRECAUTIONS

*Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.*

General

Race: In the LIFE study, Afro-American Black patients treated with atenolol were at lower risk of experiencing the primary composite endpoint and stroke compared with Afro-American Black patients treated with losartan potassium. Based on the LIFE study, the benefits of losartan potassium on the primary composite endpoint and stroke compared to atenolol do not apply to Afro-American Black patients with hypertension and left ventricular hypertrophy although both treatment regimens effectively lowered blood pressure in these patients (see 14 CLINICAL TRIALS).

Carcinogenesis and Mutagenesis

There is no evidence of carcinogenesis and mutagenesis associated with losartan (see 16 NON-CLINICAL TOXICOLOGY).

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 MINT-LOSARTAN, 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 MINT-LOSARTAN in combination with aliskiren-containing drugs is contraindicated in these patients. Co- administration of ARBs, including MINT-LOSARTAN, with other agents blocking the RAS, such as ARBs or aliskiren- containing drugs, is not recommended in any patients, as adverse outcomes cannot be excluded.

Hepatic/Biliary/Pancreatic

Hepatic 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 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY).

Immune

Hypersensitivity: 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.

Renal

Renal Impairment: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function 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.

The use of ARBs – including MINT-LOSARTAN – 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.

Hyperkalemia: In a clinical study conducted in patients with type 2 diabetes with proteinuria and hypertension, the incidence of hyperkalemia was higher in the group treated with losartan potassium (9.9%) as compared to the placebo group (3.4%), however, few patients discontinued therapy due to hyperkalemia. Careful monitoring of serum potassium is recommended (see 8 ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings and 14 CLINICAL TRIALS).

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

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, MINT-LOSARTAN 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.

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.

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. 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 (6-16 years of age):

The antihypertensive effect has been demonstrated in a dose-response study of a limited duration of three weeks, after which half of the patients continued on assigned dosage up to six weeks. Blood pressure declines were maintained in the two highest dose groups.

Renal Impairment

There are no data on the effect of losartan potassium on blood pressure in pediatric patients under the age of six years and neonate, or in pediatric patients with glomerular filtration rate <30 mL/min/1.73m2.

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function 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.

Hepatic Impairment

There are no data on the effect of losartan potassium in pediatric patients with hepatic impairments.

Long-term safety has been studied in pediatric patients, as an extension of 6 months of the above cited dose-response study.

The pharmacokinetics of losartan have been investigated in 50 hypertensive pediatric patients >1 month to <16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses). The active metabolite is formed from losartan in all age groups. Pharmacokinetics of losartan and its active metabolite are generally similar across the studied age groups and consistent with pharmacokinetic historic data in adults (see 8 ADVERSE REACTIONS and 14 CLINICAL TRIALS).

7.1.4 Geriatrics (≥ 65 years of age):

No overall differences in safety were observed between elderly and younger patients, but appropriate caution should nevertheless be used when prescribing to elderly, as increased vulnerability to drug effect is possible in this patient population. This conclusion is based on 391 of 2085 (19%) patients, 65 years and over who received losartan monotherapy in controlled trials for hypertension. This was also the finding in a controlled clinical study in type 2 diabetic patients with proteinuria and hypertension with 248 (33%) of patients 65 years of age and over and in a controlled clinical study in hypertensive patients with left ventricular hypertrophy with 2857 (62%) of patients 65 years of age and over (see 14 CLINICAL TRIALS)

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Losartan potassium has been evaluated for safety in more than 3300 patients treated for essential hypertension. Of these, 2085 were treated with losartan monotherapy in controlled clinical trials.

In open studies, over 1200 patients were treated with losartan for more than 6 months, and over 800 for more than one year.

In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences occurred in 2.3% and 3.7% of patients treated with losartan potassium and placebo, respectively.

The following potentially serious adverse reactions have been reported rarely with losartan in controlled clinical trials: syncope, hypotension.

No relevant differences between the adverse experience profile for pediatric patients and the previously reported for adult patients were identified.

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 occurred in ≥1% of patients, regardless of drug relationship:

Table 2 - Adverse Reactions Reported with losartan potassium Occurring In ≥1% of Patients

	Losartan potassium n = 2085 (%)	Placebo n = 535 (%)
Body as a Whole		
Asthenia/fatigue	3.8	3.9
Edema/swelling	1.7	1.9
Abdominal pain	1.7	1.7
Chest pain	1.1	2.6
Cardiovascular		
Palpitation	1.0	0.4
Tachycardia	1.0	1.7
Gastrointestinal		
Diarrhea	1.9	1.9
Dyspepsia	1.1	1.5
Nausea	1.8	2.8
Musculoskeletal		
Back pain	1.6	1.1
Muscle cramps	1.0	1.1
Nervous/Psychiatric		
Dizziness	4.1	2.4
Headache	14.1	17.2
Insomnia	1.1	0.7
Respiratory		
Cough	3.1	2.6
Nasal congestion	1.3	1.1
Pharyngitis	1.5	2.6
Sinus disorder	1.0	1.3
Upper respiratory infection	6.5	5.6

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-treated (2.4%) than placebo-treated (1.3%) patients.

Losartan potassium was generally well tolerated in a controlled clinical trial in type 2 diabetic patients with proteinuria and hypertension. The most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalemia (see 7 WARNINGS AND PRECAUTIONS). In hypertensive patients with left ventricular hypertrophy, the most common drug-related side effects were dizziness, asthenia/fatigue, and vertigo.

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 plus 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 for essential hypertension, the following adverse reactions were reported with losartan potassium 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

In controlled clinical trials for essential hypertension, clinically important changes in standard laboratory parameters were rarely associated with administration of losartan potassium.

Liver Function Tests: In double-blind hypertensive trials, elevations of AST and ALT occurred in 1.1% and 1.9% of patients treated with losartan monotherapy and in 0.8% and 1.3% of patients treated with placebo, respectively. When AST or ALT elevations ≥2X upper limit of normal were compared, the frequency was similar to that seen in placebo.

Hyperkalemia: In controlled clinical trials for essential hypertension, hyperkalemia (serum potassium >5.5 mEq/L) occurred in 1.5% of patients treated with losartan potassium.

In a clinical study conducted in type 2 diabetic patients with proteinuria and hypertension, 9.9% of patients treated with losartan potassium and 3.4% of patients treated with placebo developed hyperkalemia (see 7 WARNINGS AND PRECAUTIONS, Renal - Hyperkalemia).

Creatinine, Blood Urea Nitrogen: 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. No patient discontinued taking losartan potassium alone due to increased BUN or serum creatinine.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.11 gram percent and 0.09 volume percent, respectively) occurred frequently in patients treated with losartan potassium alone, but were rarely of clinical importance. In controlled clinical trials no patients were discontinued due to anemia. Discontinuation of losartan treatment due to

anemia was reported with post-marketing use of losartan.

In clinical trials, the following were noted to occur with an incidence of <1%, regardless of drug relationship: thrombocytopenia, eosinophilia.

8.5 Post-Market Adverse Reactions

Other adverse reactions reported rarely in open-label studies or post-marketing use in patients with essential hypertension, regardless of drug relationship, include anemia, thrombocytopenia (reported rarely), hepatitis, liver function tests abnormalities, vomiting, drug induced cough, asthenia, diarrhea, migraine, dysgeusia, arthralgia, pruritus, erythroderma, taste disorder, urticaria, malaise, erectile dysfunction/impotence and photosensitivity. Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

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.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Concomitant use of angiotensin receptor antagonists (ARBs) –including MINT-LOSARTAN - 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 • Potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride) • Potassium supplements • Salt substitutes containing potassium • Other drugs that may increase serum potassium (e.g., trimethoprim-containing products	T	Increases in serum potassium	Since losartan potassium 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. Potassium-containing salt substitutes should also be used with caution.
Digitalis	CT	Effect of losartan on steady-state pharmacokinetics of cardiac glycosides is not known	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.
Diuretics	T	Excessive reduction of blood pressure after initiation	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 MINT-LOSARTAN. The possibility of symptomatic hypotension with the use of MINT-LOSARTAN can be minimized by discontinuing the diuretic prior to initiation of treatment and/or lowering the initial dose of losartan (see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS, Cardiovascular - Hypotension). No drug interaction of clinical significance has been identified with thiazide diuretics.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Drugs Affecting Cytochrome P450 System • Rifampin • Ketoconazole • Fluconazole	CT	Pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined	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).

Proper/Common name	Source of Evidence	Effect	Clinical comment
Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs or aliskiren-containing drugs	T	Adverse outcomes	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)).
Lithium Salts	T	Lithium excretion may be reduced	As with other drugs which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with angiotensin II receptor antagonists.
Non-steroidal Anti-inflammatory Drugs including Cyclooxygenase-2 Inhibitors	CT	Reduce the effect of diuretics and other antihypertensive drugs	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.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Warfarin	CT	Effect of losartan on steady-state pharmacokinetics of warfarin is not known	Losartan administered for 7 days did not affect the pharmacokinetics or pharmacodynamic activity of a single dose of warfarin.

Legend: CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

MINT-LOSARTAN may be administered with or without food.

Grapefruit juice contains components that inhibit CYP 450 enzymes and may lower the concentration of the active metabolite of MINT-LOSARTAN which may reduce the therapeutic effect. Consumption of grapefruit juice should be avoided while taking MINT-LOSARTAN.

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

MINT-LOSARTAN 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.

10.2 Pharmacodynamics

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.

10.3 Pharmacokinetics

Table 4 - Summary of Losartan Pharmacokinetic Parameters in Hypertensive Adults Following Multiple Dosing, Adults given 50 mg once daily for 7 days (n=12)

	C_{max} (ng/mL)[a]	T_{max}[c]	$t_{½}$ (h)[b]	AUC_{0-24h}[a] (ng•hr/mL)[r]	CL_r (mL/min)[a]
Parent	224 ± 82	0.9	2.1 ± 0.70	442 ± 173	56 ± 23
Active Metabolite	212 ± 73	3.5	7.4 ± 2.4	1685 ± 452	20 ± 3

[a] Mean ± standard deviation
[b] Harmonic mean± standard deviation
[c] Median

Absorption:

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.

Distribution:

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.

Metabolism:

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.

Elimination:

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.

Special Populations and Conditions

- **Pediatrics**

The pharmacokinetics of losartan and its active metabolite were generally similar across the studied age groups and historical pharmacokinetic data in adults.

Table 5 - Summary of Losartan Pharmacokinetic Parameters in Hypertensive Infants and Toddlers (Group I; 3-23 months), Preschool Children (Group II; 2-5 years), School-Age Children (Group III; 6-11 years), and Adolescents (Group IV; 12-15 years) Following Multiple Dosing

	Parent	Active Metabolite
$AUC_{0\text{-}24hr}$ observed (ng•hr/mL) [a]		
Group I (n=9)	244.5±175.7	1456.5±1422.7
Group II (n=12)[†]	314.5±177.8	950.9±498.0
Group III (n=11)	251.0±265.6	1163.6±1017.5
Group IV (n=14)	303.1±123.6	1589.9±996.2
$AUC_{0\text{-}24\ hr}$ per 0.7 mg/kg[a]		
Group I (n=9)	246.1±154.0	1466.3±1498.8
Group II (n=13)	305.2±164.9	933.2±510.5
Group III (n=11)	232.6±199.4	1078.0±783.4
Group IV (n=14)	405.4±120.3	2126.8±1082.4
C_{max} observed (ng/mL)[a]		
Group I (n=9)	66.6±103.6	146.9±179.5
Group II (n=12)[†]	89.8±96.5	91.5±75.2
Group III (n=11)	98.7±94.5	139.1±148.1

	Parent	Active Metabolite
Group IV (n=14)	105.1±112.3	188.2±91.2
C_{max} per 0.7 mg/kg[a]		
Group I (n=9)	67.0±92.8	147.9±190.6
Group II (n=13)	89.5±88.3	92.0±77.6
Group III (n=11)	91.4±81.7	128.8±112.1
Group IV (n=14)	140.6±90.5	251.7±118.2
T_{max} (hr)[c]		
Group I (n=9)	1.05±1.38	5.53±2.0
Group II (n=13)	1.07±1.43	6.01±1.5
Group III (n=11)	2.03±1.79	4.46±2.1
Group IV (n=14)	1.54±1.27	5.00±1.0
Half-Life (hr)[b]		
Group I (n=9)	1.93±0.44	4.83±1.1
Group II (n=13)	2.37±1.24	5.59±1.1
Group III (n=11)	2.18±1.50	5.37±1.4
Group IV (n=14)	2.41±1.84	5.72±1.0

a Geometric Mean ± Standard Deviation
b Harmonic Mean± Standard Deviation
c Median ± Standard Deviation
† n=12: excludes AN 4051 who received 2.5 times the intended dose

A pharmacokinetic study was performed to estimate plasma and urine pharmacokinetic parameters of losartan and its active metabolite, E-3174, in infants and toddlers, preschool children, school-age children, and adolescents.

The pharmacokinetics of losartan and its active metabolite, E-3174, in this study were comparable in all age groups studied. Differences in some parameters were statistically significant, especially for the active metabolite, E-3174, when the preschool children were compared with adolescents. Importantly, the youngest patients were comparable with older pediatric patients, and the active metabolite, E-3174, was formed from losartan in all age groups studied.

Health Canada has not authorized a pediatric indication for patients less than 6 years of age.

- **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 - 30°C). Protect from light.

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

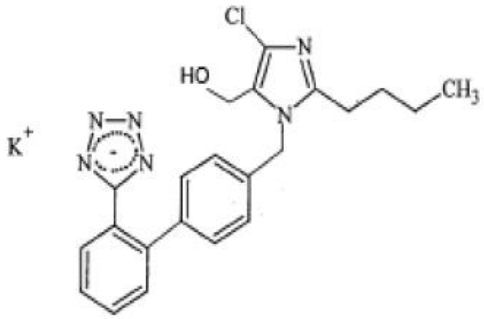
Drug Substance

Proper name: losartan potassium

Chemical name: 2-Butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl] imidazole-5-methanol, monopotassium salt

Molecular formula and molecular mass: $C_{22}H_{22}ClKN_6O$; 461.00 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 alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Adult Hypertension

Table 6 - Summary of Patient Demographics for Double-Blind, Placebo-Controlled Clinical Trials in Adult Patients with Hypertension

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age in years (Range)	Sex (%)
011	Double-blind, randomized, parallel, placebo-controlled	Oral administration, once daily Treatment groups: Losartan 10, 25, 50, 100, 150 mg Enalapril 20 mg and losartan placebo Duration: 8 weeks double-blind therapy	576	53.1 (22-88)	Male: 66 Female: 34
021	Double-blind, randomized, parallel, placebo-controlled	Oral Administration, once or twice daily Treatment groups: Losartan 50 mg once daily Losartan 100 mg once daily Losartan 50 mg twice daily Losartan placebo Duration: 4 weeks double-blind monotherapy	122	53.5 (28-76)	Male: 68 Female: 32
050	Double-blind, randomized, parallel, placebo-controlled	Oral administration, once daily Treatments group: Placebo Losartan 50 mg/placebo Losartan 50 mg/losartan 100 mg (possible titration to losartan 100 mg after 6 weeks) Duration: 12 weeks double-blind therapy	366	54 (26-78)	Male: 64 Female: 36

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age in years (Range)	Sex (%)
054	Double-blind, randomized, parallel, placebo-controlled	Oral administration, once daily Treatment Groups: Placebo Losartan 50 mg HCTZ 12.5 mg Losartan 50 mg /HCTZ 6.25 mg Losartan 50 mg/HCTZ 12.5 mg Duration: 12 weeks double-blind therapy	703	52.8 (21-79)	Male: 60 Female: 40
065	Double-blind, randomized, parallel, placebo- controlled	Oral administration, once or twice daily Placebo Losartan 25 mg once daily Losartan 50 mg once daily Losartan 25 mg twice daily Duration: 12 weeks double-blind therapy.	428	54 (24-79)	Male: 65 Female: 35

HCTZ: Hydrochlorothiazide

The antihypertensive effects of losartan potassium were demonstrated principally in 5 placebo-controlled, 6- to 12-week trials (study no 011, 021, 050, 054, 065) of dosages from 10 to 150 mg per day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparisons of two doses (50-100 mg/day) as once-daily or twice-daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race.

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65, had generally similar responses. The effect of losartan potassium was somewhat less in Black patients (usually a low-renin population).

The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks.

Table 7 - Results of Losartan Efficacy Compared to Placebo in Double-Blind, Controlled Outpatient Trials in Adult Patients with Hypertension

Study #	Treatment (Dosage in mg)	Baseline Mean DBP (S.D.) mmHg	Adjusted Mean DBP Change	Vs Placebo	Efficacy Parameter (Duration)
011	Placebo	103.3 (3.8)	-5.3	--	SuDBP (8 weeks)
	Losartan 25 mg qd	103.3 (3.7)	-6.4	NS	
	Losartan 50 mg qd	104.1 (3.7)	-10.1	**	
	Losartan 100 mg qd	104.1 (4.3)	-9.9	**	
021	Placebo	100.3 (3.6)	-2.1	--	SiDBP (4 weeks)
	Losartan 50 mg qd	100.0 (4.6)	-6.7	*	
	Losartan 100 mg qd	101.1 (4.8)	-9.7	**	
	Losartan 50 mg bid	101.4 (4.7)	-8.6	**	
021	Placebo	94.8 (5.9)	-0.8	--	ABPM 24 hr mean DBP (4 weeks)
	Losartan 50 mg qd	94.0 (6.9)	-5.6	**	
	Losartan 100 mg qd	93.8 (6.0)	-7.1	**	
	Losartan 50 mg bid	94.4 (6.9)	-9.0	**	
050	Placebo	101.3 (4.9)	-4.5	--	SiDBP (12 weeks)
	Losartan 50 mg qd	102.1 (5.1)	-7.9	**	
	Losartan 50/100 mg bid	102.2 (5.0)	-8.6	**	
054	Placebo	101.3 (5.3)	-4.0	--	SiDBP (12 weeks)
	Losartan 50 mg qd	100.9 (5.0)	-9.0	**	
065	Placebo	101.3 (5.1)	-2.1	--	SiDBP (12 weeks)
	Losartan 25 mg qd	101.8 (5.5)	-5.9	**	
	Losartan 50 mg qd	102.3 (6.3)	-6.6	**	

NS Treatment difference not statistically significant
* Treatment difference statistically significant, p≤0.05
** Treatment difference statistically significant, p≤0.01
SiDBP: Sitting diastolic blood pressure
SuDBP: Supine diastolic blood pressure
ABPM: Ambulatory blood pressure monitoring
qd: Once daily
bid: Twice daily

Type 2 Diabetic Patients with Proteinuria and Hypertension (RENAAL Study)

Table 8 - Summary of Patient Demographics for Double-Blind, Placebo-Controlled Clinical Trials in Hypertensive Patients with Type 2 Diabetes with Proteinuria

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
147 **RENAAL**	Double-blind, randomized placebo-controlled (non-ACE inhibitor, non AIIA conventional antihypertensives) multinational study	Oral administration Losartan 50 mg once daily with titration to losartan 100 mg Matching placebo Duration: 3.4 years mean follow up	1513	60 (31 to 74 years)	Male: 956 (31 to 74 years) Female: 557 (34 to 73 years)

The Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus (NIDDM) with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a large, multicenter, randomized, placebo-controlled, double-blind study conducted worldwide in 1513 hypertensive patients with type 2 diabetes and proteinuria [751 patients entered treatment with losartan potassium]. The goal of the study was to demonstrate the renal protective effects of losartan potassium over and above the benefits of blood pressure control alone. To meet this objective the study was designed to achieve equal blood pressure control in both treatment groups. Patients with proteinuria and serum creatinine of 1.3-3.0 mg/dL were randomized to receive losartan potassium 50 mg once daily titrated according to blood pressure response, or placebo, on a background of conventional antihypertensive therapy excluding ACE inhibitors and angiotensin II antagonists. Investigators were instructed to titrate study drug to 100 mg once daily as appropriate; 72% of patients were taking the 100 mg daily dose the majority of the time they were on study drug. Other antihypertensive agents (diuretics, calcium-channel blockers, alpha- or beta-blockers, and centrally acting agents) could be added as needed in both groups. Patients were followed for approximately 5 years (mean of 3.4 years).

Important inclusion criteria of the RENAAL study included: type 2 diabetes defined as: (1) diabetes diagnosed after the age of 30; (2) insulin not required within the first 6 months of diagnosis; and (3) no history of diabetic ketoacidosis; ages of 31 to 70; serum creatinine between 1.3 (1.5 for males >60 kg) and 3.0 mg/dL; and first morning urinary albumin/creatinine ratio (UA/Cr) of ≥300 mg/g (or a 24-hour urine total protein of >500 mg/day). Patients could have been normotensive or hypertensive.

Important exclusion criteria of the RENAAL study included: type 1 diabetes; history of heart failure; history of myocardial infarction or coronary artery bypass graft surgery within 1 month prior to study start, cerebral vascular accident or percutaneous transluminal coronary angioplasty within 6 months prior to study start, and history of transient ischemic attacks (TIA) within the year prior to study start; known history or current diagnosis of nondiabetic renal disease such as chronic glomerulonephritis or polycystic kidney disease; and uncontrolled diabetes, i.e., HBA1c >12%.

Table 9 - Results of the Angiotensin II Receptor Antagonist Losartan (RENAAL) Placebo-Controlled, Double-Blind Study in Hypertensive Patients with Type 2 Diabetes with Proteinuria

End Point	Losartan Group (n=751)		Placebo Group (n=762)		p-Value	Risk Reduction % (95% CI)
	No	%	No	%		
Primary composite* end point	327	(43.5)	359	(47.1)	0.022	16.1 (2 to 28)
Doubling of serum creatinine concentration	162	(21.6)	198	(26.0)	0.006	25.3 (8 to 39)
End-stage renal disease	147	(19.6)	194	(25.5)	0.002	28.6 (11 to 42)
Death	158	(21.0)	155	(20.3)	0.884	-1.7 (-27 to 19)

* The primary end point was the time to first occurrence of any one of the following events: doubling of serum creatinine concentration, end-stage renal disease (need for dialysis or transplantation) or death.

The primary endpoint of the study was the composite endpoint of doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation), or death. The results showed that treatment with losartan potassium (327 events, 43.5%) as compared with placebo (359 events, 47.1%) resulted in a 16.1% risk reduction (p=0.022) for patients reaching the primary composite endpoint. For the following individual components of the primary endpoint, the results also showed significant risk reduction in the group treated with losartan potassium as compared to placebo: 25.3% risk reduction in doubling of serum creatinine (21.6% vs 26.0%), (p=0.006); 28.6% risk reduction in end-stage renal disease (19.6% vs 25.5%), (p=0.002). The rate of the all-cause deaths component was not significantly different between losartan and placebo group, 21.0% and 20.3%, respectively.

The secondary endpoints of the study were: change in proteinuria; the rate of progression of renal disease; and the composite of morbidity and mortality from cardiovascular causes (hospitalization for heart failure, myocardial infarction, revascularization, stroke, hospitalization for unstable angina, or cardiovascular death). For the secondary endpoint of change in proteinuria, the results showed an average reduction of 34.3% in the level of proteinuria in the group treated with losartan potassium (p<0.001) over the mean of 3.4 years. For the secondary endpoint of rate of progression of renal disease, treatment with losartan potassium reduced the rate of decline in renal function during the chronic phase of the study by 13.9%, (p=0.01) as measured by the reciprocal of the serum creatinine concentration.

In this study, losartan potassium was generally well tolerated as evidenced by a similar incidence of discontinuations due to side effects compared to placebo. A tertiary endpoint in the study was assessment of quality of life. The results of this analysis suggest that there is no difference in the change of quality of life between treatment arms.

Hypertension in Pediatric Patients

Table 10 - Summary of Patient Demographics for Double-Blind, Response Study of Losartan in Children with Diastolic Hypertension

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
227	A double-blind, randomized dose-response study of losartan in children with diastolic hypertension	Oral administration, once daily Losartan 2.5 mg, 25 mg, or 50 mg for patients weighing <50 kg Losartan 5 mg, 50 mg, or 100 mg for patients who weigh ≥50 kg Duration: 3 weeks double-blind treatment period	177	12 (6 to 16 years)	Male: 99 Female: 78

In a clinical study involving 177 hypertensive pediatric patients 6 to 16 years of age, patients who weighed ≥20 kg to <50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighed ≥50 kg received either 5, 50 or 100 mg of losartan daily. Losartan administration once daily lowered trough diastolic blood pressure in a dose-dependent manner. The dose response to losartan was observed across all subgroups (e.g., age, tanner stage, gender, and race). Evaluation of dose response based on the mean weight adjusted dose indicates that a starting dose of losartan 0.75 mg/kg (up to 50 mg) once daily is appropriate. However, the lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/kg, did not appear to offer consistent antihypertensive efficacy. In this study, losartan potassium up to an average daily dose of 1.44 mg/kg (maximum 100 mg) once daily, is generally tolerated in hypertensive children.

Table 11 – Results of the Losartan Pediatric Dose-Response Study—Summary of Weight-Adjusted Dose Responses (Intention-to-Treat Approach)

Dose	N	Day 1 (SiDBP in mmH)	Day 15 (SiDBP in mmH)	Day 22 (SiDBP in mmH)	Mean Change (Day 15-Day 1) (SD)	Mean Change (Day 22-Day 1) (SD)	95% CI For Mean Change (Day 22-Day 1)	
Low (2.5/5 mg)	70	87.92	80.80	81.91	-7.12 (6.47)	-6.01 (7.61)	-7.82,	4.19
Middle (25/50 mg)	40	89.38	78.40	77.73	-10.98 (8.66)	-11.65 (9.08)	-14.55,	-8.75
High (50/100 mg)	64	88.80	78.56	76.59	-10.24 (9.14)	-12.21 (8.86)	-14.42,	-10.00

N = Patients with both baseline (on Day 1) and post dose measurements
SD = Standard deviation

Mean Change = Measurement on Day 15 (or 22) minus measurement on Day 1
CI = Confidence Interval
SiDBP: Sitting diastolic blood pressure

Overall, no significant differences in antihypertensive effect of losartan were detected when patients were analyzed according to age (<, ≥12 years old) or gender. While blood pressure was reduced in all racial groups examined, too few non-white patients were enrolled to compare the dose-response of losartan in non-white subgroup.

Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study in Patients with ECG-documented Left Ventricular Hypertrophy (LVH)

Table 12 - Summary of Patient Demographics for Double-Blind Study Comparing Losartan - and Atenolol-Based Therapies in Hypertensive Patients with ECG-Documented Left Ventricular Hypertrophy (LVH)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
P925C1 ("LIFE")	Double-blind study comparing losartan - and atenolol-based therapies in hypertensive patients with ECG-documented left ventricular hypertrophy (LVH)	Oral administration Patients randomized to receive once daily losartan 50 mg (n=4605) or atenolol 50 mg (n=4588) Mean length of follow-up- 4.8 years.	9193	67 (55 to 80 years)	Male: 4230 (46 %) Female: 4963 (54 %)

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) was a multicentre, randomized, double-blind study comparing losartan potassium - and atenolol-based therapies in 9193 hypertensive patients with ECG-documented left ventricular hypertrophy (LVH). The primary endpoint was a composite of cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction (MI). A 15% relative difference in the primary endpoint was selected to demonstrate superiority between the treatment groups with 80% power. A primary event occurred in 11% of the losartan potassium -based group and 13% of the atenolol- based group yielding a relative difference of 13% (adjusted hazard ratio of 0.87 (CI 0.77, 0.98) and p=0.021). The individual components of the primary composite endpoint did not consistently support the overall result. The difference between the groups was primarily the result of an effect on stroke. Treatment with losartan potassium reduced the risk of stroke by 25% relative to atenolol (p=0.001) (see Figure 1 and Table 13). For the cardiovascular mortality component, there was a non-significant trend in favor of the losartan potassium -based therapy, while for the myocardial infarction component there was a non-significant difference in favor of atenolol-based treatment. Although the LIFE study favored losartan potassium over atenolol with respect to the primary composite endpoint, corroborative results from a confirmatory study are not available. A per-protocol analysis, which excluded patients with important protocol violations and censored patients 14 days after permanently discontinuing study medications or 14 days after starting prohibited therapy, showed that the primary endpoint was consistent but, did not reach statistical significance (hazard ratio, 0.865, 95%

CI 0.748, 1.002; p=0.053). The statistical power of the per-protocol analysis was lower than for the intent-to-treat analysis because approximately one third of the events were excluded.

Patients aged 55-80 years, with previously treated or untreated hypertension and ECG signs of LVH were included in the study. According to NHANES III, the prevalence of LVH, established by ECG, in patients with hypertension who are similar to the patients in the LIFE study is 12.8% in White patients and 26.8% in Black patients in the general population. The following patients were excluded: patients with secondary hypertension; myocardial infarction or stroke within the previous six months; angina pectoris requiring treatment with β-blockers or calcium-antagonists; heart failure or left ventricular ejection fraction of 40% or less; or a disorder that, in the treating physician's opinion, required treatment with losartan-based or another angiotensin-II type 1-receptor antagonist, atenolol or another β-blocker, hydrochlorothiazide, or angiotensin-converting-enzyme inhibitors. Patients were randomized to receive once daily losartan potassium 50 mg (n=4605) or atenolol 50 mg (n=4588). If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan potassium or atenolol was then increased to 100 mg once daily. If necessary, other antihypertensive treatments (e.g., increase in dose of hydrochlorothiazide therapy to 25 mg or addition of other diuretic therapy, calcium- channel blockers, alpha-blockers, or centrally acting agents, but not ACE inhibitors, angiotensin II antagonists, or beta-blockers) were added to the treatment regimen to reach the goal blood pressure.

Of the randomized 9193 patients, 54% were female and 6% were Black. The mean age was 67 years with 62% being 65 years or older. At baseline, 13% had diabetes, 14% had isolated systolic hypertension, 16% had coronary heart disease, and 8% had cerebrovascular disease. There were no significant differences in baseline demographics, clinical characteristics and medical history between the two groups. Baseline mean blood pressure was 174/98 mmHg in both treatment groups. The mean length of follow-up was 4.8 years. At the end of study or at the last visit before a primary endpoint, 77% of the group treated with losartan potassium and 73% of the group treated with atenolol were still taking study medication. Of the patients still taking study medication, the mean doses of losartan potassium and atenolol were both about 80 mg/day, and 15% were taking atenolol or losartan as monotherapy, while 77% were also receiving hydrochlorothiazide (at a mean dose of 20 mg/day in each group). Blood pressure reduction measured at trough was similar for both treatment groups, but blood pressure was not measured at any other time of the day. At the end of study or at the last visit before a primary endpoint, the averaged blood pressures were 144.1/81.3 mmHg for the group on losartan-based therapy and 145.4/80.9 mmHg for the atenolol- based therapy patients. The difference in systolic blood pressure of 1.3 mmHg was significant (p<0.001), while the difference of 0.4 mmHg in diastolic blood pressure was not significant (p=0.098).

Table 13 - Results of the LIFE STUDY Primary Composite Endpoint, Components of the Primary Endpoint

and Secondary Endpoints

	Losartan-based Therapy (N = 4605)	Atenolol-based Therapy (N = 4588)	Relative Risk Reduction†	95% CI	p-Value
	Number of events (%)	**Number of events (%)**			
Primary Composite Endpoint	508 (11)	588 (13)	13%	2% to 23%	0.021
Components of Primary Composite Endpoint (as a first event)					
Stroke (nonfatal‡)	209 (4.5)	286 (6.2)			
Myocardial infarction (nonfatal‡)	174 (3.8)	168 (3.7)			
Cardiovascular mortality	125 (2.7)	134 (2.9)			
Secondary Endpoints (any time in study)					
Stroke (fatal/nonfatal)	232 (5)	309 (7)	25%	11% to 37%	0.001
Myocardial infarction (fatal/nonfatal)	198 (4)	188 (4)	-7%	-13% to 12%	0.491
Cardiovascular mortality	204 (4)	234 (5)	11%	-7% to 27%	0.206
Due to CHD	125 (3)	124 (3)	-3%	-32% to 20%	0.839
Due to Stroke	40 (1)	62 (1)	35%	4% to 67%	0.032
Other§	39 (1)	48 (1)	16%	-28% to 45%	0.411

† Adjusted for baseline Framingham risk score and level of electrocardiographic left ventricular hypertrophy

‡ First report of an event, in some cases the patient died subsequently to the event reported

§ Death due to heart failure, non-coronary vascular disease, pulmonary embolism, or a cardiovascular cause other than stroke or coronary heart disease

Table 13 shows the results obtained for the primary composite endpoint, components of the primary endpoint and those for the secondary endpoints. It can be seen that the primary composite endpoint reached statistical significance almost entirely due to the stroke component.

The results obtained for the primary composite endpoint are shown graphically in Figure 1.

Figure 1 - Observed Kaplan-Meier Curve—Primary Composite Endpoint

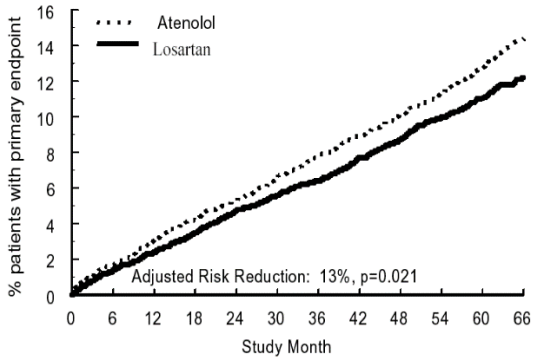


Figure 1. Kaplan-Meier estimates of the primary endpoint of time to cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction in the groups treated with Losartan potassium and atenolol. The Risk Reduction is adjusted for baseline Framingham risk score and level of electrocardiographic left ventricular hypertrophy.

Although the LIFE study favored losartan potassium based therapy over atenolol-based therapy with regards to stroke, it should be remembered that stroke was a secondary endpoint in the LIFE study. A difference was observed between the two treatment groups in terms of the number of patients with stroke who also had atrial fibrillation: Losartan potassium group (13.4%) and atenolol group (20.5%).

Other clinical endpoints of the LIFE study were: total mortality, hospitalization for heart failure or angina pectoris, coronary or peripheral revascularization procedures, and resuscitated cardiac arrest. There were no significant differences in the rates of these endpoints between the losartan potassium and atenolol groups.

In the LIFE study, Afro-American Black patients treated with atenolol-based treatment were at lower risk of experiencing the primary composite endpoint compared with Afro-American Black patients treated with losartan-based treatment. In the subgroup of Afro-American Black patients (n=533), there were 29 primary endpoints among 263 patients on atenolol (11%, 26 per 1000 patient-years) and 46 primary endpoints among 270 patients (17%, 42 per 1000 patient-years) on losartan potassium. This finding could not be explained on the basis of differences in the populations other than race or on any imbalances between treatment groups. In addition, blood pressure reductions in both treatment groups were consistent between Afro-American Black and non-Black patients. Regarding stroke, the results favoured atenolol- based therapy in Afro-American Blacks. The LIFE study provides no evidence that the benefits of losartan- based treatment on reducing the risk of cardiovascular events in hypertensive patients with left ventricular hypertrophy apply to Afro-American Black patients.

14.2 Comparative Bioavailability Studies

A randomized, double blind, two treatment, two sequence, two period, single oral dose, crossover, bioequivalence study comparing Mint-Losartan (losartan potassium) 100 mg film coated tablets (Mint Pharmaceuticals Inc.) with Cozaar® (losartan potassium) 100 mg tablets (Merck Frosst Canada Ltd.) in 39 healthy adult, male subjects under fasting conditions was conducted.

Summary Table of the Comparative Bioavailability Data

Losartan (1 x 100 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference**	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	1058.2 1094.3 (25.1)	1073.9 1118.0 (28.8)	98.5	93.4 - 103.9
AUC_I (ng.h/mL)	1081.3 1117.3 (24.7)	1094.2 1138.2 (28.5)	98.8	93.9 – 104.0
C_{max} (ng.h/mL)	648.0 720.7 (50.1)	645.3 708.5 (45.4)	100.4	86.4 - 116.7
T_{max}§ (h)	1.3 (55.4)	1.2 (46.5)	-	-
$T_{½}$§ (h)	2.4 (64.5)	2.3 (31.4)	-	-

* Mint-Losartan (losartan potassium) 100 mg tablets (Mint Pharmaceuticals Inc.).

** COZAAR® (losartan potassium) 100 mg tablets (Merck Frosst Canada Ltd.) were purchased in Canada.

§ Expressed as arithmetic 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 14).

Table 14 - Acute Toxicity

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

Route	Species	Sex	LD_{50} Values	Maximum Tolerated Dose
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. There were no findings that would preclude administration at the therapeutic dosage level (see Table 15).

Table 15 - Chronic Toxicity

a) Oral Administration

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.

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

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

Species	Duration	No. of Animals/Group	Dose mg/kg/day	Effects
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.
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) I.V. Administration

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 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.

Genotoxicity:

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 showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Reproductive and Developmental Toxicology:

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

Teratology

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.

17 SUPPORTING PRODUCT MONOGRAPHS

1) COZAAR (Tablets, 25 mg, 50 mg and 100 mg), submission control 260621, Product Monograph, Organon Canada Inc. (JUL 06, 2022)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

MINT-LOSARTAN

Losartan Potassium Tablets

Read this carefully before you start taking **MINT-LOSARTAN** 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 **MINT-LOSARTAN**.

Serious Warnings and Precautions

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

What is MINT-LOSARTAN used for?

MINT-LOSARTAN is used in adults to:

- lower high blood pressure.
- provide kidney protection by delaying the worsening of kidney disease in type 2 diabetic patients with protein in the urine (proteinuria) and high blood pressure.

MINT-LOSARTAN is used in children (6 to 16 years of age) to:

- lower high blood pressure.

How does MINT-LOSARTAN work?

MINT-LOSARTAN is an angiotensin receptor blocker (ARB). It lowers blood pressure. This medicine does not cure high blood pressure. It helps to control it. Therefore, it is important to continue taking MINT-LOSARTAN regularly even if you feel fine.

What are the ingredients in MINT-LOSARTAN?

Medicinal ingredients: losartan potassium.

Non-medicinal ingredients: cellulose microcrystalline hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, pregelatinised starch and titanium dioxide.

Although MINT-LOSARTAN tablets contain potassium, this amount is too small to replace potassium supplements. If your doctor has prescribed potassium supplements, continue to follow their advice.

MINT-LOSARTAN comes in the following dosage forms:
Tablets: 25 mg, 50 mg and 100 mg.

Do not use MINT-LOSARTAN if:

- you are allergic to losartan potassium or any of the non-medicinal ingredients in MINT-LOSARTAN.
- 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 MINT-LOSARTAN. Talk about any health conditions or problems you may have, including if you:

- have had an allergic reaction to any drug used to lower blood pressure, including angiotensin converting enzymes (ACE) inhibitors.
- are taking an ACE inhibitor.
- have narrowing of an artery or a heart valve.
- have had a heart attack or stroke.
- are taking a salt substitute that contains potassium, potassium supplements, a potassium-sparing diuretic (a specific kind of "water pill" that makes your body keep potassium), or other drugs that may increase potassium levels (such as trimethoprim-containing products).
- are on a low salt diet.
- are on dialysis.
- are dehydrated or suffer from excessive vomiting, diarrhea or sweating.
- have difficulty urinating or produce no urine.
- have heart failure.
- have diabetes, liver or kidney disease.
- are pregnant, planning to become pregnant or think you are pregnant
- are breastfeeding or plan to breastfeed

Other warnings you should know about:

Sun exposure: You may become sensitive to the sun while taking MINT-LOSARTAN. Exposure to sunlight should be minimized until you know how you respond.

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 MINT-LOSARTAN, as there may be a sudden fall in blood pressure.

Testing and check-ups: During treatment with MINT-LOSARTAN, your healthcare professional may monitor:

- Your kidney function
- Your blood pressure
- The amount of potassium in your blood
- Your liver function

Driving and using machines: Before doing tasks which require special attention, wait until you know how you respond to MINT-LOSARTAN. 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 MINT-LOSARTAN:

- Other medications used to lower blood pressure such as diuretics.
- Digoxin, a heart medication.
- Lithium used to treat bipolar disease.

- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include ibuprofen, naproxen, and celecoxib.
- Warfarin used to thin the blood and prevent blood clots.
- Antibiotics used to treat bacterial infections, such as rifampin and erythromycin.
- Fluconazole, used to treat fungal infections.
- Phenobarbital, used to treat epilepsy.
- Cimetidine, used to treat heartburn and stomach ulcers.
- Agents increasing serum potassium, such as potassium supplements, salt substitutes containing potassium, a potassium-sparing diuretic (a specific kind of "water pill") or other drugs that may increase serum potassium (e.g., trimethoprim-containing products).
- Grapefruit juice (which should be avoided while taking MINT-LOSARTAN).

How to take MINT-LOSARTAN:

- Take MINT-LOSARTAN exactly as prescribed.
- It is recommended to take your dose at about the same time every day.
- MINT-LOSARTAN may be taken with or without food, but it should be taken the same way each day.

Usual dose:

<u>High blood pressure:</u>

Adults:

- The usual starting dose is 50 mg once daily. The usual dose range is 50 to 100 mg once daily.

Children (6 to 16 years of age) who can swallow tablets:

- For patients who weigh between 20 kg and less than 50 kg, the recommended dose is 25 mg once daily. The dose can be increased by your healthcare professional to a maximum of 50 mg once daily.
- For patients who weigh 50 kg or more, the starting dose is 50 mg once daily. The dose can be increased by your healthcare professional to a maximum of 100 mg once daily.

<u>Type 2 diabetes patients with protein in the urine and high blood pressure:</u>

Adults:

- The usual starting dose is 50 mg once daily. Your healthcare professional may increase the dose to 100 mg once daily.

Overdose:

If you think you, or a person you are caring for, have taken too much MINT-LOSARTAN, 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 MINT-LOSARTAN?

These are not all the possible side effects you may have when taking MINT-LOSARTAN. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- diarrhea
- vomiting
- fatigue
- back or leg pain
- muscle cramps
- change in taste
- dizziness
- headache
- rash

MINT-LOSARTAN 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			
Increased levels of potassium in the blood: generally feeling unwell, irregular heartbeats and muscle weakness		√	
Low Blood Pressure: dizziness, fainting, light-headedness (may occur when you go from lying or sitting to standing up)	√		
UNCOMMON			
Allergic reaction: difficulty breathing or swallowing, hives, skin rash and swelling of the face, lips, throat or tongue			√
Kidney Disorder: change in frequency of urination, fatigue, nausea, swelling of extremities, vomiting		√	
Liver Disorder: abdominal pain, dark urine, loss of appetite, nausea, vomiting, yellowing of the skin or eyes		√	
RARE			
Rhabdomyolysis: dark brown urine, muscle pain that you cannot explain, muscle tenderness or weakness		√	
VERY RARE			
Decreased Platelets: bleeding, bruising, fatigue, small purple or red dots under the skin and weakness		√	

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 MINT-LOSARTAN at room temperature (15°C-30°C). Protect from light.

Keep out of reach and sight of children.

If you want more information about MINT-LOSARTAN:

- 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 www.mintpharmacetuicals.com, or by calling 1-877-398-9696 .

This leaflet was prepared by Mint Pharmaceuticals Inc.

Last Revised: April 18, 2023