PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PRINIVIL®

(lisinopril tablets, Merck Standard)

Tablets 10 and 20 mg oral

ANGIOTENSIN-CONVERTING ENZYME INHIBITOR

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RECENT MAJOR LABEL CHANGES

7. WARNINGS AND PRECAUTIONS	05/2021
9. DRUGS INTERACTIONS	05/ 2021

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

PRINIVIL® (lisinopril tablets) is indicated for:

- **Hypertension**

PRINIVIL® is indicated in the treatment of essential hypertension and in renovascular hypertension. It may be used alone or concomitantly with thiazide diuretics. A great majority of patients (>80%) with severe hypertension required combination therapy. PRINIVIL® has been used concomitantly with beta-blockers and calcium antagonists, but the data on such use are limited.

- **Heart Failure**

PRINIVIL® is indicated in the management of symptomatic congestive heart failure as adjunctive treatment with diuretics and, where appropriate, digitalis. Treatment with PRINIVIL® should be initiated under close medical supervision, usually in a hospital.

- **Treatment Following Acute Myocardial Infarction**

PRINIVIL® is indicated in the treatment of hemodynamically stable patients as early as within 24 hours following acute myocardial infarction, to improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, ASA and beta-blocker(s).

Therapy with PRINIVIL® should be reassessed after six weeks. If there is no evidence of symptomatic or asymptomatic left ventricular dysfunction, treatment with PRINIVIL® can be stopped.

PRINIVIL® should not be used if systolic blood pressure is less than 100 mmHg, if clinically relevant renal failure is present, if there is a history of bilateral stenosis of the renal arteries (see 7 WARNINGS and PRECAUTIONS).

In using PRINIVIL®, attention should be given to the risk of angioedema (see 7 WARNINGS and PRECAUTIONS).

1.1 Pediatrics

- Pediatrics (<6 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use in children under the age of 6. See 4 DOSAGE AND ADMINISTRATION.
- Pediatrics (6-16 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of PRINIVIL® in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use. See 4 DOSAGE AND ADMINISTRATION.

1.2 Geriatrics

- Evidence from clinical studies and experience suggests that use in the geriatric population is associated with similar safety and effectiveness (see 4 DOSAGE AND ADMINISTRATION).

2 CONTRAINDICATIONS

PRINIVIL® (lisinopril tablets) is contraindicated in patients who:

- are hypersensitive to any component of this product;
- have a history of angioneurotic edema relating to previous treatment with an angiotensin-converting enzyme inhibitor;
- have hereditary or idiopathic angioedema
- Concomitant use of angiotensin-converting enzyme inhibitors (ACEIs) – including PRINIVIL® – with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR <60 ml/min/1.73 m^2) is contraindicated (see 7 WARNINGS AND PRECAUTIONS, and 9 DRUG INTERACTIONS).
- PRINIVIL® is contraindicated in combination with a neprilysin inhibitor (e.g., sacubitril). Do not administer PRINIVIL® within 36 hours of switching to or from sacubitril/valsartan, a product containing a neprilysin inhibitor. (See 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS.)

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

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

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Since absorption of PRINIVIL® tablets (lisinopril tablets) is not affected by food, the tablets may be administered before, during or after meals.
- PRINIVIL® should be administered in a single daily dose.
- PRINIVIL® should be taken at the same time each day. The splitting of PRINIVIL® tablets is not advised.
- Dosage adjustments should be based on the clinical response of each individual patient.

4.2 Recommended Dose and Dosage Adjustment

- **Essential Hypertension**

In patients with essential hypertension, not on diuretic therapy, the usual recommended starting dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response: the usual dosage range is 10 to 40 mg per day, administered in a single daily dose. In some patients, achievement of optimal blood pressure reduction may require two to four weeks of therapy. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. The maximum dose used in long-term controlled clinical trials was 80 mg/day. If blood pressure is not controlled with PRINIVIL® alone, a low dose of a diuretic

may be added. Hydrochlorothiazide 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of PRINIVIL®.

***Diuretic Treated Patients**:* In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of PRINIVIL®. The diuretic should be discontinued, if possible, for two to three days before beginning therapy with PRINIVIL® to reduce the likelihood of hypotension (see 7 WARNINGS AND PRECAUTIONS). The dosage of PRINIVIL® should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with PRINIVIL® alone, diuretic therapy may be resumed as described above.

If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (see 7 WARNINGS AND PRECAUTIONS, 9 Drug Interactions).

A lower starting dose is required in the presence of renal impairment, in patients in whom diuretic therapy cannot be discontinued, patients who are volume- and/or salt-depleted for any reason, and in patients with renovascular hypertension.

***Dosage Adjustment in Renal Impairment**:* Dosage in patients with renal impairment should be based on creatinine clearance as outlined in the Table below:

Creatinine Clearance		**Starting Dose mg/day**
mL/s	mL/min	
0.5-1.17	31-70	5.0-10.0
0.17-0.49	10-30	2.5-5.0
<0.17 (including patients on dialysis)	<10 (including patients on dialysis)	2.5*

* Dosage and/or frequency of administration should be adjusted depending on the blood pressure response

The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., polyacrylonitrile [PAN] and treated concomitantly with an ACE inhibitor) (see 7 WARNINGS AND PRECAUTIONS).

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

Renovascular Hypertension
Some patients with renovascular hypertension, especially those with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, may develop an exaggerated response to the first dose of PRINIVIL®. Therefore, a lower starting dose of 2.5 or 5 mg is recommended. Thereafter, the dosage may be adjusted according to the blood pressure response.

Congestive Heart Failure
PRINIVIL® is to be used in conjunction with a diuretic and where appropriate digitalis. Therapy must be initiated under close medical supervision, usually in a hospital. Blood pressure and renal function should be monitored, both before and during treatment with PRINIVIL®, because severe hypotension and, more rarely, consequent renal failure have been reported (see 7 WARNINGS AND PRECAUTIONS).

Initiation of therapy requires consideration of recent diuretic therapy and the possibility of severe salt-/volume-depletion. If possible, the dose of diuretic should be reduced before beginning treatment.

The recommended initial dose is 2.5 mg per day. If required, the dose should be increased gradually, depending on the patient response. The usual effective dosage range is 5–20 mg per day administered in a single daily dose. Dose titration may be performed over a 2–4 week period, or more rapidly if indicated by the presence of residual signs and symptoms of heart failure.

Treatment Following Acute Myocardial Infarction
Treatment of hemodynamically stable patients may be started as early as within 24 hours following the onset of symptoms of myocardial infarction. Patients should receive, as appropriate, standard recommended treatments (see 1 INDICATIONS).

The first dose of lisinopril is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily thereafter.

Patients with a low systolic blood pressure (between 100 and 120 mmHg) when treatment is started or during the first three days after the infarct should be given a lower dose, 2.5 mg orally. Treatment with PRINIVIL® must not be initiated in patients who are at risk of serious hemodynamic deterioration (see 7 WARNINGS and PRECAUTIONS). After three days if hypotension occurs (systolic blood pressure less than or equal to 100 mmHg), a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mmHg for more than one hour), PRINIVIL® should be withdrawn.

Renal function should be assessed before and during therapy with PRINIVIL® (see 7 WARNINGS AND PRECAUTIONS).

Dosing should normally continue for six weeks. At that time, patients with signs or symptoms of heart failure should continue with PRINIVIL® (see 4 DOSAGE AND ADMINISTRATION).

PRINIVIL® is compatible with intravenous or transdermal glyceryl trinitrate.

Pediatric Patients
For patients who can swallow tablets, the dose should be individualized according to patient profile and blood pressure response. The recommended initial dose is 2.5 mg in patients 20 to <50 kg and 5 mg in patients ≥50 kg. PRINIVIL® is given once daily. The dosage should be adjusted according to the needs of the patient to a maximum of 20 mg daily in patients 20 to <50 kg and 40 mg in patients ≥50 kg (see 10 CLINICAL PHARMACOLOGY, 10.2 Pharmacodynamics, and 10.3 Pharmacokinetics).

PRINIVIL® is not recommended in pediatric patients <6 years or with glomerular filtration rate <30 mL/min/1.73 m^2 (see 10 CLINICAL PHARMACOLOGY, 10.2 Pharmacodynamics, and 10.3 Pharmacokinetics).

4.5 Missed Dose

Patients should be instructed that if they miss a dose of Prinivil, they should take the next dose as soon as possible. If no more than six hours have elapsed since the missed dose, the patient can take that day's dose of medication and then return to the regularly scheduled time. The Patient should not double the dose.

5 OVERDOSAGE

The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. If available, angiotensin II may be beneficial.

Lisinopril may be removed from the general circulation by hemodialysis (see 7 WARNINGS and PRECAUTIONS, Anaphylactoid Reactions during Membrane Exposure).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Tablet 10 mg, 20 mg	calcium phosphate, corn starch, magnesium stearate, mannitol, pregelatinized starch, and yellow and/or red iron oxides

Tablets PRINIVIL®, 10 mg, are light yellow, oval-shaped compressed tablets, engraved MSD 106 on one side and scored on the other. Available in blister packages of 28 tablets.

Tablets PRINIVIL®, 20 mg, are peach, oval-shaped compressed tablets, engraved MSD 207 on one side and scored on the other. Available in blister packages of 28 tablets.

The splitting of PRINIVIL® tablets is not advised.

COMPOSITION
PRINIVIL® is supplied as 10 mg and 20 mg tablets for oral administration. In addition to the active ingredient lisinopril, each tablet contains the following non-medicinal ingredients: calcium phosphate, corn starch, iron oxide, magnesium stearate, mannitol, and pregelatinized starch. The splitting of PRINIVIL® tablets is not advised.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Angioedema
Angioedema has been reported in patients treated with PRINIVIL® (lisinopril tablets). This may occur at any time during treatment. Angioedema associated with shock may be fatal. If angioedema occurs, PRINIVIL® should be promptly discontinued and the patient should be observed until the swelling subsides. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient. Very rarely, fatalities have been reported due to angioedema associated with laryngeal edema or tongue edema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. When there is airway obstruction, emergency therapy should be administered promptly when indicated. This includes giving subcutaneous adrenaline (0.5 mL 1:1000), and/or maintaining a patent airway. The patient should be under close medical supervision until complete and sustained symptom resolution has occurred.

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

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see 2 CONTRAINDICATIONS).

Patients receiving coadministration of ACE inhibitor and mTOR (mammalian target of rapamycin) inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema. Caution should be used when these drugs are used concomitantly.
Patients receiving concomitant ACE inhibitor and neprilysin inhibitor therapy may be at increased risk for angioedema (see 2 CONTRAINDICATIONS and 9 DRUG INTERACTIONS).

Patients receiving concomitant ACE inhibitor and dipeptidyl peptidase IV (DPP-IV) inhibitors such as alogliptin, linagliptin, saxagliptin, and sitagliptin may be at increased risk for angioedema (see 9 DRUG INTERACTIONS). Caution should be used when these drugs are used concomitantly.

Carcinogenesis and Mutagenesis
See 16 NON-CLINICAL TOXICOLOGY.

Cardiovascular

Dual Blockade of the Renin-Angiotensin System (RAS)
There is evidence that co-administration of angiotensin-converting enzyme inhibitors (ACEIs), such as PRINIVIL®, or of angiotensin receptor antagonists (ARBs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR <60 ml/min/1.73 m^2). Therefore, the use of PRINIVIL® in combination with aliskiren-containing drugs is contraindicated in these patients (see 2 CONTRAINDICATIONS). Further, co-administration of ACEIs,

including PRINIVIL®, with other agents blocking the RAS, such as ARBs or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.

Hypotension: Symptomatic hypotension has occurred after administration of PRINIVIL®, usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, vomiting, or possibly in patients with renin-dependent renovascular hypertension (see 4 DOSAGE AND ADMINISTRATION). In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because blood pressure could potentially fall, patients at risk for hypotension should start therapy under very close medical supervision, usually in a hospital. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of lisinopril and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (see 8 ADVERSE REACTIONS).

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response may not be a contraindication to further doses. These can usually be given to hypertensive patients without difficulty once the blood pressure has increased after volume expansion. However, lower doses of PRINIVIL® and/or reduced concomitant diuretic therapy should be considered.

If hypotension occurs during treatment following acute myocardial infarction, consideration should be given to PRINIVIL® discontinuation (see 8 ADVERSE REACTIONS, and 4 DOSAGE AND ADMINISTRATION, Treatment Following Acute Myocardial Infarction).
In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with PRINIVIL®. If hypotension occurs, a reduction of dose or discontinuation of therapy should be considered.

Hypotension Following Acute Myocardial Infarction: Lisinopril treatment following acute myocardial infarction must not be initiated in patients at risk of further serious hemodynamic deterioration after vasodilator treatment. These include patients with systolic blood pressure of 100 mmHg or lower or those in cardiogenic shock.

During the first three days following the infarction, dosage reduction should occur if systolic blood pressure is between 100 and 120 mmHg (see 4 DOSAGE AND ADMINISTRATION).
Patients with myocardial infarction in the GISSI-3 study treated with PRINIVIL® had a higher (9.0% vs 3.7%) incidence of persistent hypotension (systolic blood pressure less than 90 mmHg for more than 1 hour) than patients treated with placebo.

Valvular Stenosis, Hypertrophic Cardiomyopathy
There is concern on theoretical grounds that patients with aortic stenosis or hypertrophic cardiomyopathy might be at particular risk of decreased coronary perfusion when treated with vasodilators.

PRINIVIL® should be given with caution to these patients.

Ear/Nose/Throat

A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of PRINIVIL® has been reported.
Such a possibility should be considered as part of the differential diagnosis of the cough.

Endocrine and Metabolism

Hypoglycemia: Diabetic patients treated with oral antidiabetic agents or insulin starting an ACE inhibitor should be told to closely monitor for hypoglycemia, especially during the first month of combined use. In addition, hypoglycemia appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment (see 9 DRUG INTERACTIONS).

Hematologic

Neutropenia/Agranulocytosis: Agranulocytosis and bone marrow depression have been caused by angiotensin-converting enzyme inhibitors. Several cases of agranulocytosis and neutropenia have been reported in which a causal relationship to lisinopril cannot be excluded. Current experience with the drug shows the incidence to be rare. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and renal disease.

Hepatic/Biliary/Pancreatic

Patients with Impaired Liver Function: Hepatitis, jaundice (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with lisinopril in patients with or without pre-existing liver abnormalities (see 8 ADVERSE REACTIONS). In most cases the changes were reversed on discontinuation of the drug.

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

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. PRINIVIL® should be used with particular caution in patients with pre-existing liver abnormalities. In such patients, baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply.

Immune

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

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

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

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

Renal

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

The use of ACEIs – including PRINIVIL® – or ARBs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR <60 ml/min/1.73 m^2) (see 2 CONTRAINDICATIONS and 9 DRUG INTERACTIONS).

In acute myocardial infarction, treatment with lisinopril should not be initiated in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 177 µmol/L and/or proteinuria exceeding 500 mg/24 hour. If renal dysfunction develops during treatment with PRINIVIL® (lisinopril tablets) (serum creatinine concentration exceeding 265 µmol/L or a doubling from the pre-treatment value), then the physician should consider withdrawal of PRINIVIL®.

Use of PRINIVIL® should include appropriate assessment of renal function.

Hyperkalemia: In clinical trials hyperkalemia (serum potassium >5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.0% of patients with congestive heart failure. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, potassium-containing salt substitutes or other drugs that may increase serum potassium (e.g., trimethoprim-containing products) (see also 9 DRUG INTERACTIONS).

The use of potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that may increase serum potassium, particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal, arrhythmias.

If concomitant use of PRINIVIL® and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

7.1 Special Populations

7.1.1 Pregnant Women

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, PRINIVIL® should be discontinued as soon as possible.

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

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

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

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

7.1.2 Breast-feeding

The presence of concentrations of ACE inhibitor have been reported in human milk. Use of ACE inhibitors is not recommended during breast-feeding.

7.1.3 Pediatrics

Antihypertensive effects of lisinopril have been established in hypertensive pediatric patient aged 6 to 16 years. There are no data of the effects of lisinopril in hypertensive patients under the age of 6 or in patients with glomerular filtration rate <30 mL/min/1.73 m^2. (See 10 CLINICAL PHARMACOLOGY, and 4 DOSAGE AND ADMINISTRATION).

7.1.4 Geriatrics

In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of PRINIVIL®. Pharmacokinetic studies, however, indicate that maximum blood levels

and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution (see 4 DOSAGE AND ADMINISTRATION).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequent clinical adverse reactions were: dizziness (4.4%), headache (5.6%), asthenia/fatigue (2.7%), diarrhea (1.8%) and cough (3.0%), all of which were more frequent than in placebo-treated patients.

For adverse reactions which occurred in hypertensive patients and patients with congestive heart failure treated with PRINIVIL® (lisinopril tablets) in controlled clinical trials, comparative incidence data are listed in the table below.

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.

Table 2: INCIDENCE OF ADVERSE REACTIONS OCCURRING IN PATIENTS TREATED WITH PRINIVIL® IN CONTROLLED CLINICAL TRIALS

	HYPERTENSION (2633 PATIENTS) %	CONGESTIVE HEART FAILURE (636 PATIENTS) %
Cardiovascular		
Hypotension	0.8	5.2
Orthostatic effects	0.9	1.3
Chest pain	1.1	7.4
Angina	0.3	3.8
Edema	0.6	2.5
Palpitation	0.8	1.9
Rhythm disturbances	0.5	0.6
Dermatologic		
Rash	1.0	5.0
Pruritus	0.5	1.4

	HYPERTENSION (2633 PATIENTS) %	CONGESTIVE HEART FAILURE (636 PATIENTS) %
Gastrointestinal		
Diarrhea	1.8	6.1
Nausea	1.9	4.9
Vomiting	1.1	2.4
Dyspepsia	0.5	1.9
Anorexia	0.4	1.4
Constipation	0.2	0.8
Flatulence	0.3	0.5
Nervous System		
Dizziness	4.4	14.2
Headache	5.6	4.6
Paresthesia	0.5	2.8
Depression	0.7	1.1
Somnolence	0.8	0.6
Insomnia	0.3	2.4
Vertigo	0.2	0.2
Musculoskeletal		
Muscle cramps	0.5	2.2
Back pain	0.5	1.7
Leg pain	0.1	1.3
Shoulder pain	0.2	0.8
Other		
Asthenia/Fatigue	2.7	7.1
Blurred vision	0.3	1.1
Fever	0.3	1.1
Flushing	0.3	0.3
Gout	0.2	1.7

	HYPERTENSION (2633 PATIENTS) %	CONGESTIVE HEART FAILURE (636 PATIENTS) %
Decreased libido	0.2	0.2
Malaise	0.3	1.1
Respiratory		
Cough	3.0	6.4
Dyspnea	0.4	7.4
Orthopnea	0.1	0.9

Angioedema
Angioedema has been reported in patients receiving PRINIVIL® (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with PRINIVIL® should be discontinued and appropriate therapy instituted immediately (see 7 WARNINGS and PRECAUTIONS).

In very rare cases intestinal angioedema has been reported with angiotensin-converting enzyme inhibitors, including lisinopril.

Hypotension
In hypertensive patients, hypotension occurred in 0.8% and syncope occurred in 0.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.3% of hypertensive patients (see 7 WARNINGS and PRECAUTIONS).

In patients with congestive heart failure, hypotension occurred in 5.2% and syncope occurred in 1.7% of patients. Hypotension and dizziness were causes for discontinuation of therapy in 1.7% of these patients.

Treatment Following Acute Myocardial Infarction
In a controlled, open trial, involving 19,394 acute myocardial infarction patients (GISSI-3, see 1 INDICATIONS), comparing lisinopril alone, transdermal glycerol trinitrate, lisinopril and transdermal glycerol trinitrate, or control (no treatment), the most frequent in-hospital adverse events at 6 weeks were as follows:

Table 3: Incidence of adverse reactions occurring in patients treated with lisinopril, transdermal glycerol trinitrate, lisinopril and transdermal glycerol trinitrate, or control

	Control	Lisinopril	Lisinopril + GTN	GTN alone
Event	n=4729 %	n=4713 %	n=4722 %	n=4731 %
Persistent hypotension	3.6	8.8	9.3	3.9
Shock	2.5	2.8	2.2	1.9
Renal dysfunction	1.1	2.4	2.4	1.1
Stroke	0.6	0.6	0.9	0.8
Re-infarction	2.2	2.2	2.2	1.9
Hemorrhagic events	1.2	1.3	1.1	0.9
Post-infarction angina	13.2	13.9	12.3	11.8
Ventricular fibrillation	3.1	2.5	2.4	2.2
Sustained ventricular tachycardia	2.5	2.1	1.8	2.3
Atrial flutter or fibrillation	6.4	6.3	5.3	5.7
Complete atrioventricular block	2.4	2.9	2.5	2.1
Asystole	1.2	1.2	1.3	1.2
Intraventricular septal rupture	0.3	0.4	0.2	0.2
Papillary muscle rupture	0.3	0.4	0.5	0.4
Late CHF (>4 days)	4.5	4.5	4.2	4.2

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The adverse experience profile for pediatric patients appears to be similar to that seen in adult patients.

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

Clinical Trial Findings

Serum Electrolytes

Hyperkalemia and hyponatremia have occurred (see 7 WARNINGS and PRECAUTIONS).

Creatinine, Blood Urea Nitrogen
Increases in blood urea nitrogen and serum creatinine, usually reversible upon discontinuation of therapy, were observed in 1.1 and 1.6% of patients, respectively, with essential hypertension treated with PRINIVIL® alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis (see 7 WARNINGS and PRECAUTIONS). Reversible increases in blood urea nitrogen (14.5%) and serum creatinine (11.2%) were observed in approximately 12.0% of patients with congestive heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased.

Hematology
Decreases in hemoglobin and hematocrit (mean decreases of approximately 0.9 g percent and 0.6 vol percent, respectively) occurred frequently in patients treated with PRINIVIL® but were rarely of clinical importance in patients without some other cause of anemia.

Rarely, hemolytic anemia has been reported.

Agranulocytosis and bone marrow depression, manifested as anemia, thrombocytopenia or leucopenia, have been caused by angiotensin-converting enzyme inhibitors, including lisinopril. Several cases of agranulocytosis and neutropenia have been reported in which a causal relationship to lisinopril cannot be excluded (see 7 WARNINGS and PRECAUTIONS).

Hepatic
Elevations of liver enzymes and/or serum bilirubin have occurred (see 7 WARNINGS and PRECAUTIONS).

Discontinuations
Overall, 1.0% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.8%), serum creatinine (0.1%) and serum potassium (0.1%).

8.5 Post-Market Adverse Reactions

Other Events in Controlled Clinical Trials or Post-Marketing Experience
Additional adverse reactions which were reported rarely, either during controlled clinical trials or after the drug was marketed, include:

Cardiovascular
- Myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high-risk patients (see 7 WARNINGS and PRECAUTIONS)
- Tachycardia

Dermatologic
- Alopecia
- Diaphoresis
- Pruritis
- Urticaria

Endocrine
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Gastrointestinal
- Abdominal pain and indigestion
- Dry mouth
- Pancreatitis
- Vomiting

Hematologic
- Hemolytic anemia

Hepatic
- Hepatitis
- Jaundice (hepatocellular and/or cholestatic)
- Liver function abnormalities
- Hepatic failure

Metabolic
Cases of hypoglycemia in diabetic patients on oral antidiabetic agents or insulin have been reported (see 9 DRUG INTERACTIONS).

Nervous System
- Mental confusion
- Mood alterations
- Paresthesia
- Vertigo

Respiratory
- Bronchospasm
- Rhinitis
- Sinusitis

Severe Skin Disorders
- Erythema multiforme
- Pemphigus
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Cutaneous pseudolymphoma

Special Senses
- Taste disorders

Urogenital
- Acute renal failure
- Impotence
- Oliguria/anuria
- Renal dysfunction
- Uremia

A symptom complex has been reported which may include fever, vasculitis, myalgia, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leukocytosis. Rash, photosensitivity, or other dermatologic manifestations may also occur.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

- Please see section 9.4 drug-drug interaction

9.2 Drug Interactions Overview

- Please see section 9.4 drug-drug interaction

9.3 Drug-Behavioural Interactions

- No information available

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 potential magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4- Established or Potential Drug-Drug Interactions

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Agents Affecting Sympathetic Activity		Beta-adrenergic blocking drugs add some further antihypertensive effect to lisinopril.	Agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) may be used with caution.
Agents Causing Renin Release		The antihypertensive effect of PRINIVIL® is augmented by antihypertensive agents that cause renin release (e.g., diuretics).	

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Dual Blockade of the Renin-Angiotensin System (RAS) with ACEIs, ARBs or aliskiren-containing drugs		Dual Blockade of the Renin-Angiotensin System with ACEIs, ARBs or aliskiren-containing has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.	Dual Blockade of the Renin-Angiotensin System with ACEIs, ARBs or aliskiren-containing drugs is contraindicated in patients with diabetes and/or renal impairment, and is generally not recommended in other patients. See 2 CONTRAINDICATIONS, 7 WARNINGS and PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS).

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Agents Increasing Serum Potassium		Since lisinopril decreases aldosterone production, elevation of serum potassium may occur.	Potassium sparing diuretics such as spironolactone, triamterene or amiloride, or potassium supplements should be given only for documented hypokalemia and with caution and with frequent monitoring of serum potassium since they may lead to a significant increase in serum potassium. Potassium-containing salt substitutes or other drugs that may increase serum potassium (e.g., trimethoprim-containing products) should also be used with caution (see also 7 WARNINGS and PRECAUTIONS).
Gold		Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including lisinopril.	
Hypotension— Patients on Diuretic Therapy		Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with lisinopril.	The possibility of symptomatic hypotension with lisinopril can be minimized by discontinuing the diuretic prior to initiation of treatment with lisinopril and/or lowering the initial dose of lisinopril (see 7 WARNINGS and PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Lithium Salts		As with other drugs which eliminate sodium, the lithium elimination may be reduced.	The serum lithium levels should be monitored carefully if lithium salts are to be administered.
Mammalian Target of Rapamycin (mTOR) Inhibitors		Patients taking concomitant mTOR inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema.	Caution should be used when these drugs are used concomitantly (see 7 WARNINGS and PRECAUTIONS).
Neprilysin Inhibitors		Patients taking a concomitant neprilysin inhibitor (e.g., sacubitril) may be at increased risk for angioedema	(see 2 CONTRAINDICATIONS and 7 WARNINGS and PRECAUTIONS).

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
NSAIDs		Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs. 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 ACE inhibitors or angiotensin II receptor antagonists may result in further deterioration of renal function. Cases of acute renal failure, usually reversible, have been reported. Indomethacin may diminish the antihypertensive efficacy of concomitantly-administered PRINIVIL®.	The antihypertensive effect of ACE inhibitors or angiotensin II receptor antagonists may be attenuated by NSAIDs including selective COX-2 inhibitors. The co-administration of ACE inhibitors or angiotensin II receptor should therefore be administered with caution in this patient population.

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Dipeptidyl peptidase IV (DPP-IV) inhibitors (e.g. alogliptin, linagliptin, saxagliptin, sitagliptin)	C	Patients taking concomitant DPP-IV inhibitors may be at increased risk for angioedema	Caution should be used when using DPP-IV and ACE inhibitors concomitantly (see 7 WARNINGS and PRECAUTIONS).

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

9.5 Drug-Food Interactions

Interactions with food have not been established.

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

PRINIVIL® (lisinopril tablets) is an angiotensin-converting enzyme (ACE) inhibitor which is used in the treatment of hypertension, congestive heart failure and following myocardial infarction in hemodynamically stable patients.

Angiotensin-converting enzyme is a peptidyl dipeptidase which catalyzes the conversion of angiotensin I to the pressor substance, angiotensin II. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release) and decreased aldosterone secretion. Although the latter decrease is small, it results in a small increase in serum K^+. In patients treated with PRINIVIL® and a thiazide diuretic there was essentially no change in serum potassium (see 7 WARNINGS and PRECAUTIONS).

ACE is identical to kininase II. Thus, PRINIVIL® may also block the degradation of bradykinin, a potent vasodilator peptide. However, the role that this plays in the therapeutic effects of PRINIVIL® is unknown.

While the mechanism through which PRINIVIL® lowers blood pressure is believed to be primarily the suppression of the renin-angiotensin-aldosterone system, PRINIVIL® also lowers blood pressure in patients with low-renin hypertension.

10.2 Pharmacodynamics

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

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

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

The antihypertensive effect of angiotensin-converting enzyme inhibitors is generally lower in Black than in non-Black patients.

Administration of PRINIVIL® to patients with congestive heart failure reduces afterload and preload of the heart, resulting in an increase in cardiac output, without reflex tachycardia. Exercise tolerance is improved.

10.3 Pharmacokinetics

The pharmacokinetics of lisinopril were studied in 29 pediatric hypertensive patients between 6 years and 16 years with glomerular filtration rate >30 mL/min/1.73 m^2. After doses of 0.1 to 0.2 mg/kg, steady state peak plasma concentrations of lisinopril occured within 6 hours and the extent of absorption based on urinary recovery was about 28%. These values are similar to those obtained previously in adults. The typical value of lisinopril oral clearance (systemic clearance/absolute bioavailability) in a child weighing 30 kg is 10 L/h, which increases in proportion to renal function.

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

In a study in elderly healthy subjects (65 years and above), a single dose of lisinopril 20 mg produced higher serum concentrations than those seen in young healthy adults given a similar dose. In another study, single daily doses of lisinopril 5 mg were given for 7 consecutive days to young and elderly healthy volunteers and to elderly patients with congestive heart failure. Maximum serum concentrations of lisinopril on Day 7 were higher in the elderly volunteers than in the young, and still higher in the elderly patients with congestive heart failure. Renal clearance of lisinopril was decreased in the elderly, particularly in the presence of congestive heart failure.

Absorption
Based on urinary recovery, the extent of absorption of lisinopril is approximately 25%, with large inter-subject variability (6–60%) at all doses tested (5–80 mg). Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract.

Following multiple doses of lisinopril, the effective half-life of accumulation is 12 hours.

Distribution:

After oral administration of PRINIVIL®, peak serum concentrations of lisinopril occur within approximately 7 hours, although patients with recent myocardial infarction have demonstrated an increase in time to peak serum concentration to about 8 to 10 hours. Declining serum concentrations exhibit a prolonged terminal phase which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose. Lisinopril does not bind serum proteins other than ACE.

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

Elimination
The elimination of lisinopril in patients with renal insufficiency is similar to that in patients with normal renal function until the glomerular filtration rate is 30 mL/min or less. With renal function ≤30 mL/min, peak and trough lisinopril levels increase, time to peak concentration increases and time to steady state is prolonged (see 4 DOSAGE AND ADMINISTRATION).

11 STORAGE, STABILITY AND DISPOSAL
Store at room temperature (15°C–30°C).

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

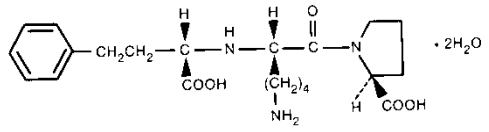
Drug Substance

Proper name: Lisinopril

Chemical name: (S)-1-[N^2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dihydrate.

Molecular formula and molecular mass: $C_{21}H_{31}N_3O_5 \bullet 2H_2O$; 441.53

Structural formula:



Physicochemical properties: Lisinopril is a white to off-white crystalline powder. Lisinopril contains three chiral centers and is optically active. The pKa values of Lisinopril determined by aqueous acidic/basic potentiometric titration at 25°C for pKa1 and pKa2 are 2.5 and 4.0 respectively.

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

14 CLINICAL TRIALS

Pediatric Patients :In a clinical study involving 115 hypertensive pediatric patients 6 to 16 years of age, patients who weighed <50 kg received either 0.625, 2.5, or 20 mg of lisinopril daily and patients who weighed ≥50 kg received either 1.25, 5, or 40 mg of lisinopril daily. At the end of 2 weeks, lisinopril administered once daily lowered trough blood pressure in a dose-dependent manner with consistent antihypertensive efficacy demonstrated at doses >1.25 mg (0.02 mg/kg). This effect was confirmed in a withdrawal phase, where the diastolic pressure rose by about 9 mmHg more in patients randomized to placebo than it did in patients who were randomized to remain on the middle and high doses of lisinopril. The dose-dependent antihypertensive effect of lisinopril was consistent across several demographic subgroups: age, Tanner stage, gender, race. In this study, lisinopril was generally well-tolerated.

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

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

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

Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotoxic effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to angiotensin-converting enzyme inhibitors (captopril and enalapril) with maternal and fetotoxic effects apparent at or below the recommended therapeutic dosage levels in man.

Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorptions at an oral dose of lisinopril of 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). A single intravenous dose of 15 mg/kg of lisinopril administered to pregnant rabbits on gestation days 16, 21 or 26 resulted in 88% to 100% fetal death.
By whole body autoradiography, radioactivity was found in the placenta following administration of labelled lisinopril to pregnant rats, but none was found in the fetuses.

Table 5 - Toxicology

Study	Species/Strain	No. of Animals/Group	Route	Dose	Results
MECHANISM OF ACTION					
In vitro ACE inhibitory activity*	Hog plasma		*In vitro*		IC_{50}=1.7 ± 0.5 nM
Augmentation of contractile response to bradykinin	Guinea pig ileum	7 segments	*In vitro*		AC_{50}=1.6 nM
In vivo ACE inhibition in the rat**	Male Sprague/Dawley	8	I.V.		ID_{50}=2.3 (1.7–3.1) µg/kg
Duration of ACE inhibitory activity of lisinopril in rats**	Male Sprague/Dawley	4	I.V.	3 & 10 µg/kg	Duration approx. 110 min.
In vivo ACE inhibitory activity of lisinopril in conscious rats**	Sprague/Dawley	3–5	P.O.	0.03–3.0 mg/kg (single dose)	Duration of at least 360 min.
In vivo ACE inhibition in anesthetized dogs**	Mongrel	6	I.V.	1–30 µg/kg	ID_{50}=6.5 µg/kg
In vivo ACE inhibitory activity of lisinopril in conscious dogs**	Mongrel	3	P.O.	0.05–1.0 mg/kg (single dose)	Duration of action between 6–24 hrs

* Inhibition of enzymatic activity of hog plasma ACE using ^{14}C labeled substrate.

** Blockage of functional (pressor) response to AI challenge.

Study	Species/Strain	No. of Animals/Group	Route	Dose	Results
EFFECTS ON BLOOD PRESSURE					
Antihypertensive activity in renal hypertensive dogs (single doses)	Mongrel	3	P.O.	0.3 mg/kg with and without hydrochlorothiazide	After 2 hours: Lisinopril alone: 5% reduction in mean systolic pressure vs pretreatment. Lisinopril + HCTZ=11% reduction in mean systolic pressure vs pre-treatment.
Antihypertensive activity in rats on a sodium-deficient diet (single doses)	Male Sprague/Dawley	5	P.O.	0.03–3.0 mg/kg daily for 4 days	After 2 hours: 11% reduction in mean systolic pressure vs pretreatment at 1 mg/kg. 22% reduction in mean systolic pressure vs pre-treatment at 3 mg/kg. Consistent response over 4 days.
Antihypertensive activity in 2 kidney Grollman hypertensive rats (single doses)	Male Sprague/Dawley	6–7	P.O.	1 & 3 mg/kg	At 2 hours: approx. 6% reduction in mean systolic pressure vs pretreatment with the antihypertensive effect lasting up to 24 hours.
Antihypertensive activity in spontaneously hypertensive rats with and without hydrochlorothiazide	SH rats	3–6	P.O.	1.25 mg/kg HCTZ=50 mg/kg daily for 3 days	Enhancement of hypotensive activity over 3–5 days. 2 hours after drug administration, lisinopril alone reduced the average mean arterial pressure from 198 to 161 mmHg. In combination with HCTZ, the average mean arterial pressure was reduced from 202 to 132 mmHg.
Antihypertensive activity in spontaneously hyper-tensive rats (single doses)	SH rats	3–9	P.O. & I.V.	0.1–20 mg/kg	Slight fall in blood pressure at 0.312–5 mg/kg P.O. Pronounced fall at 20 mg/kg P.O. and 0.1 mg/kg I.V. with statistically significant reductions being observed for the majority of time points between 1/2-18 hours.

Table 6 – Acute Toxicity of Lisinopril

LD_{50} Values:

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

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

Table 7 - Subacute/Chronic Toxicology

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

Table 7 - Subacute/Chronic Toxicology (continued)

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

Table 7 - Subacute/Chronic Toxicology (continued)

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Effects
Dog	3-Month with 1-Month Recovery (high dose)	Control 5 M + 5 F 3, 10, 30 mg/kg/day 3 M + 3 F 100 mg/kg/day 8 M + 8 F Recovery Control 2 M + 2 F 100 mg/kg/day 5 M + 5 F	Oral	3, 10, 30 and 100	Eight of 16 dogs given 100 mg died or were killed because of poor physical condition. One of 6 dogs given 30 mg was killed because of poor physical condition. At 10 mg or greater increased BUN and dilation of renal tubules was seen. Fatty degeneration of renal tubular epithelium occurred at the 2 highest dosage levels. The changes are reversible as only slight dilation of renal tubules was present in some animals given 100 mg after 4 weeks of recovery.
Rabbit	2-Week	6 F	Oral	15 (1, 6 & 13 doses) with and without saline	Renal tubular basophilia and renal tubular dilation (considered sequela to necrosis) were seen after 6 and 13 doses in unsupplemented rabbits. Two supplemented rabbits (6 doses) also had the same renal lesion. One rabbit drank very little saline and had increases in BUN, creatinine and potassium. Increases in these parameters were seen in unsupplemented animals after 1, 6, and 13 doses.

Table 8 - Teratology Studies

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

Table 9 - Fertility and Late Gestation and Lactation with Postnatal Evaluation Studies

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

Table 10 - Genotoxicity Studies

Study	Test System	Dose	Results
Mutagenesis			
Microbial mutagen with and without metabolic activation	Salmonella typhimurium TA1535, TA1537, TA98, TA100 Escherichia coli WP2, WP2 uvrA	up to 2000 µg/plate up to 10 mg/plate	Negative for mutagenic potential
In vitro V-79 mammalian cell mutagenesis with and without metabolic activation	Chinese Hamster Lung Cell	up to 10 mM (4.42 mg/mL)	Negative for mutagenic potential
DNA Damage			
In vitro alkaline elution	Rat Hepatocyte	up to 30 mM (13.25 mg/mL)	Negative for induction of DNA single strand breaks
Chromosomal Evaluation			
In vitro chromosomal aberration assay with and without metabolic activation	Chinese Hamster Ovary	up to 30 mM (13.25 mg/mL)	Negative for induction of chromosomal aberration
In vivo chromosomal aberration assay	Bone Marrow Cells of Male Mice	up to 5000 mg/kg	Negative for increases in chromosomal aberrations

Table 11 - Carcinogenicity Studies

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

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PRINIVIL®

(lisinopril tablets, Merck Standard)

Read this carefully before you start taking **PRINIVIL®**. 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 **PRINIVIL®**.

Serious Warnings and Precautions

- You should not take PRINIVIL® while you are pregnant. Taking it while you are pregnant can cause injury and even death to your baby. If you become pregnant while taking this drug, **stop** taking it and get in touch with your doctor as soon as possible.

What is PRINIVIL® used for?

PRINIVIL® is used to:

- treat high blood pressure
- treat heart failure
- reduce the risk of having another heart attack.

It can be used alone or along with other medications to treat your condition.

How does PRINIVIL® work?

PRINIVIL® belongs to a group of drugs called Angiotensin Converting Enzymes (ACE) inhibitors. These types of drugs block your body from making a chemical called angiotensin II. When this chemical enters your blood:

- your blood vessels become narrower. When this happens your blood has less space to move in.
- it also triggers a hormone that makes your body hold on to water.

Having more fluid in your body, in a narrow space will cause your blood pressure to go up.

ACE inhibitors help to lower your blood pressure by:

- reducing the amount of angiotensin II in your body. This allows your blood vessels to relax and become wider. It makes it easier for your blood to flow through your blood vessels.
- lowering the amount of water your body retains.

The lowering of your blood pressure makes it easier for your heart to pump blood. It can also help your heart work better if you have heart failure.

This drug does not cure high blood pressure or congestive heart failure but it helps control these conditions.

What are the ingredients in PRINIVIL®?
Medicinal ingredients: Lisinopril
Non-medicinal ingredients: calcium phosphate, corn starch, magnesium stearate, mannitol, pregelatinized starch, and yellow and/or red iron oxides.

PRINIVIL® comes in the following dosage forms:
Tablets: 10 mg (light yellow) and 20 mg (peach).
PRINIVIL® 5 mg tablets are no longer available, but this strength, as lisinopril, is available at the pharmacy.

Do not use PRINIVIL® if you:
- are allergic to lisinopril or to any of the other ingredients in PRINIVIL®.
- have had an allergic reaction (angioedema):
    a) to any other ACE inhibitor. You can tell you are taking or have taken an ACE inhibitor because these types of drugs have ingredients that end with –'PRIL" (such as enalapril and captopril) or
    b) have been diagnosed with hereditary angioedema. This is an increased risk of getting an allergic reaction that is passed down through your family, or
    c) where the reason for it is not known

  Signs of an allergic reaction include:
    - swelling of the hands, feet, ankles, face, lips, tongue and throat
    - suddenly having trouble breathing or swallowing

  Make sure that you tell your doctor, nurse or pharmacist that this has happened to you before.

- have diabetes or kidney disease and are already taking:
    - a blood pressure-lowering medicine that contains aliskiren (such as Rasilez) or
    - an angiotensin receptor blocker (drugs that have ingredients that end in "-SARTAN").

  Taking these drugs at the same time as PRINIVIL® is not recommended.
- are taking a medicine containing a neprilysin inhibitor (e.g., sacubitril). Do not take PRINIVIL® for at least 36 hours before or after you take sacubitril/valsartan, a medicine containing a neprilysin inhibitor.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PRINIVIL®. Talk about any health conditions or problems you may have, including if you:
- are breastfeeding. It is possible that PRINIVIL® passes into breast milk. You should not breast-feed while you are taking it.
- have liver disease
- have low blood pressure
- have heart and blood vessel disease
- are at risk for developing high levels of potassium in your blood. This can be serious and can happen if you:
    - are taking:
        - a salt substitute that contains potassium
        - potassium supplements
        - a potassium-sparing diuretic (a specific kind of "water pill" that makes your body hold onto potassium such as spironolactone, triamterene or amiloride).

    - other drugs that may increase serum potassium (e.g., trimethoprim-containing products).
  - have diabetes or any kidney problems.
- have diabetes and are taking oral medications or insulin. You should closely monitor yourself for low blood glucose levels especially during the first month of taking PRINIVIL®.
- have recently suffered from excessive vomiting or severe diarrhea
- are planning to have dental or any other type of surgery and will be given anesthesia. Tell your doctor or dentist that you are taking this drug.
- Are taking a medicine containing a neprilysin inhibitor (e.g., sacubitril).

Other warnings you should know about:

Low Blood Pressure: You may feel dizzy or light headed:

- particularly in the first few days after you start taking PRINIVIL®. You should lie down if this happens. You should avoid driving or doing any tasks that require special attention.
- when you exercise or when the weather is hot.

If you faint, **stop** taking the drug and talk to your doctor.

Blood tests: While you are taking PRINIVIL® your doctor may do blood tests to check:

- the level of white blood cells in your blood
- the potassium levels in your blood.
- that your kidneys are working properly

Cough: You may develop a cough while taking PRINIVIL®. This usually goes away once you stop taking it or when the dose is lowered.

Black patients: you are at a higher risk for having an allergic reaction (angioedema).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with PRINIVIL®:

- Drugs that lower your blood pressure. These include:
  - diuretics ("water pills")
  - aliskiren-containing drugs (such as Rasilez)
  - angiotensin receptor blockers (ARBs)
  - other drugs that are used to lower blood pressure
- Drugs that can increase the levels of potassium in your blood. These include:
  - potassium-sparing drugs (such as spironolactone, triamterene or amiloride)
  - potassium supplements
  - salt substitutes that contain potassium
  - other drugs that may increase serum potassium (e.g., trimethoprim-containing products)
- Drugs used to treat diabetes (including oral drugs and insulin)
- Lithium (used to treat a certain kind of depression)
- Injectable gold (in the form of gold sodium aurothiomalate) used to treat arthritis

- Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) used to reduce pain and swelling (such as naproxen, ibuprofen and celecoxib)
- Drugs used for mTOR inhibitor therapy (such as temsirolimus, sirolimus, everolimus). These drugs are used to lower the body's ability to reject a transplant or to treat certain cancers. Taking these drugs together with PRINIVIL® could increase the risk for an allergic reaction called angioedema.
- A medicine containing a neprilysin inhibitor (e.g., sacubitril). Taking these drugs together with PRINIVIL® could increase the risk for an allergic reaction called angioedema.
- Indomethacin (used to treat pain and swelling)
- Certain drugs that you can buy without a prescription are known to cause your blood pressure to go up. These include drugs:
    - to control your hunger
    - for asthma
    - to treat colds and coughs
    - to treat allergies (such as hayfever)
    - to treat sinus problems
- DPP-IV inhibitors (e.g. alogliptin, linagliptin, saxagliptin, sitagliptin)

You should not take these types of medicines unless you have talked it over with your doctor first.

How to take PRINIVIL®:
Swallow the tablet **whole. You should not split or break the tablets.**
If your doctor has given you specific instructions to follow, for example to eat a low salt diet or to lose weight, you should follow them.

Take PRINIVIL®:
- exactly as your doctor has told you how to take it
- once a day at about the same time every day
- with or without food

Usual dose:
Your doctor has decided on the best dose for you based on your needs.
Even if you feel better, you should not stop taking this medicine unless your doctor tells you to.

Overdose:

If you think you, or a person you are caring for, have taken too much PRINIVIL®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Symptoms of an overdose include:
- feeling light headed or dizzy. This can happen because of a sudden or extreme drop in blood pressure.

Missed Dose:
- If it has been **less** than 6 hours since you missed taking it, take your dose as soon as possible and then go back to your regular schedule.
- If it has been **more** than 6 hours since you missed taking it, skip the missed dose. Take the next dose at your usual time.

Do not take two doses at the same time.

What are possible side effects from using PRINIVIL®?
These are not all the possible side effects you may have when taking [Brand name]. If you experience any side effects not listed here, tell your healthcare professional.

- Dry cough
- Sore throat
- Stuffy or runny nose
- Unusual tiredness and/or weakness
- Headache
- Pain in the abdomen
- Hair loss
- Changes in your mood or confusion
- Changes in taste
- Impotence (not able to have an erection)

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			
Low Blood Pressure: Dizziness, light-headedness or fainting especially during the first few days of starting PRINIVIL®, following exercise, and/or when it is hot and you have lost a lot of water by sweating.	X		
Increased Levels of Potassium in the Blood: irregular heartbeat, muscle weakness and generally feeling unwell		X	
Diarrhea	X		
UNCOMMON			
Allergic Reaction (angioedema): swelling of face, eyes, lips, tongue and/ or throat, hands or feet.			X
Kidney Disorder: change in the frequency of urination, nausea, vomiting, swelling of the extremities (hands and feet), fatigue		X	

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	
Liver Disorder (jaundice): yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of weight		X	
Electrolyte Imbalance: weakness, drowsiness, muscle pain or cramps, irregular heartbeat		X	
Rash		X	
RARE			
Decreased Platelets: bruising, bleeding, fatigue and weakness		X	
Decreased White Blood Cells: infections, fatigue, aches, pains and flu –like symptoms		X	
Heart Attack: chest pain and/or discomfort, pain in the jaw, shoulders, arm and/or back, shortness of breath, sweating, light-headedness, nausea			X
Cerebro-vascular accident/ Stroke: weakness, trouble speaking, trouble seeing, headache, dizziness			X
Skin Disorders: Steven Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), pemphigus			X
UNKNOWN			
Fever, loss of appetite and itching		X	

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.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 your tablets:

- between 15°C - 30°C
- in the original packaging
- away from heat, direct sunlight, and damp places

Keep out of reach and sight of children.
Do not take PRINIVIL® after the expiry date on the package.

If you want more information about PRINIVIL:

- 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 [website], or by calling 1-800-[phone number].

This leaflet was prepared by Merck Canada Inc

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