PRODUCT MONOGRAPH

PrLONITEN®
(Minoxidil Tablets USP)

2.5 mg and 10 mg

ANTIHYPERTENSIVE

®TM Pharmacia & Upjohn Company LLC
Pfizer Canada Inc., Licensee
17,300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

Date of Revision:
November 14, 2013

Submission Control No: 167423

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION....3
SUMMARY PRODUCT INFORMATION....3
INDICATIONS AND CLINICAL USE....3
CONTRAINDICATIONS....3
WARNINGS AND PRECAUTIONS....4
ADVERSE REACTIONS....7
DRUG INTERACTIONS....9
DOSAGE AND ADMINISTRATION....10
OVERDOSAGE....12
ACTION AND CLINICAL PHARMACOLOGY....12
STORAGE AND STABILITY....14
DOSAGE FORMS, COMPOSITION AND PACKAGING....14

PART II: SCIENTIFIC INFORMATION....15
PHARMACEUTICAL INFORMATION....15
DETAILED PHARMACOLOGY....16
TOXICOLOGY....17
REFERENCES....21

PART III: CONSUMER INFORMATION....22

PrLONITEN®

(minoxidil)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
oral	tablet 2.5 mg , 10 mg	Colloidal silicon dioxide, corn starch, lactose, magnesium stearate, microcristaline cellulose

INDICATIONS AND CLINICAL USE

Because of the potential for serious adverse effects, LONITEN (minoxidil) is indicated only for:

- The treatment of severe hypertension that is symptomatic or associated with target organ damage and is not manageable with maximum therapeutic doses of a diuretic plus two other antihypertensive drugs.

At the present time, use in milder degrees of hypertension is not recommended because of the benefit-risk relationship in such patients has not been defined.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- In pheochromocytoma because it may reflexively stimulate secretion of catecholamines from the tumor.
- In pulmonary hypertension associated with mitral stenosis.
- In patients with severe hepatic impairment.

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

LONITEN is not recommended during pregnancy and in women of childbearing potential not using contraception. Neonatal hypertrichosis has been reported following exposure to minoxidil during pregnancy.

General

Salt and Water Retention:

Congestive Heart Failure - Concomitant use of an adequate diuretic is required. LONITEN (minoxidil) must usually be administered concomitantly with a diuretic adequate to prevent fluid retention and possible congestive heart failure, a high-ceiling (loop) diuretic is almost always required. Hemodilution may occur leading to a temporary (during the first 28 weeks of treatment) decrease in hematocrit, hemoglobin, and erythrocyte count (by approximately 7% initially which then recovers to pretreatment levels). Fluid and electrolyte balance and body weight should be monitored closely.

When using a concomitant diuretic to prevent or treat fluid retention, careful attention to adjusting the dosage of the diuretic is required for maximum safety and efficacy (See DOSAGE AND ADMINISTRATION: Concomitant Therapy).

If LONITEN is used without a diuretic, retention of several hundred mili-equivalents of salt and corresponding volumes of water can occur within a few days, leading to increased plasma and interstitial fluid volume and local and generalized edema. Diuretic treatment, alone or in combination with restricted salt intake, will usually minimize fluid retention, although reversible edema did develop in approximately 10% of non-dialysis patients so treated. Diuretic effectiveness was limited mostly by disease-related impaired renal function. The condition of patients with pre-existing congestive heart failure occasionally deteriorated in association with fluid retention although because of the fall in blood pressure (reduction of afterload), more than twice as many improved than worsened. Rarely, refractory fluid retention may require discontinuation of LONITEN.

Provided that the patient is under close medical supervision, it may be possible to resolve refractory salt retention by discontinuing LONITEN for 1 or 2 days and then resuming treatment in conjunction with vigorous diuretic therapy.

Cardiovascular

Tachycardia: LONITEN increases the heart rate. This increase can be partly or entirely prevented by the concomitant administration of a beta-adrenergic blocking drug or other sympathetic nervous system suppressant. Round-the-clock effectiveness of the sympathetic

suppressant should be assured. In addition, angina may worsen or appear for the first time during LONITEN treatment, probably because of the increased oxygen demands associated with increased heart rate and cardiac output. This can usually be prevented by sympathetic blockade. Concomitant treatment to prevent tachycardia is usually required.

When using a concomitant sympatholytic to prevent tachycardia, careful attention to adjusting the dosages of the beta blocker or other sympathetic nervous system suppressant is required for maximum safety and efficacy (see DOSAGE AND ADMINISTRATION: Concomitant Therapy).

Myocardial Infarction: LONITEN has not been used in patients who have had a myocardial infarction within the preceding month. It is possible that a reduction of arterial pressure with LONITEN might further limit blood flow to the myocardium, although this might be compensated by decreased oxygen demand because of lower blood pressure.

Pericarditis, Pericardial Effusion and Tamponade: Observe patients for signs and symptoms of pericardial effusion.

Although there is no evidence of a causal relationship, there have been multiple reports of pericarditis occurring in association with minoxidil.

Pericardial effusion, occasionally with tamponade, has been observed in about 3% of treated patients not on dialysis, especially those with inadequate or compromised renal function. Although in many cases the pericardial effusion was associated with a connective tissue disease, the uremic syndrome, congestive heart failure, or marked fluid retention, there have been instances in which these potential causes of effusion were not present. Patients should be observed closely for any suggestion of a pericardial disorder, and echocardiographic studies should be carried out if suspicion arises. More vigorous diuretic therapy, dialysis, pericardiocentesis, or surgery may be required. If the effusion persists, withdrawal of LONITEN should be considered in light or other means of controlling the hypertension and the patient's clinical status.

Endocrine and Metabolism

Hair Change
Abnormal hair growth is a common occurrence with LONITEN (minoxidil) treatment (See ADVERSE REACTIONS). This is especially disturbing to women and children and patients should be thoroughly informed about this effect before therapy with LONITEN is begun.

Skin

Hypersensitivity
Hypersensitivity to LONITEN, manifested as a skin rash including rare reports bullous eruptions and Stevens-Johnson syndrome, has been seen.

Special Populations

Pregnant Women: The safety for use of LONITEN in pregnancy has not been established. Studies in animals have shown reproductive toxicity (see TOXICOLOGY). Minoxidil has been shown to reduce the conception rate in rats and to show evidence of increased fetal absorption in rabbits when administered at five times the human dose. There was no evidence of teratogenic effects in rats and rabbits. LONITEN is not recommended during pregnancy and in women of childbearing potential not using contraception. Neonatal hypertrichosis has been reported following exposure to minoxidil during pregnancy.

Nursing Women: Minoxidil has been reported to be excreted in human milk. A risk to the suckling child cannot be excluded. As a general rule, nursing should not be undertaken while a patient is on LONITEN.

Hypertension: Hazard of Rapid Control of Blood Pressure in patients with severe/malignant hypertension- In patients with very severe blood pressure elevation, too rapid control of blood pressure, especially with intravenous agents, can precipitate cerebrovascular accidents and myocardial infarction. Although such events have not been unequivocally associated with LONITEN use, total experience is limited at present.

Any patient with malignant hypertension should have initial treatment with LONITEN carried out in a hospital setting, both to assure that blood pressure is falling and to assure that it is not falling more rapidly than intended.

Renal Impairment: Renal failure or dialysis patients may require smaller doses of LONITEN and should have close medical supervision to prevent exacerbation of renal failure or precipitation of cardiac failure. If LONITEN therapy must be discontinued in a patient who has been treated effectively, the drug should be phased out gradually or replaced with another antihypertensive agent. Careful monitoring of the patient's blood pressure during the treatment adjustment is necessary.

Hepatic Impairment: LONITEN is contraindicated in patients with severe hepatic impairment. For mild and moderate hepatic impairment, dosage adjustment should be considered, starting therapy at a reduced dosage and titrating up to the lowest effective dose to obtain desired therapeutic effect. (See DOSAGE and ADMINISTRATION section).

Pediatrics (< 18 years of age): Use in children has been limited to date, particularly in infants. The recommendations under DOSAGE AND ADMINISTRATION can be considered only a rough guide and careful titration is essential.

Geriatrics (> 65 years of age): Clinical studies of LONITEN Tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should

be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Monitoring and Laboratory Tests

Salt and Water Retention: fluid and electrolyte balance and body weight should be closely monitored (see WARNINGS AND PRECAUTIONS, Salt and Water Retention).

Pericardial Effusion: Patients should be observed for signs and symptoms of pericardial effusion (see WARNINGS AND PRECAUTIONS, Cardiovascular, Pericarditis, Pericardial Effusion, and Tamponade).

Myocardial Infarction: Use after myocardial infarction-LONITEN Tablets have not been used in patients who have had a myocardial infarction within the preceding month. It is possible that a reduction of arterial pressure with LONITEN might further limit blood flow to the myocardium, although this might be compensated by decreased oxygen demand because of lower blood pressure (see WARNINGS AND PRECAUTIONS – Cardiovascular, Myocardial Infarction)

Renal failure/dialysis: patients may require smaller doses of LONITEN and should have close medical supervision to prevent exacerbation of renal failure or precipitation of cardiac failure.

ECG Changes: Changes in direction and magnitude of the ECG T-waves occur in approximately 60% of patients treated with LONITEN. In rare instances, large negative amplitude of the T-wave may encroach upon the ST segment, but the ST segment is not independently altered. These changes usually disappear with continuance of treatment and revert to the pre-treatment state if LONITEN is discontinued. No symptoms have been associated with these changes.

Laboratory tests: Those laboratory tests which are abnormal at the time of initiation of minoxidil therapy, such as urinalysis, renal function tests, EKG, chest X-ray, echocardiogram, etc., should be repeated at intervals to ascertain whether improvement or deterioration is occurring under minoxidil therapy. Initially such tests should be performed frequently, e.g., 1-3 month intervals; later as stabilization occurs, at intervals of 6-12 months.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Elongation, thickening, and enhanced pigmentation of fine body hair (hypertrichosis), are seen in about 80% of patients taking LONITEN (minoxidil). This develops within 3 to 6 weeks after starting therapy. It is usually first noticed on the temples, between the eyebrows, between the hairline and the eyebrows, or in the sideburn area of the upper lateral cheek, later extending to the back, arms, legs and scalp. Upon discontinuation of LONITEN, new hair growth stops, but 1 to 6 months may be required for restoration to pretreatment appearance. No endocrine

abnormalities have been found to explain the abnormal hair growth; thus, it is hypertrichosis without virilism.

Clinical Trial Adverse Drug Reactions

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

Common Clinical Trial Adverse Drug Reactions (≥1%)

General Disorders: Edema associated with or independent of weight gain (See WARNINGS AND PRECAUTIONS, Salt and Water Retention) - Concomitant Use of Adequate Diuretic is Required). Temporary edema, developed in 7% of patients who were not edematous at the start of therapy.

Cardiac Disorders: Tachycardia (see WARNINGS AND PRECAUTIONS, Cardiovascular, tachycardia. Concomitant Treatment to Prevent Tachycardia is usually required); Pericarditis (≥10%); Pericardial effusion, Cardiac tamponade; Angina pectoris (frequency unknown)

Gastro-intestinal Disorders: Gastro-intestinal Disorders

Metabolism and Nutrition Disorders: Fluid retention

Skin and Subcutaneous Tissue Disorders: Hypertrichosis, Hair changes (≥10%)

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

Blood and Lymphatic System Disorder: Leukopenia, Thrombocytopenia; Anemia (frequency unknown)
Cardiovascular: Pleural effusion

Reproductive System and Breast Disorders: Breast tenderness

Skin and Subcutaneous Tissue Disorders: Stevens - Johnson syndrome, dermatitis bullous, rash; Toxic Epidermal Necrolysis (frequency unknown)

Abnormal Hematologic and Clinical Chemistry Findings

Electrocardiogram abnormal (≥10%) (T wave, ST interval) (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests);

Hemo-dilution-hematocrit, hemoglobin and erythrocyte count (temporary decrease); Alkaline phosphatase increased, (≥1%)

Blood creatinine increased, blood urea increased (frequency unknown)

DRUG INTERACTIONS

Drug-Drug Interactions

Glucuronidation
Minoxidil is metabolized in the liver predominantly by conjugation with glucuronic acid to form minoxidil O-glucuronide, the primary metabolite. As a result, strong UDP glucuronosyl transferase (UGT) inhibitors (e.g. probenecid, valproic acid, and atazanavir) may increase plasma concentrations of minoxidil. Therefore, a dose adjustment and safety monitoring is advised when initiating treatment or avoid coadministration with minoxidil. (See DOSAGE and ADMINISTRATION and ACTION and CLINICAL PHARMACOLOGY –Pharmacokinetics - Metabolism sections).

Guanethidine - Although LONITEN does not itself cause orthostatic hypotension, its administration to patients already receiving guanethidine can result in profound orthostatic effects. If at all possible guanethidine should be discontinued well before LONITEN is begun. Where this is not possible, LONITEN therapy should be started in the hospital and the patient should remain institutionalized until severe orthostatic effects are no longer present or the patient has learned to avoid activities that provoke them.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Drug-laboratory interactions have not been established.

Drug-Lifestyle Interactions

Effects on ability to drive and use machines
No studies on the effect of minoxidil on the ability to drive or use machines have been performed. The ability to drive or operate machinery may be influenced by the individual response to treatment, particularly at the start of therapy. Caution is advised.

DOSAGE AND ADMINISTRATION

Dosing Considerations

If LONITEN therapy must be discontinued in a patient who has been treated effectively, the drug should be phased out gradually or replaced with another antihypertensive agent. Careful monitoring of the patient's blood pressure during the treatment adjustment is necessary.

Recommended Dose and Dosage Adjustment

Patients over 12 Years of Age:
The recommended initial daily dosage of LONITEN (minoxidil) is 5 mg given in two divided doses. Daily dosage can be increased to 10, 20 and then to 40 mg per day in divided doses, at 3 day intervals or longer, if required for optimum blood pressure control. The effective dosage range is usually 10 to 40 mg per day. In certain patients, doses up to a maximum of 100 mg per day may be attempted, recognizing the probability of an increase in the incidence and severity of adverse reactions.

Patients under 12 Years of Age: The initial recommended daily dosage is 0.2 mg/kg LONITEN in two divided doses. The dosage may be increased by 0.1 to 0.2 mg/kg/day increments, at 3 day intervals or longer, until optimum blood pressure control is achieved. The effective dosage range is usually 0.25 to 1.0 mg/kg/day. The maximum recommended dose is 50 mg/day.

Dose Regimen: The magnitude of within-day fluctuation of arterial pressure during therapy with LONITEN is directly proportional to the extent of pressure reduction. When the targeted blood pressure has been reached, a change from twice daily to once daily dosing with LONITEN may be tried in those patients in whom the diastolic pressure has been reduced less than 30 mm Hg. If supine diastolic pressure has been reduced more than 30 mm Hg, the twice daily dosage schedule should be maintained.

Dosage Adjustment: Dosage must be titrated carefully according to individual response. Intervals between dosage adjustments normally should be at least 3 days since the full response to a given dose is not obtained for at least that amount of time.

Where a more rapid management of hypertension is required, a 5 mg dose can be given every 6 hours if the patient is hospitalized and carefully monitored (See WARNINGS).

Special Population:

Renal Impairment: Renal failure or dialysis patients may require smaller doses of LONITEN and should have close medical supervision to prevent exacerbation of renal failure or precipitation of cardiac failure.

Mild to moderate Hepatic Impairment: Dosage adjustment should be considered, starting therapy at a reduced dosage and titrating to the lowest dose to obtain desired therapeutic effect. See

WARNINGS and PRECAUTIONS section.

Dosage Adjustment with concomitant therapy:

Strong UGT inhibitors: Consider lower doses when initiating treatment or avoid coadministration with minoxidil (See Drug Interactions section).

Diuretics: To prevent fluid retention and possible congestive heart failure, LONITEN must be used in conjunction with a high ceiling (loop) diuretic in patients relying on renal function for maintaining salt and water balance. Diuretics have been used at the following dosages when starting therapy with LONITEN: hydrochlorothiazide (50 mg b.i.d.) or other thiazides at equi-effective dosage; chlorthalidone (50 to 100 mg once daily); furosemide (40 mg b.i.d).

If excessive salt and water retention results in a weight gain of more than 2.0 kg, diuretic therapy should be changed to furosemide; if the patient is already taking furosemide, dosage should be increased in accordance with the patient's requirements. Rarely, refractory fluid retention may require discontinuation of LONITEN. Provided that the patient is under close medical supervision, it may be possible to resolve refractory fluid retention by discontinuing LONITEN for 1 or 2 days and then resuming treatment in conjunction with vigorous diuretic therapy.
In dialysis patients also receiving diuretic therapy, use of LONITEN may create the need to raise diuretic dosage or to increase the frequency or duration of dialysis in order to maintain salt and water balance.

Sympathetic Nervous System Suppressants: The preferred agent to achieve sympathetic nervous system suppression is a ß-blocker equivalent to an adult propranolol dosage of 80 to 160 mg/day. Higher doses may be required when patients, pretreated with a ß-blocker, have an increase in heart rate exceeding 20 beats per minute or when simultaneous introduction of LONITEN and a ß-blocker causes an increase in heart rate exceeding 10 beats per minute.

If beta blockers are contraindicated, methyldopa (250 to 750 mg b.i.d.) may be used instead. Methyldopa must be given for at least 24 hours before starting therapy with LONITEN because of the delay in the onset of methyldopa's action. Limited clinical experience indicates that clonidine may also be used to prevent tachycardia induced by LONITEN; the usual dosage is 0.1 to 0.2 mg twice daily.

Sympathetic nervous system suppressants may not completely prevent an increase in heart rate due to LONITEN but usually do prevent tachycardia. Typically, patients receiving a beta blocker prior to initiation of therapy with LONITEN have a bradycardia and can be expected to have an increase in heart rate toward normal when LONITEN is added. When treatments with LONITEN and a beta blocker, or other sympathetic nervous system suppressant, are begun simultaneously, their opposing cardiac effects usually nullify each other, leading to little change in heart rate.

OVERDOSAGE

There have been only a few instances of deliberate or accidental overdosage with LONITEN (minoxidil). When exaggerated hypotension is encountered, it is most likely to occur in association with residual sympathetic nervous system blockade from previous therapy (guanethidine-like effects of α-adrenergic blockade). The recommended treatment is intravenous administration of normal saline.

Sympathomimetic drugs, such as norepinephrine or epinephrine, should be avoided because of their excessive cardiac-stimulating action. Phenylephrine, angiotensin II, vasopressin and dopamine, which reverse the effects of LONITEN, should only be used if inadequate perfusion of a vital organ is evident.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

LONITEN (minoxidil) is an orally effective direct acting peripheral vasodilator that reduces elevated systolic and diastolic blood pressure by decreasing peripheral vascular resistance. The smooth musculature of the resistance vessels is considered to be the site of action for the relaxant effect of minoxidil. The active metabolite of minoxidil activates the ATP-modulated potassium (K^+ATP) channel causing K^+ efflux, hyperpolarization, and smooth muscle relaxation.

Pharmacodynamics

Because of peripheral vasodilatation, sympathetic reflexes mediated by baroreceptors secondarily increase heart rate and myocardial contractility, thereby increasing cardiac output. In addition, the plasma renin activity is increased via sympathetic nervous system stimulation, which results in an increased angiotensin II concentration with subsequent increased aldosterone secretion. In this way, the renal sodium excretion is reduced and extracellular volume increased. The pulmonary artery pressure may occasionally increase after the administration of minoxidil alone. However, these adverse effects are decreased with the recommended concomitant therapy (beta-blocker plus diuretic).

Pharmacokinetics

Absorption: Absorption: After oral administration in humans, minoxidil is at least 90% absorbed in the gastrointestinal tract. Minoxidil is detected within 30 minutes in the plasma. Maximum plasma levels of the parent drug are reached within the first hour after administration and decline rapidly thereafter.

Bioavailability: Comparative studies on the bioavailability of tablets and oral solutions (each containing 5 mg minoxidil) in hypertensive patients showed bioequivalent behaviour with regard to the average area under the serum level curve (AUC), maximum blood concentrations, time until reaching them (approximately 40 minutes), and the type of effect (antihypertensive). The chronic oral administration of minoxidil leads neither to accumulation nor to a change of the availability compared with administration of a single dose.

Distribution: Minoxidil is not bound to plasma proteins and does not cross the blood-brain barrier.

Metabolism: At least 90% of the administered drug is metabolized in the liver, predominantly by conjugation with glucuronic acid at the N-oxide position in the pyrimidine ring, but also by conversion to more polar products. The primary metabolite in humans is the minoxidil O-glucuronide. Some polar metabolites are also produced.
Avoid coadministration of minoxidil with strong UDP glucuronosyl transferase (UGT) inhibitors (e.g. probenecid, valproic acid, and atazanavir) which may increase plasma concentrations of minoxidil or adjust dosage and monitor safety when coadministration is considered. (See WARNINGS and PRECAUTIONS, DRUG INTERACTIONS, DOSAGE and ADMINISTRATION and Special Populations and Conditions below).

Excretion: Known metabolites exert much less pharmacologic effect than minoxidil itself, and all are excreted principally in the urine. Minoxidil does not bind to plasma proteins, and its renal clearance corresponds to the glomerular filtration rate. In the absence of functional renal tissue, minoxidil and its metabolites can be removed by hemo-dialysis, although this does not rapidly reverse its pharmacological effect.

The extent and time-course of blood pressure reduction by minoxidil do not correspond closely to its concentration in plasma. After a single oral dose, blood pressure usually starts to decline within one-half hour, reaches a minimum between 2 and 3 hours, and recovers at an arithmetically linear rate of about 30% / day. The average plasma half-life in man is approximately 4 hours. The total duration of effect is several days (approximately 72 hours). When minoxidil is administered chronically, the time required to achieve maximum effect on blood pressure is inversely related to the size of the dose.

Special Populations and Conditions

Renal Insufficiency: Pericardial effusion, occasionally with tamponade, has been observed in about 3% of treated patients not on dialysis, especially those with inadequate or compromised renal function. Patients should be observed closely for any suggestion of a pericardial disorder, and echocardiographic studies should be carried out if suspicion arises. More vigorous diuretic therapy, dialysis, pericardiocentesis, or surgery may be required (see WARNINGS AND PRECAUTIONS).

To prevent fluid retention and possible congestive heart failure, LONITEN must be used in conjunction with a high ceiling (loop) diuretic in patients relying on renal function for

maintaining salt and water balance (see DOSAGE AND ADMINISTRATION).

Hepatic Impairment: The pharmacokinetics of minoxidil has not been studied in patients with moderate to severe hepatic impairment. In a pharmacokinetic study in patients with mild cirrhosis, eight patients with biopsy-proven mild cirrhosis and eight healthy subjects received minoxidil 5 mg. The elimination rate constant of minoxidil was significantly reduced by approximately 21% and AUC increased approximately 50% in patients with cirrhosis relative to healthy controls. (See WARNINGS and PRECAUTIONS and DOSAGE and ADMINISTRATION sections). Minoxidil is contraindicated in patients with severe hepatic impairment. For mild and moderate hepatic impairment, dosage adjustment should be considered, starting therapy at a reduced dosage and titrating up to the lowest effective dose to obtain desired therapeutic effect. (See WARNINGS & PRECAUTIONS-SPECIAL POPULATIONS section).

STORAGE AND STABILITY

LONITEN should be stored at controlled room temperature (15 to 30^{o}C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

LONITEN tablets are supplied as 2.5 mg and 10 mg tablets, in bottles of 100

LONITEN 2.5 mg tablets: each round, white tablet is scored and embossed with a “U” and 121 on one side and 2 ½ on the other side.

LONITEN 10 mg tablets: each round, white tablet is scored and embossed with a “U” and 137 on one side and 10 on the other side.

Non-medicinal ingredients (both strengths): cornstarch, lactose, magnesium stearate, microcrystalline cellulose and silicon dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

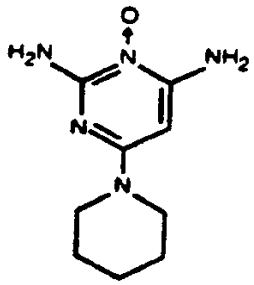
Drug Substance

Proper name: minoxidil

Chemical name: 2,4,-Pyrimidinediamine,6-(1-piperidinyl)-3,oxide

Molecular formula and molecular mass: C9H15N5O
209.25

Structural formula:



Physicochemical properties: A white or off-white, odourless, crystalline solid that is soluble in water to the extent of approximately 2 mg/mL; it is readily soluble in propylene glycol or ethanol, and is almost insoluble in acetone, chloroform or ethyl acetate. It has a melting point of 248^{o}C, a pKa of 4.60, a logP of 0.6 (octanol/water pertition coefficient), and pH in aqueous solution of 7.0 (due to very low solubility in water).

DETAILED PHARMACOLOGY

Non-clinical Pharmacology

Minoxidil produces a dose-related reduction in mean arterial blood pressure following oral administration to rats, dogs, monkeys, and minipigs. The onset of action was within 2 hours regardless of the route of administration, and the activity persisted at near maximum for more than 24 hours.

Minoxidil acts on vascular smooth muscle to reduce resistance to blood flow. This effect appears to be direct since it was not antagonized by beta-adrenergic, cholinergic, or histaminergic blocking agents or by decentralization with higher spinal anesthesia. The vasculature of dogs remained responsive to the vasoconstrictor action of norepinephrine, angiotensin II and vasopressin and to vasodilator action of acetylcholine, histamine, glyceryl-trinitrate, and isoproterenol.

In dogs measurements with radio-labelled microspheres indicated that minoxidil increased blood flow to the myocardium 8-11 fold, 60-70% to skin, skeletal muscle, pancreas and gastrointestinal tract whereas blood flow to the adrenals, kidneys, spleen, liver and the central nervous system was unchanged. Vascular resistance was reduced in all tissues studied with the exception of the liver.

The administration of minoxidil to intact dogs markedly increased cardiac output, heart rate and left ventricular dP/dt in association with the decreased total peripheral resistance. These changes in cardiac function did not appear to be a direct effect. Sympathetic nerve tone was increased as evidenced by increased urinary excretion of norepinephrine and augmented blood pressure reduction in response to ganglionic blockade, but sympathetic activity alone did not account for the increase in heart rate and cardiac output. Chronic stimulation of the carotid sinus nerves or ganglionic blockade more effectively prevented the cardiac hyperactivity associated with minoxidil treatment suggesting an important component of the heart changes is a withdrawal of vagal tone.

Minoxidil produced an acute reduction in renal salt and water excretion in rats and dogs but did not significantly influence renal hemodynamics.

At approximately a 15% expansion of total body exchangeable sodium, in chronically treated animals, salt and water balance were re-established at an expanded~~,~~ extracellular fluid volume. Hypersecretion of mineralocorticosteroids, which occurred during minoxidil treatment, did not explain this salt retaining action. Also, sodium clearance increased when minoxidil was delivered directly into the renal artery and~~,~~ thus, direct activation of electrolyte reabsorptive transport in the kidney did not account for the retention phenomenon. Minoxidil-induced salt and water retention and attendant extracellular fluid volume expansion was reduced by concomitant administration of hydrochlorothiazide.

Minoxidil elevated plasma glucose concentration in rats at doses of 1.5 mg/kg. Minoxidil did not alter intravenous glucose tolerance to any extent unless very large doses (100 mg/kg) were used.

TOXICOLOGY

General Overview:
In non-clinical studies in a variety of species, minoxidil induces several types of cardiac lesions including epicarditis, necrotic and hemorrhagic lesions of the myocardium and papillary muscles, and cardiac hypertrophy and dilation. These changes occur only in the context of profound hypotension and tachycardia and reflect haemodynamic and/or hypoxic stress rather than direct cytotoxicity. As extensive clinical experience with the drug has accumulated, it has become apparent that these cardiac lesions do not occur in humans treated with minoxidil.

Non-clinical Toxicology

Acute Toxicity

SPECIES	ROUTE	LD_{50} (mg/kg)
Mouse	Oral	2457
	Intraperitoneal	1001
	Intravenous	51
Rat	Oral	1321
	Intraperitoneal	759
	Intravenous	49

Signs of toxicity: CNS depression and acute pulmonary congestion

Concomitant therapy with either prednisone and anti-thymocyte globulin, hydrochlorothiazide and propranolol or digoxin, and furosemide did not appreciably alter the LD_{50} for minoxidil.

Repeat-Dose Toxicity Studies

3 - Day Studies (Rat, Dog)
Minoxidil was administered orally to rats and dogs at daily doses up to 100 and 10 mg/kg respectively for 3 days. In rats, a dose related slight increase in the number of mitoses in hepatocytes was seen. In Beagle dogs, epicardial and myocardial cellular infiltrations, hypertrophy and hyperplasia of the mesothelial cells, small focal hemorrhages and myocardial atrial lesions were observed at 1.0 and 10 mg/kg doses. These findings were more frequent and severe at the higher dose. In mongrel dogs, there were minimal to mild sub-epicardial

hemorrhages present in the right atrium and/or right auricle which may represent the early stages of right atrial lesions as seen in the longer term studies.

1 - Month Studies (Monkey, Dog, Mini-pig and Rat)
Minoxidil was administered orally to monkeys at 20 mg/kg/day; to dogs at 0.5 and 1 mg/kg/day, and at 20 and 100 mg/kg/day; to mini-pigs at 20 mg/kg/day and to rats at 300 mg/kg/day. Grossly observed cardiac hypertrophy was reported in the monkey study (the 4-OH metabolite of minoxidil at the same dose showed no effect). In dogs, lesions of the right atrium and/or auricle were seen at all doses. Local myocardial cell atrophy and/or degeneration was reported at doses as low as 1 mg/kg/day. The 20 mg/kg dose produced degenerative right auricular heart lesions as did the 4-OH metabolite of minoxidil. The high dose resulted in the death of all dogs probably due to profound alteration in electrolyte balance. In the mini-pig study blood pressure was depressed, heart rate elevated and total body water and exchangeable sodium were increased. Cardiac hypertrophy was observed. In rats, repression of body weight gain, decreased food consumption reduced erythrocyte levels, increased liver and heart weights, indications of cardiac hypertrophy and electrolyte imbalance were observed.

1-Year Studies (Rat, Monkey, Dog)
Minoxidil was administered orally to rats at 10, 30, and 100 mg/kg/day, monkeys at 3.5, 7 and 14 mg/kg/day and dogs at 3, 10 and 30 mg/kg/day. In rats, repression in body weight gain occurred at 100 mg/kg/day and a dose related increase in liver, kidney, adrenal and heart weights were seen. One high dose female monkey with chronic glomerulonephritis died from cardiac failure and minoxidil probably contributed because of its salt and water retaining action. In the dog study, degenerative right auricular heart lesions were found at all dose levels. Evidence of chronic electrolyte disturbance was noted in dogs at the highest dose.

22-Month Study (Rat)
Minoxidil was administered orally to rats at 3, 10 and 30 mg/kg/day. Increased heart weights were observed at the highest dose.

No carcinogenic potential was apparent.

Mutagenicity
Minoxidil did not prove to be mutagenic in any of the numerous tests for mutagenic potential. An equivocal result was recorded in an *in vitro* cytogenetic assay using Chinese hamster cells at long exposure times, but a similar assay using human lymphocytes was negative.

Carcinogenicity
In oral carcinogenicity studies in rats and mice, considered most relevant to orally administered minoxidil, no carcinogenic potential was identified in rats, while tumors observed in mice were considered incidental. A dermal carcinogenicity study in mice showed an increased incidence of hormone-mediated tumors (mammary adenomas and adenocarcinomas in the females at all dose levels (8, 25 and 80 mg/kg/day) was attributed to Hyperprolactinemia), which were not considered relevant to humans when treated topically with minoxidil for hair loss.

Dietary administration of minoxidil to mice for up to 2 years was associated with an increased incidence of malignant lymphomas in females at all dose levels (10, 25 and 63 mg/kg/day) and an increased incidence of hepatic nodules in males (63 mg/kg/day). There was no effect of dietary minoxidil on the incidence of malignant liver tumors.

Reproduction and Teratology

In a fertility study with male and female rats that received one to five times the maximum recommended human oral antihypertensive dose of minoxidil (multiples based on a 50 Kg patient), a dose-dependent reduction of the conception rate was found. The no observed adverse effect level (NOAEL) for this finding was 1 mg/kg per day in treated rats.

Male rats received minoxidil in oral doses of 3 or 10 mg/kg/day for 60 days prior to and during the 14 day breeding period. Female rats received the same dose for 14 days prior to and during breeding, and throughout gestation. A reduction in conception rate was observed. No increase in the incidence of fetal resorption in treated dams was seen. The average number of live pups per litter was significantly decreased in both treatment groups, but live pups from treated dams were significantly heavier than live pups from control dams.

Minoxidil, when given orally to pregnant rats and rabbits on gestation days 6 through 15 and 18 respectively, at dose levels of 3 and 10 mg/kg/day showed no teratogenic effect. Increased fetal resorption occurred in rabbits. The same dose administered to rats from the 15^{th} day of gestation until pups were weaned at 21 days showed no effect of treatment on various parameters related to gestation, parturition and lactation.

When a minoxidil suspension was given subcutaneously to pregnant rats in doses of 0,1,11, and 120 mg/kg, no teratogenic changes were found in the fetuses from the rats dosed at 0, 1 and 11 mg/kg of minoxidil. Increased fetal mortality, still birth, external malformations and skeletal anomalies and variations were observed at 120 mg/kg. This dose also caused decreased maternal weight gain and food consumption and thus the fetal effects noted could have resulted from maternal toxicity.

Teratogenicity has been demonstrated in the rat at doses above 80mg/kg/day. Oral administration of minoxidil has been associated with evidence of increased fetal resorption in rabbits at doses associated with maternal toxicity. Teratogenicity was not demonstrated in the rabbit.

Cardiac Lesions

Cardiac Lesions in Animals – In non-primate animal studies LONITEN produced several types of myocardial lesions as well as other adverse cardiac effects. These included necrotic and hemorrhagic lesions of the myocardium and papillary muscles and cardiac hypertrophy and dilation.

- Dog Atrial Lesion: Oral doses of 0.5 mg/kg for several days up to 1 month or longer produced a grossly visible hemorrhagic lesion of the right atrium of the dog. Replacement of myocardial cells by proliferating fibroblasts and angioblasts;

phagocytosis; and hemosiderin accumulation in macrophages was observed.

- Papillary Muscle Lesion: In dog, rat and minipig necrosis of the papillary muscles and, in some cases, sub-endocardial areas of the left ventricle were seen following a few days treatment. Beta-adrenergic receptor blockade reduced the incidence and severity.
- Hemorrhagic Lesions: were seen in the epicardium, endocardium and walls of small coronary arteries and arterioles after acute minoxidil treatment in dogs. Left atrial hemorrhagic lesions were seen in mini-pigs.

Longer term treatment in rats, dogs and monkeys showed cardiac hypertrophy and cardiac dilation (in rats). Hydrochlorothiazide partly reversed the increased heart weight in monkeys.

Cardiac Lesions in Humans- As greater experience with minoxidil has accumulated, it has become apparent that these cardiac lesions so described in the dog, mini-pig, and other non-primates, do not occur in humans. Human autopsy experience has revealed the following: Among 242 autopsies performed on patients who received LONITEN Tablets, cardiac pathology was detected in only 8 instances. In every instance, the conclusion has been reached that the human heart lesions were decidedly different in individual elements and constellation of changes from both the atrial and ventricular lesions seen in animals. Among 224 autopsies performed on patients never exposed to LONITEN Tablets, the cardiac pathology observed, especially in the right atrium, entirely encompassed the pathologic findings seen in the LONITEN cases. The inference of these observations is that the pathologic findings in hearts of LONITEN treated hypertensive patients were not attributable to LONITEN administration, but rather to disease processes which were common to patients in these two studies.

Drug Interaction Studies:

No evidence of alteration in toxicity when minoxidil was given concomitantly with (a) hydrochlorothiazide and propranolol in rats and monkeys for up to 1 month, and (b) furosemide and digoxin in rats for 1 month. Hydrochlorothiazide partially reduced increases in heart weight and total body exchangeable sodium produced by minoxidil in a 1 month monkey study. (See DRUG INTERACTIONS)**.**

REFERENCES

1. Bryan RK, Hoobler SW, Rosenweig J, Weller JM. Effect of Minoxidil on blood pressure and hemodynamics in severe hypertension. Am J Cardiol 1977; 39:796.
2. Dargie HJ, Dollery CT, Daniel J. Minoxidil in resistant hypertension. Lancet 1977; 515.
3. Dormois JC, Young JL, Nies A. Minoxidil in severe hypertension: Value when conventional drugs have failed. Am Heart J 1976; 90:360.
4. Ducharme DW, Freyburger WA, Graham BE, Carlson RG. Pharmacologic properties of minoxidil: a new hypotensive agent. J Pharmacol Exp Ther 1973; 184:662.
5. Klotman PE, Grim CE, Weinberger MH, Judson WE. The effect of minoxidil on pulmonary and systemic hemodynamics in hypertensive man. Circulation 1977; 55:294.
6. Mitchell HC, Pettinger WA. Long-term treatment of refractory hypertensive patients with Minoxidil. JAMA 1978; 239:2131.
7. Mutterperl RE, Diamond FB, Lowenthal DT. Long-term effects of minoxidil in the treatment of malignant hypertension in chronic renal failure. J Clin Pharmacol 1976; 16(10):498.
8. Nawar T, Nolin L, Plante GE, Caron C, Monthambault P. Long-term treatment of severe hypertension with minoxidil. CMAJ 1977; 19:1178.
9. O'Mally K, and McNay JL. A method for achieving blood pressure control expeditiously with oral minoxidil. Clin Pharmacol Ther 1975; 18:39.
10. Pennisi AJ, Singsen BH, Ettenger RB, Hanson V, Fine RN. Minoxidil therapy in children with severe hypertension. J Pediatr 1977; 90:813.
11. Pettinger WA, Mitchell HC. Minoxidil - an alternative to nephrectomy for refractory hypertension. N Engl J Med 1973; 289:167.
12. Shen D, O'Mally K, Gibaldi M, McNay JL. Pharmacodynamics of minoxidil as a guide for individualizing dosage regimens in hypertension. Clin Pharmacol Res 1975; 17:593.
13. Sinaiko AR, Mirkin BL. Management of severe childhood hypertension with minoxidil: A controlled clinical study. J Pediatr 1977; 91:138.
14. Zins GR. Alterations in renal function during vasodilator therapy. Recent Advances in renal physiology and pharmacology. University Park Press Baltimore 1974;165

PART III: CONSUMER INFORMATION

Pr LONITEN®
(minoxidil tablets)

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

ABOUT THIS MEDICATION

What the medication is used for:
LONITEN is used for the treatment of severe hypertension that is difficult to control. It is taken with other medicines.

What it does:
LONITEN tablets contain minoxidil which is a powerful drug for lowering the blood pressure. It works by relaxing and enlarging certain small blood vessels so that blood flows through them more easily.

Who should take LONITEN:
There are many people with high blood pressure but most of them do not need LONITEN. LONITEN is used ONLY when your doctor decides that:
1. Your blood pressure is severe;
2. Your high blood pressure is causing symptoms or damage of vital organs and
3. Other medicines did not work well enough or had very disturbing side effects.

LONITEN should be taken only when a doctor prescribes it. Never give any of your LONITEN tablets, or any other high blood pressure medicine, to a friend or a relative.

When it should not be used:
Do not take LONITEN:
- **If you think you might be allergic to the active ingredient minoxidil or any other nonmedicinal ingredients listed in the section below (What the nonmedicinal ingredients are).**
- **If your high blood pressure is caused by hormones from a tumour (phaeochromocytoma) usually near the kidneys.**
- **If you have pulmonary hypertension associated with a heart valve disorder (mitral stenosis).**
- **If you have severely reduced liver function**

What the medicinal ingredient is:
Minoxidil

What all the nonmedicinal ingredients are:
Colloidal silicon dioxide, corn starch, lactose, magnesium stearate, and microcristaline cellulose.

What dosage forms it comes in:
2.5 mg and 10 mg tablets

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

LONITEN is not recommended during pregnancy and in women of childbearing potential not using contraception. Neonatal hypertrichosis has been reported following exposure to minoxidil during pregnancy.

Temporary changes in some blood parameters may occur, including a decrease in hematocrit, hemoglobin and red blood cell count. Body weight and blood count should be monitored closely.

BEFORE you use LONITEN talk to your doctor or pharmacist if:

- You are taking prescription and/or non-prescription products (especially other medications for high blood pressure, diuretics (water pills), and guanethidine
- You have or have ever had heart disease, a heart attack, pheochromocytoma or kidney disease. If you are pregnant, plan to become pregnant, or are breast-feeding

LONITEN tablets encourage salt and water to remain in your body. Too much salt and water in the body can make you feel breathless, wheezy, sick and tired, and can stop LONITEN working properly. LONITEN also makes your heart beat faster.

To avoid these problems, your doctor will prescribe two other medicines for you to take with LONITEN. One will be a water tablet (diuretic) to help your body get rid of excess water, and the other a beta-blocker or similar medicine to prevent your heart from beating too fast.

You should weigh yourself daily and keep an accurate record of your weight while you are taking this medicine. Tell your doctor if you put on more than 2 to 3 pounds (1 to 1.5 kg). The cause could be extra fluid in your body. Tell your doctor if you think you have gained weight - even though it may not be due to the medicine.

You may have increased hair growth (hypertrichosis) after starting treatment; this usually emerges in the face but subsides with continued treatment. This side effect is reversible upon stopping treatment but may take 1 to 6 months.

Your doctor will want to make regular checks on your blood pressure and general health. You should also have occasional checks on your heart. If you have an ECG test (to check the electrical activity of your heart) or any blood tests, remind your doctor that you are taking Loniten, as it can change the results.

Driving and operating machines
Do not drive a car or operate machinery until you know how LONITEN affects you.

Pregnancy and Breast-feeding:
LONITEN is not recommended, if you are pregnant or trying to become pregnant. You should only take LONITEN if your doctor tells you to. LONITEN passes into the breast milk and is not recommended if you breast-feeding unless your doctor thinks it is

necessary.

If you are pregnant or breast-feeding you should ask your doctor for advice before taking any medicine.

INTERACTIONS WITH THIS MEDICATION

You should always tell your doctor if you are taking any other medicine including those obtained without prescription. It is particularly important you tell your doctor about any other medicine you are taking to reduce your high blood pressure. These drugs may interact with LONITEN by causing blood pressure to drop too low and/or cause a sudden drop in blood pressure when standing up. In particular, tell your doctor if you are taking guanethidine, probenecid, valproic acid or atazanavir. Your treatment of Loniten should be monitored and the dosage may need to be adjusted.

PROPER USE OF THIS MEDICATION

Usually, your doctor will prescribe two other medicines along with LONITEN. These will help lower blood pressure and will help prevent undesired effects of LONITEN.

Often, when a medicine like LONITEN lowers blood pressure, your body tries to return the blood pressure to the original, higher level. It does this by holding on to water and salt (so there will be more fluid to pump) and by making your heart beat faster.

To prevent this, your doctor will usually prescribe a water tablet to remove the extra salt and water from your body and another medicine to slow your heart beat.

LONITEN tablets come in two strengths (2.5 mg and 10 mg) that are marked on each tablet. Pay close attention to the tablet markings to be sure you are taking the correct strength. Your doctor may prescribe half a tablet; the tablets are scored (partly cut on one side) so that you can easily break them.

When you first start taking LONITEN, your doctor may need to see you often in order to adjust your dosage. Take all your medicine according to the schedule prescribed by your doctor. Do not skip any doses.

Remember, do not stop taking LONITEN, or any of your other high blood pressure medicines, without checking with your doctor. Make sure that any doctor treating or examining you knows that you are taking high blood pressure medicines, including LONITEN.

Usual dose:
Always take the tablets exactly as your doctor tells you to. Your doctor will prescribe a suitable dose for you. The dose prescribed will depend on how you respond to the medicine. Your doctor might change your daily dose gradually to get the best results.

The table below shows the usual starting dose for adults and children over the age of 12 and for children under the age of 12.

	Usual Daily Dose
Adults and children over the age of 12	Usual starting daily dose is 2.5 mg, two times per day. Your doctor may increase the dose to 10, 20 and then to 40 mg per day in divided doses, at 3 day intervals or longer.
Children 12 years and under Dose depends on body weight	Usual starting daily dose is 0.2 mg per each kilogram of body weight per day, taken in 2 divided doses. Your doctor may increase the dose by 0.1 to 0.2 mg/kg/day increments, at 3 day intervals or longer,

There should be at least three days between each change of dose.

LONITEN may also be given to you in hospital to reduce your blood pressure very quickly. It would be given by a doctor or nurse under strictly monitored conditions at increasing doses of 5 mg every 6 hours until your blood pressure is normal.

You may take LONITEN with water or with other liquids, either with or between meals.

You must follow your doctor's instructions exactly, taking all the prescribed medicines, in the right amounts, each day. These medicines will decrease the side effects you might otherwise have and will also help keep your blood pressure down.

Overdose:
Taking too many tablets may make you unwell. If you take too many tablets, tell your doctor straight away.

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

Missed Dose:
If you should forget a dose of LONITEN, wait until it is time for your next dose, then continue with your regular schedule. Do not take a double dose to make up for a missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

LONITEN can cause side effects and the following have been reported in patients with high blood pressure being treated with LONITEN:

hair color changes, gastrointestinal intolerance, breast tenderness, rash,

Hair Growth:
About 8 out of 10 patients who have taken LONITEN noticed that fine body hair grew darker or longer on certain parts of the body. This happened about three to six weeks after beginning treatment. The hair may first be noticed on the forehead and temples, between the eyebrows, or on the upper part of the cheeks. Later, hair may grow on the back, arms, legs, or scalp. Although hair

growth may not be noticeable to some patients, it often is bothersome in women and children. Unwanted hair can be controlled with a hair remover or by shaving. The extra hair is not permanent it disappears within 1 to 6 months of stopping LONITEN. Nevertheless, you should not stop taking LONITEN without first talking to your doctor.

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical help
		Only if severe	In all cases	
Very Common	Increase in heart rate (fast heartbeat) 20 beats or more per minute over your normal pulse while at rest,		√	
	Abnormal electro-cardiogram (ECG),		√	
	Difficulty in breathing, especially when lying down		√	
Common	Weight Gain If you gain quickly 5 or more pounds (two or more kg) or if there is any swelling or puffiness in the face, hands, ankles, or stomach area, this could be a sign that you are retaining body fluids,		√	
	Shortness of breath, difficulty breathing, dizziness, lightheadedness or fainting.		√	
Uncommon	Chest pain, shortness of breath, palpitations light-headedness, passing out		√	
Rare	Flu-like symptoms (headache, malaise, fever, sore throat, joint pain), rash, serious skin reaction with blistering of the skin, mouth, eyes and genitals)			√
	Inflammation and blistering of the skin			√
	Increase risk of bleeding or bruising		√	
Not known	New or worsening of pain in the chest, arm or shoulder or signs of severe indigestion (angina), reduce kidney function resulting in increased creatinine and urea levels in your blood			√
	swelling of the ankles, feet or fingers associated with or without weight gain,		√	

This is not a complete list of side effects. For any unexpected effects while taking LONITEN, contact your doctor or pharmacist.

HOW TO STORE IT

Store at controlled room temperature (15° – 30°C)
Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

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

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

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

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.Pfizer.ca
or by contacting the sponsor, Pfizer Canada Inc., at:
1-800-463-6001

This leaflet was prepared by Pfizer Canada Inc.

Last revised: November 14, 2013