

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

LONITEN[®] 10 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each LONITEN tablet contains 10 mg minoxidil.

Excipient(s) with known effect

- Lactose monohydrate,

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

LONITEN 10 mg tablets are white to light tan circular, half oval, scored tablets marked '10' on one side and 'U' and '137' on the reverse side.

The pure compound is soluble in water to the extent of approximately 2 mg/mL and is readily soluble in propylene glycol or ethanol.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LONITEN (minoxidil) is an orally active peripheral vasodilator.

Indicated as adjunctive therapy in adults with severe refractory hypertension which has failed to respond to extensive multiple therapy.

When used in combination with an accompanying diuretic and beta-blocker, minoxidil (LONITEN) has been shown to reverse encephalopathy and retinopathy in severe hypertensives.

4.2 Dose and method of administration

Dose

The usual adult dosage range of LONITEN is 5-40 mg/day. The maximum recommended dosage is 100 mg/day.

LONITEN therapy can be initiated with a single or divided daily dosage. If the desired reduction in diastolic pressure is greater than 30 mm Hg, divided dosage will minimise diurnal fluctuations. Dosage adjustments should be made at intervals of 3 days or longer.

A more rapid reduction of pressure can be achieved using continuous blood pressure monitoring and incremental doses of 5 mg every 6 hours.

Dosage requirements may be lower in patients with renal failure or undergoing chronic dialysis.

For patients with hepatic impairment dosage adjustment should be considered, starting therapy at a reduced dose once daily and titrating up to the lowest effective dose to obtain desired therapeutic effect (see section 5.2).

Prior to introducing LONITEN, it is recommended that the antihypertensive therapy be adjusted to a regimen consisting of a diuretic and a beta-adrenergic blocking agent. When other sympathetic nervous system suppressants are used, the initial dosage of LONITEN should be reduced.

Children and Adolescents (Patients over 12 years of age)

Initial Dosage: 5 mg as a single daily dosage.

Incremental Increases: 5-10 mg/day, at 3 day intervals, until 50 mg/day is reached: then in increments of 25 mg/day up to a maximum of 100 mg/day.

Concomitant Medications

Diuretics

LONITEN must be given with sufficient diuretic therapy to maintain salt and water balance in all patients who are not on dialysis. When excessive water retention results in a weight gain exceeding 2.0 - 2.5 kg while on a thiazide or chlorthalidone, a more potent diuretic, e.g. frusemide should be used.

Sympathetic Nervous System Suppressants

Initially most patients will require a sympathetic nervous system suppressant to limit a LONITEN-induced rise in heart rate. The preferred agent is a beta-blocker equivalent to an adult propranolol dosage of 80-160 mg/day. Higher doses may be required when pre-treated patients have an increase in heart rate exceeding 20 beats/minute or when simultaneous introduction causes an increase exceeding 10 beats/minute. When beta-blockers are contraindicated, methyldopa or clonidine may be used instead and should be started 24 hours prior to LONITEN.

4.3 Contraindications

LONITEN is contraindicated in phaeochromocytoma and pulmonary hypertension secondary to mitral stenosis.

LONITEN is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

4.4 Special warnings and precautions for use

Salt and Water Retention

If used alone, LONITEN can cause a significant retention of salt and water, producing dependent oedema; puffiness of face, eyes or hands, neck vein distention, hepatojugular reflux. Haemodilution may occur leading to a temporary decrease in haematocrit, haemoglobin and erythrocyte count (by approximately 7% initially), which then recovers to pre-treatment levels. Chest X-rays may show evidence of pulmonary vascular engorgement. The clinical condition of some patients with symptomatic heart failure may deteriorate under these circumstances. The patient's body weight, fluid and electrolyte balance should be monitored, and if there is evidence of fluid retention, then diuretic treatment alone or in combination with restricted salt intake will minimise this response.

Refractoriness to these measures may require temporary discontinuation of LONITEN therapy for 1 or 2 days, during which there may be partial loss of blood pressure control.

Salt and water retention in excess of 2 to 2.5 kg of weight gain may diminish the effectiveness of LONITEN; therefore, patients should be carefully instructed about compliance to diuretic usage and limitation of their sodium intake (see section 4.2).

Tachycardia

Reflex tachycardia and possibly angina pectoris may develop in patients with unsuspected coronary artery disease, unless protected against LONITEN-induced tachycardia with beta-adrenergic blocking drugs or other suitable sympathetic nervous system suppressants. Patients with unstable angina pectoris or angina pectoris of recent onset should be protected with these agents before starting LONITEN therapy.

Orthostatic Hypotension

The blood pressure lowering effect of LONITEN is additive to concurrent antihypertensive agents. The interaction of LONITEN with agents that produce orthostatic hypotension may result in excessive blood pressure reduction (see section 4.5).

Hypertension

In patients with pulmonary hypertension associated with mitral valve regurgitation, caution is necessary to avoid excessive tachycardia.

LONITEN is not recommended for the treatment of patients with labile or mild hypertension.

LONITEN should not be used for extended therapy in hypertension readily ameliorated by surgery, e.g. coarctation of the aorta, primary aldosteronism, or unilateral, large vessel renal artery stenosis.

Hypertrichosis

Elongation, thickening and enhanced pigmentation of fine body hair (hypertrichosis), unassociated with endocrine abnormalities, is seen in most patients. It is usually first noticed in the facial area 3 to 6 weeks after starting therapy, may recede slightly during prolonged

therapy, and is reversed 1 to 3 months after LONITEN is discontinued. All patients should be fully informed of this possible effect before commencing LONITEN therapy.

Cardiac Lesions

Right atrial lesions have been found in dogs treated with minoxidil at dosages as low as 0.5 mg/kg/d. Similar lesions have been produced with the 4-hydroxy metabolite (20 mg/kg/d) in the beagle dog; however, studies in other species with either minoxidil or the 4-hydroxy metabolite have not produced these changes.

In addition haemorrhagic lesions of the coronary arteries were observed mainly in the right atrium of dogs (and the left atrium of mini-pigs).

In dogs, mini-pigs, rats and hamsters necrosis of the papillary muscles and, in some cases, subendocardial areas of the left ventricle were observed following a few days treatment. Beta adrenergic receptor blockade reduced the incidence and severity of the alterations.

There was no evidence in 78 autopsied patients that similar lesions have occurred in humans receiving minoxidil. However studies to date cannot exclude the possibility of such lesions occurring in man.

ECG Alterations

Approximately 60% of patients exhibit ECG alterations in the direction and magnitude of their T-waves soon after starting LONITEN therapy. Large changes may encroach on the ST segment, but the ST segment is not independently altered and there is no evidence of myocardial ischaemia. These asymptomatic changes usually disappear with continuing LONITEN treatment. The ECG reverts to the pre-treatment state if LONITEN is discontinued.

Pericarditis, Pericardial Effusion and Tamponade

There have been multiple reports of pericarditis occurring in association with LONITEN.

Pericardial effusion, and occasionally tamponade, has been detected in 3% to 4% of patients treated with a LONITEN containing regimen. In more than one-half of these cases, the effusion had been evident pre-trial or occurred among chronic dialysis patients. Most of the effusions in non-dialysis patients were attributed to factors such as uraemia, massive volume overload, congestive heart failure, and open A-V shunt, or an infectious, autoimmune or connective tissue disease. LONITEN-treated patients should be closely monitored for any suggestion of a pericardial effusion and echocardiography should be carried out if suspicion arises. More vigorous diuretic therapy, dialysis, pericardiocentesis, or surgery may be required. If effusion persists, withdrawal of LONITEN should be considered in light of other means of controlling the hypertension and the patient's clinical status.

Renal Failure or Dialysis Patients

Those patients with renal failure or on haemodialysis may require smaller doses of LONITEN (see section 4.2).

Myocardial Infarction

Patients who have had a myocardial infarction should be only treated with LONITEN after a stable post-infarction state has been established.

4.5 Interaction with other medicines and other forms of interaction

Guanethidine

While minoxidil itself does not cause orthostatic hypotension, its administration to patients already receiving guanethidine can result in profound orthostatic effects. If possible, guanethidine should be discontinued well before minoxidil is begun. If this is not feasible, minoxidil therapy should be instituted in the hospital and the patient monitored carefully for orthostatic events.

4.6 Fertility, pregnancy and lactation

Fertility

No data available.

Pregnancy - Category C

Minoxidil has been associated with hypertrichosis in the newborn infant following exposure *in utero*.

LONITEN is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Minoxidil has been reported to be excreted in human milk. A risk to the suckling child cannot be excluded, therefore it is not recommended for nursing mothers unless the expected benefits outweigh any potential risk.

4.7 Effects on ability to drive and use machinery

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.

4.8 Undesirable effects

Most patients receiving LONITEN have experienced a diminution of pre-existing adverse medical events attributable to their disease or previous therapy. New events or events likely to increase include: peripheral oedema associated with, or independent of, weight gain; increases in heart rate; hypertrichosis; a temporary decline in haemoglobin and haematocrit; and a temporary rise in creatinine and BUN.

Infrequently reported side effects include hypotension, gastrointestinal intolerance, rash and breast tenderness.

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very Rare < 1/10,000	Frequency Not Known (cannot be estimated from available data)
Blood and Lymphatic System Disorders				Leucopenia, Thrombocytopenia		
Metabolism and Nutrition Disorders		Fluid retention, Oedema				
Cardiac Disorders	Tachycardia, Pericarditis	Pericardial effusion, Cardiac tamponade				Angina pectoris
Gastro-intestinal Disorders		Gastro-intestinal disorder				
Respiratory, Thoracic and Mediastinal Disorders			Pleural effusion			
Skin and Subcutaneous Tissue Disorders	Hypertrichosis, Hair colour changes			Stevens-Johnson syndrome, Dermatitis bullous, Rash		Toxic epidermal necrolysis
Reproductive System and Breast Disorders			Breast tenderness			
Investigations	Electrocardiogram abnormal					

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Signs and Symptoms

Hypotension resulting from the administration of minoxidil has occurred on only a few occasions. When exaggerated hypotension is encountered it is most likely to occur when minoxidil is used in association with antihypertensive agents which block sympathetic nervous system responses (guanethidine-like effects of alpha-adrenergic blockage) and compensatory mechanisms. Sinus tachycardia has also been reported.

Treatment of Overdosage

Due to patient-to-patient variation in blood levels, it is difficult to establish an overdosage warning level. In general, a substantial increase above 2000 ng/mL should be regarded as overdosage, unless the physician is aware that the patient has taken no more than the maximum dose. Treatment is primarily symptomatic and supportive. Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within 1 hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. Recommended treatment for hypotension is intravenous administration of normal saline. Sympathomimetic drugs, such as noradrenaline, should be avoided because of their excessive cardiac-stimulating action. Phenylephrine, angiotensin II and vasopressin, which reverse the effect of LONITEN, should be used only if inadequate perfusion of a vital organ is evident.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

LONITEN selectively relaxes arteriolar smooth muscle which reduces peripheral vascular resistance and lowers systemic blood pressure. This is accomplished without a diminution of nutritional flow to body tissues or interference with normal vasomotor reflexes.

LONITEN does not directly stimulate the heart or electrolyte reabsorption of the kidney. However, LONITEN administration elicits a reflex mediated increase in cardiac output; salt and water retention; and a rise in plasma renin activity. These effects are diminished by the simultaneous administration of diuretics and beta-adrenergic blocking agents.

5.2 Pharmacokinetic properties

Absorption

Gastrointestinal absorption is rapid and amounts to at least 95% of the administered dose. Serum levels of the parent drug peak within the first hour.

Distribution

LONITEN does not bind to plasma proteins, or enter the central nervous system, or accumulate in body tissues.

The plasma elimination half-life of LONITEN is approximately 4-4.5 hours but the duration of its hypotensive action may exceed 24 hours. This disparity between blood level and pharmacological effect and the large volume of distribution indicates extensive tissue localisation of the drug. However, on chronic treatment accumulation does not occur and the pharmacological effect is slowly reversible.

With an effective oral dose, blood pressure usually starts to decline within one-half hour, reaches a minimum between 2 and 3 hours, and recovers at a rate of approximately 30%/day. During daily administration there is a cumulative effect which reaches a steady state after 3 to 7 days. The magnitude of the blood pressure response is related to the extent of the original diastolic elevation above 85 mm Hg, and is proportional to the logarithmic function of the dose administered. When the desired diastolic reduction is greater than 30 mm Hg, twice a day dosing is advised to keep the diurnal variation within 10 mm Hg.

Biotransformation

Metabolism is predominantly by glucuronic acid conjugation.

Elimination

Metabolites are excreted principally in the urine and can be removed by haemodialysis in anephric patients. Haemodialysis does not however, rapidly reverse the pharmacological effect of LONITEN.

Special Populations

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% in patients with cirrhosis. Although not statistically significant, AUC increased approximately 50% in patients with cirrhosis relative to healthy controls. For patients with hepatic impairment dosage adjustment should be considered (see section 4.2).

5.3 Preclinical safety data

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Silicon dioxide
- Lactose monohydrate
- Magnesium stearate
- Maize starch
- Microcrystalline cellulose

6.2 Incompatibilities

No data available.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C, protect from moisture.

6.5 Nature and contents of container

LONITEN 10 mg tablets are supplied in HDPE bottles of 100.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

26 January 2017

10. DATE OF REVISION OF THE TEXT

20 May 2019

Summary table of changes

Section changed	Summary of new information
All	New Data Sheet format in accordance with Medsafe guidance