SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

LONITEN® 5 mg tablets

LONITEN® 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each LONITEN 5 mg tablet contains 5 mg minoxidil.

Each LONITEN 10 mg tablet contains 10 mg minoxidil.

Contains sugar (lactose monohydrate).

Excipients with known effect

Each LONITEN 5 mg tablet contains 94 mg lactose monohydrate.

Each LONITEN 10 mg tablet contains 90 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

LONITEN 5 mg and 10 mg tablets are round white tablets.

LONITEN 5 mg tablets are imprinted with a "5" on one side of the tablet with a "U" with a "score" and then "U" on the other side of tablet.

LONITEN 10 mg tablets are imprinted with a "10" on one side of the tablet with a "U" with a "score" and then "137" on the other side of tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LONITEN is indicated as adjunctive therapy in adults with severe refractory hypertension which has failed to respond to extensive multiple therapy. LONITEN should be used concurrently with a sympathetic nervous system suppressant and a diuretic to initiate therapy.

4.2 Posology and method of administration

Posology

The usual adult dosage range of LONITEN is 5 to 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 mmHg, 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 undergoing chronic dialysis. Prior to introducing LONITEN, it is recommended that the antihypertensive therapy be adjusted to a regimen consisting of a diuretic and beta-adrenergic blocking medicine. When other sympathetic nervous system suppressants are used, the initial dosage of LONITEN should be reduced.

Patients over 12 years of age

Initial dosage: 5 mg as a single or divided 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 therapy

Diuretics

LONITEN must be given with sufficient diuretic therapy to maintain salt and water balance in all patients who are on dialysis. When excessive water retention results in a weight gain exceeding 2 kg, the type of diuretic should be changed or an aldosterone antagonist should be added. In children, diuretic dosage should be proportional to body weight.

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 medicine 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.

Special populations

Renal failure or dialysis patients

Those patients with renal failure or on haemodialysis may require smaller doses of LONITEN.

Hepatic impairment

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).

Method of administration

For oral use.

4.3 Contraindications

LONITEN is contraindicated in:

- Patients with a known hypersensitivity to minoxidil or any of the excipients of LONITEN (listed in section 6.1)
- Pulmonary hypertension associated with mitral stenosis
- Phaeochromocytoma because it may stimulate secretion of catecholamines from the tumour through its antihypertensive action
- Pregnancy and lactation (see section 4.6)
- Severe liver impairment

4.4 Special warnings and precautions for use

Pericarditis, pericardial effusion and tamponade

Pericarditis, pericardial effusion and tamponade, have been observed. LONITEN-treated patients should be periodically monitored for signs of symptoms of these events and, if found, appropriate therapy should be instituted. If the effusion persists, LONITEN should be withdrawn and other means of controlling the hypertension should be used.

Myocardial infarction

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

Renal failure or dialysis patients

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

Dermatologic hypertrichosis

Elongation, thickening, and enhanced pigmentation of fine body hair have been seen in the majority of patients taking LONITEN. No endocrine abnormalities have been found to explain abnormal hair growth. All patients should be fully informed of this possible effect before commencing LONITEN therapy.

It is usually first noticed in the facial area within 3 to 6 weeks after starting therapy, and may recede slightly during prolonged therapy. Upon discontinuation of LONITEN, new hair growth stops, but it may take one to six months for restoration of pre-treatment appearance.

Altered laboratory findings

ECG changes

A high percentage 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.

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; hepatomegaly and a positive hepatojugular reflux. Chest X-rays may show evidence of pulmonary vascular engorgement.

LONITEN should be used in combination with a diuretic to prevent fluid retention oedema, and possibly congestive heart failure. Haemodilution may occur leading to temporary decrease in haematocrit, haemoglobin, and erythrocyte count (by approximately 7% initially which then recovers

to pre-treatment levels). The patient's body mass, fluid and electrolyte balance, should be monitored, and if there is evidence of fluid retention, the more vigorous diuretic treatment alone or in combination with restricted salt intake should be instituted.

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 2,0 kg of weight gain may diminish the effectiveness of LONITEN, therefore, patients should be carefully instructed about compliance with diuretic usage and limitation of their electrolyte intake.

Tachycardia

Because LONITEN is a vasodilator, reflex tachycardia may occur; 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 medicines before starting LONITEN therapy.

General

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.

Lactose

LONITEN contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

The blood pressure lowering effect of LONITEN is additive to concurrent anti-hypertensive medicines. The interaction of LONITEN with medicines that produce orthostatic hypotension may result in excessive blood pressure reduction.

4.6 Fertility, pregnancy and lactation

Pregnancy

LONITEN is contraindicated during pregnancy and in women of childbearing potential not using contraception. There is limited data from the use of LONITEN in pregnant women. Studies in animals have shown reproductive toxicity (see section 4.3).

Breastfeeding

LONITEN has been reported to be excreted in human milk. A risk to the suckling child cannot be excluded. LONITEN should not be used by women who are breastfeeding their babies.

4.7 Effects on ability to drive and use machines

No studies on the effect of LONITEN 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

Tabulated summary of adverse reactions

The table below contains side effects categorised as follows utilising the incidence rates: 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).

MedDRA System organ class	**Frequency**	**Undesirable effect**
Blood and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia
Metabolism and nutrition disorders	Common	Fluid retention, oedema, puffiness of face, eyes or hands
Cardiac disorders	Very common	Tachycardia, pericarditis
	Common	Pericardial effusion, cardiac tamponade
Respiratory, thoracic and mediastinal disorders	Uncommon	Pleural effusion
Gastrointestinal disorders	Common	Gastrointestinal disorder
Skin and subcutaneous tissue disorders	Very common	Hypertrichosis, hair colour changes
	Rare	Stevens-Johnson syndrome, dermatitis bullous, rash
Investigations	Very common	Electrocardiogram

Salt and water retention: See section 4.4.

Tachycardia: See section 4.4.

Pericarditis, pericardial effusion and tamponade: See section 4.4.

Post-marketing adverse events

MedDRA System organ class	**Undesirable effects**

Blood and lymphatic system disorders	Decline in haemoglobin, decline in haematocrit, blood urea increase, hypotension
Cardiac disorders	Angina pectoris
Vascular disorders	Neck vein distension, positive hepatojugular reflux, pulmonary vascular engorgement
Hepato-biliary disorders	Hepatomegaly
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis
Reproductive system and breast disorders	Breast tenderness, gynaecomastia, polymenorrhoea
Investigations	Temporary rise in creatinine

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Hypotension may occur. Recommended treatment is intravenous administration of normal saline. Sympathomimetic medicines, such as noradrenaline or adrenaline, should be avoided because of their excessive cardiac-stimulating action. Phenylephrine, angiotensin II, and vasopressin which reverse the effects of LONITEN should only be used if inadequate perfusion of a vital organ is evident.

5. PHARMACEUTICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1 Vasodilators, hypertensive medicines

Mechanism of action

Minoxidil lowers the elevated systolic and diastolic blood pressure by decreasing peripheral vascular resistance via vasodilation. The smooth musculature of the resistance vessels is 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, hyperpolarisation, and smooth muscle relaxation.

Secondary effects

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 increase after the administration of minoxidil alone, but it decreases with the recommended concomitant therapy (beta-blocker plus diuretic).

5.2 Pharmacokinetic properties

Absorption

After oral administration in humans, at least 90 % of minoxidil is absorbed in the gastrointestinal tract. Minoxidil is detected within 30 minutes in the plasma. Maximum plasma levels are reached 60 minutes after administration.

Distribution

Minoxidil is not bound to plasma proteins.

Minoxidil does not cross the blood-brain barrier.

Biotransformation

At least 90 % of the administered minoxidil is metabolised in the liver. The primary metabolite in humans is the minoxidil O-glucuronide. Some polar metabolites are also produced. The known metabolites have a weaker antihypertensive effect than the active ingredient itself.

Elimination

In humans, minoxidil plasma concentrations decrease with an average half-life of approximately 4 hours. However, the duration of action is over several days.

This disparity between blood level and pharmacological effect, and the large volume of distribution induces extensive tissue localisation of the medicine.

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 % per 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 mmHg, and is proportional to the logarithmic function of dose administered. When the desired diastolic reduction is greater than 30 mmHg, twice a day dosing is advised to keep the diurnal variation within 10 mmHg.

Metabolites are excreted principally in the urine.

Minoxidil and its metabolites are dialysable. Haemodialysis does not, however, rapidly reverse the pharmacological effect of minoxidil.

The renal clearance of minoxidil corresponds to the glomerular filtration rate.

No substantial changes in the glomerular filtration rate and the renal plasma flow could be detected under minoxidil.

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, starting therapy at a reduced dose and titrating up to the lowest effective dose to obtain desired therapeutic effect.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Microcrystalline cellulose

Corn starch

Colloidal silicone dioxide

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

6.5 Nature and contents of the container

Bottles of 100 tablets containing 5 mg or 10 mg.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

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South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBERS

LONITEN 5 mg: N/7.1/165

LONITEN 10 mg: N/7.1/166

9. DATE OF FIRST AUTHORISATION

18 August 1982

10. DATE OF REVISION OF THE TEXT

09 August 2021

BOTSWANA: S2

Loniten 5 mg - Reg. No.: B9312055

Loniten 10 mg – Reg. No.: B9312060

NAMIBIA:

Loniten 10 mg - Reg. No.: 90/7.1/001323

Loniten 5 mg – Reg. No.: 90/7.1/001324