# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Loniten 5 mg tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg minoxidil

Excipient(s) with known effect:
Each tablet contains 94 mg of lactose Monohydrate

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet
Round, white to light tan, biconvex tablet, 5 imprinted on one side, scored on the reverse with a 'U' on either side of the score.

The score line has no practical function; these tablets should not be broken in half.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Minoxidil is indicated for the treatment of severe hypertension that is symptomatic or associated with target organ damage. It is indicated for the treatment of hypertension not controlled adequately by a combination of a diuretic and a sympathetic suppressant agent such as a beta blocker. Additionally, it is indicated in hypertension that is not manageable with maximum therapeutic doses of a diuretic plus two other antihypertensive drugs.

It should not be used as the sole agent to initiate therapy. It is a peripheral vasodilator and should be given in conjunction with a diuretic, to control salt and water retention, and a betaadrenergic blocking agent, or appropriate substitute, to control reflex tachycardia.

### 4.2 Posology and method of administration

**Posology**

*Patients over 12 years and adults*

The recommended starting dose is 5 mg per day. If required, this dosage can later be increased up to 20 mg, and then to 40 mg daily (given as a single dose or in two divided doses). Dose increases should be made at increments of 5 mg to 10 mg minoxidil per day at intervals of three or more days. If a dose of 50 mg of minoxidil has been reached, the dose may be increased by 25 mg minoxidil per day to a maximum dose of 100 mg per day.

If the desired decrease of diastolic blood pressure exceeds 30 mmHg, dosage should be divided to two daily doses to keep daily blood pressure fluctuations as low as possible.

Patients younger than 12 years of age

The use of minoxidil in children is restricted to children with severe hypertension associated with target organ damage where other treatment has failed. The data regarding the use of minoxidil in children is very limited, especially in infants. The dosage recommendations can only be considered as a rough guide to treatment at present as this is based on the publication of a few case reports and studies involving a small number of children. The starting dose used based on these reports is 0.2mg/kg of minoxidil as a single or divided dose. Careful titration increasing in steps of 0.1 to 0.2 mg/kg/day at intervals of at least 3 days is essential. The effective dose range is 0.25 to 1.0 mg/kg/day. The maximum dose is 50mg/day.

Treatment of children with minoxidil should only be initiated under the close supervision of a specialist in hospital.

*Elderly patients*
At present there are no extensive clinical studies with Loniten in patients over age 65. There is data indicating that elevated systolic and diastolic pressures are important risk factors for cardiovascular disease in individuals over age 65. However, elderly patients may be sensitive to the blood pressure lowering effect of Loniten and thus caution is urged in initiating therapy as orthostatic hypotension may occur. It is suggested that 2.5 mg per day be used as the initial starting dose in patients over 65 years of age.

*Renal failureor dialysis patients*
Dosage requirements may be lower in dialysis patients. Minoxidil is removed from the blood by dialysis, but its pharmacological action, once established is not reversed. Therefore haemodialysis patients should take Loniten either after or at least two hours before dialysis.
Those patients with renal failure may also require smaller doses of minoxidil.

*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).

*Rapid reduction of blood pressure*
Under hospital monitoring conditions, rapid reduction of blood pressure can be achieved using continuous blood pressure monitoring and incremental doses of 5 mg every six hours.

*Concomitant antihypertensive therapy*

It is recommended that, where possible, antihypertensive therapy, other than a beta-adrenergic blocking agent and a diuretic be discontinued before Loniten treatment is started. It is recognised that some antihypertensive agents should not be abruptly discontinued. These drugs should be gradually discontinued during the first week of Loniten treatment.

Minoxidil causes sodium retention and if used alone can result in several hundred milli- equivalents of salt being retained together with a corresponding volume of water.

Therefore, in all patients who are not on dialysis, Loniten must be given in conjunction with a diuretic in sufficient dosage to maintain salt and water balance. Examples of the daily dosages of diuretics commonly used when starting therapy with Loniten include:

1. Hydrochlorothiazide (100 mg) - or other thiazides at equi-effective dosage.

2. Chlortalidone (100 mg).

3. Furosemide (80 mg).

If excessive water retention results in a weight gain of more than 3 pounds when a thiazide or chlortalidone is being used, diuretic therapy should be changed to furosemide, the dose of which may be increased in accordance with the patient's requirements. Diuretic dosage in children should be proportionally less in relation to weight.

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 per minute or when simultaneous introduction causes an increase exceeding 10 beats per minute. When beta-blockers are contraindicated, alternatives such as methyldopa (250 to 750 mg twice daily) may be used instead and should be started 24 hours prior to Loniten.
Sympathetic nervous system suppressant may not completely prevent an increase in heart rate due to minoxidil but usually do prevent tachycardia.

<u>Method of Administration</u>
Oral administration

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Minoxidil is contraindicated in patients with a phaeochromocytoma because it may stimulate secretion of catecholamines from the tumour through its antihypertensive action.

**4.4 Special warnings and precautions for use**

Salt and water retention

If used alone, minoxidil can cause a significant retention of salt and water leading to physical signs such as oedema, and to clinical deterioration of some patients with heart failure.

Diuretic treatment alone, or in combination with restricted salt intake is, therefore, necessary for all patients taking minoxidil. 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 bodyweight, fluid and electrolyte balance should be monitored for evidence of fluid retention.

Salt and water retention in excess of 1 to 1.5 kg may diminish the effectiveness of minoxidil. Patients should, therefore, be carefully instructed about compliance with diuretic therapy and a detailed record of body weight should be maintained.

The product should be used with particular attention to maintenance of salt and water balance in patients with renal impairment, but who are not on dialysis.

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

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

Tachycardia
Because minoxidil is a vasodilator, reflex tachycardia may occur and possibly angina pectoris may occur in patients at risk; it is recommended that minoxidil be used in combination with beta-adrenergic blocking agent or other sympathetic nervous system suppressants to blunt or prevent such a response.

Hypertrichosis
Hypertrichosis occurs in most patients treated with minoxidil and all patients should be warned of this possibility before starting therapy. Most patients will experience an elongation, thickening and enhanced pigmentation of fine body hair. Usually these signs will emerge 3 to 6 weeks after starting treatment. They initially emerge in the face, and they may slightly subside with continued treatment. However, hypertrichosis was hardly or not at all tolerable in less than 10% of patients. Spontaneous reversal to the pre-treatment state can be expected one to six months after cessation of therapy.

ECG alterations
Soon after starting minoxidil therapy approximately 60% of patients exhibit ECG alterations in the direction and magnitude of their T waves. Large changes may encroach on the ST segment, unaccompanied by evidence of ischaemia. These asymptomatic changes usually disappear with continuing minoxidil treatment. The ECG reverts to the pre-treatment state when minoxidil is discontinued.

Thrombocytopenia and leucopoenia
Thrombocytopenia and leucopoenia have been rarely reported.

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

Pericardial effusion and occasionally tamponade, has been observed in about 3% - 5% of treated patients not on dialysis. While in many cases, the pericardial effusion is associated with other potential aetiologies, there have been cases in which these potential causes of effusion were not present. Patients should be observed closely for any suggestion of a pericardial effusion

and pericardiocentesis or surgery may be required. If the effusion persists, withdrawal of minoxidil should be considered in light of other means of controlling the hypertension and the patient's clinical status.

Paediatric population

Children strictly require appropriate and individualised dosing of minoxidil, beta- blockers and diuretics. They should be under close specialist supervision in hospital. Caution is required when there is significant renal impairment. The development of peripheral oedema or any signs suggestive of congestive heart failure or of pericardial or pleural effusion should be carefully watched for. Renal function should be monitored. Body weight and urine output should be monitored.

Regular follow up must be ensured during treatment with minoxidil.
Before starting treatment parents and carers should be warned of the likely occurrence of hypertrichosis.

This medicine 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 medicinal products and other forms of interactions**

The effect of minoxidil may be additive to concurrent antihypertensive agents and other agents with blood pressure lowering effects. The interaction of minoxidil with sympathetic-blocking agents such as guanethidine or betanidine may produce excessive blood pressure reduction and/or orthostatic hypotension.

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**

Pregnancy
There is limited data from the use of minoxidil in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Minoxidil 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.

Breast-feeding
Minoxidil has been reported to be excreted in human milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from minoxidil therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
In a fertility study with male and female rats, a dose-dependent reduction of the conception rate was found.

**4.7 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.*

**4.8 Undesirable effects**

Most patients receiving minoxidil experience a diminution of pre-existingside-effectsattributable to their disease or previous therapy. New events or side-effects likely to increase are included in the following table:

Frequencies are defined as:

Verycommon **(≥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)**
Not known **(cannot be estimated from the available data)**.

| **MedDRASystem Organ Class** | **Frequency** | **UndesirableEffects** |
|---|---|---|
| **Blood and LymphaticSystemDisorders** | Rare | Leukopenia, thrombocytopenia |
| **Metabolism and Nutrition Disorders** | Common | Fluidretention, oedema |
| **Cardiac Disorders** | Very Common | Tachycardia, pericarditis |
| | Common | Pericardialeffusion,cardiac tamponade |
| | Not Known | Angina pectoris |
| **Respiratory, Thoracic and Mediastinal Disorders** | Uncommon | Pleuraleffusion |
| **Gastrointestinal Disorders** | Common | Gastrointestinaldisorder |
| **Skin and Subcutaneous Tissue Disorders** | Very Common | Hypertrichosis, hair colour changes |
| | Rare | Stevens-Johnsonsyndrome,dermatitis bullous, rash, |
| | Not known | Toxic epidermal necrolysis |
| **Reproductive System and Breast Disorders** | Uncommon | Breast tenderness |
| **General Disorders and Administration Site Conditions** | Not known | Peripheral oedema associated with or independent of weight gain |
| **Investigations** | Very Common | ECG abnormal |
| | Not known | Blood creatinine increased Blood urea increased |

Salt and Water Retention– see section 4.4.

Tachycardia – see section 4.4.

Pericarditis, Pericardial Effusion and Tamponade – see section 4.4.

Paediatric population

Post authorisation experience has shown that, in a particular study, out of 50 patientson oral minoxidil, one case involved a two year old female with a historyof chronicrenal failure and peritoneal dialysis who developed pericardial effusion from whichshe recovered after treatment.

In addition, the estimated total exposure (based on onlynine months of data) wasabout 17,000 patient-years with however no appreciable use in children.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie; E-mail: medsafety@hpra.ie

**4.9 Overdose**

If exaggerated hypotension is encountered, it is most likely to occur in association with residual sympathetic nervous system blockade (guanethidine-like effects or alpha-adrenergic blockade). Recommended treatment is intravenous administration of normal saline. Sympathomimetic drugs, such as noradrenaline (norepinephrine) or adrenaline (epinephrine), should be avoided because of their excessive cardiac-stimulating action. Phenylephrine, angiotensin II and vasopressin, which reverse the effect of minoxidil, should be used only if inadequate perfusion of a vital organ is evident.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Pyrimidine derivatives
ATC Code: C02DC01

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 must be regarded as 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.

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

Paediatric population

As severe hypertension requiring multi-drug therapy is uncommon in children, paediatric use of minoxidil was limited in the development programme and has remained so in published literature. Data available in children younger than 10 years of age is very limited; it involves approximately 40 patients, eight of whom were under one year of age.

**5.2 Pharmacokinetic properties**

About 90% of an oral dose of minoxidil is absorbed in the gastrointestinal tract. Minoxidil is detected within 30 minutes in the plasma. Following oral administration the maximum hypotensive effect usually occurs after 2-3 hours. The action may persist for several days.
Maximum plasma levels are reached 60 minutes after administration.
Minoxidil is not bound to plasma proteins.
Minoxidil does not cross the blood-brain barrier.

Metabolism

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. Minoxidil and its metabolites are dialyzable. 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.

**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 behaviour compared with administration of a single dose.

Paediatric population

No pharmacokinetic data regarding minoxidil in the paediatric population is currently available**.**

**Hepaticimpairment**

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

**5.3 Preclinical safety data**

Cardiac lesions in animals
Innon-clinical studies in a variety of species, minoxidil induces several types of cardiaclesions including necrotic and haemorrhagic 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 greater experience with the drug has accumulated, it has become apparent that these cardiac lesions do not occur in humans treated with minoxidil.

Carcinogenicity
In oral carcinogenicity studies in rats and mice, considered most relevant to orally administered minoxidil, no carcinogenic potential was identified in rats, while tumoursobserved in mice were considered incidental. A dermal carcinogenicity study in mice showed an increased incidence of hormone-mediated tumours, which were not considered relevant tohumans.

Reproduction toxicity
In a fertility study with male and female rats, a dose-dependent reduction of the conceptionrate was found. Thenoobservedadverseeffectlevel(NOAEL)forthisfindingwas 1 mg/kgper day in treated rats. The doses corresponded to one to five times the maximum dose usedin humans to treat hypertension.

Teratogenicity has been demonstrated in the rat at doses above 80 mg/kg/day. Oraladministration of minoxidil has been associated with evidence of increased foetal resorption inrabbitsatdoses associated with maternal toxicity. Teratogenicity was not demonstrated intherabbit.

No data regarding juvenile animal toxicity studies is currently available.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Lactose monohydrate

Microcrystalline cellulose
Maize starch
Colloidal anhydrous silica
Magnesium stearate

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

Store below 25°C.
Store in the original package in order to protect from moisture.

**6.5 Nature and contents of container**

High density polyethylene (HDPE) bottles with low density polyethylene (LDPE) caps. Each bottle contains 100 tablets.

20-25 micron aluminium foil/250 micron opaque polyvinyl chloride (PVC) blister. Pack contains 60 tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

**8 MARKETING AUTHORISATION NUMBER**

PA0822/130/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authoristaion: 07 February 1980

Date of last renewal:  07 February 2010

**10 DATE OF REVISION OF THE TEXT**

October 2020