SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Minoxidil POA Pharma 2.5 mg Tablets

Minoxidil POA Pharma 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Minoxidil POA Pharma 2.5 mg Tablets

Each tablet contains 2.5 mg of minoxidil.

Minoxidil POA Pharma 10 mg Tablets

Each tablet contains 10 mg of minoxidil.

Excipients with known effect

Each 2.5 mg tablet contains 55.81 mg of lactose.

Each 10 mg tablet contains 223.25 mg of lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Minoxidil POA Pharma 2.5 mg Tablets

Round, white to off white tablets, approximately 5.5 mm in diameter, with score line on one side and “2.5” engraved on the other side. The score line is not intended for breaking the tablet.

Minoxidil POA Pharma 10 mg Tablets

Round, white to off white tablets, approximately 9 mm in diameter, with score line on one side and “10” engraved on the other side. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypertension when maximum therapeutic doses of other antihypertensive drugs, even when used in combination (combination of beta-adrenergic blocking agent with a diuretic and a vasodilator or comparable triple combinations), have not shown sufficient success (therapy-resistant hypertension).

Minoxidil should be given in conjunction with a diuretic and a beta-adrenergic blocking agent.

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 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, the dosage should be divided into two daily doses to keep daily blood pressure fluctuations as low as possible.

If a rapid decrease in blood pressure is desired, this can be achieved with continuous monitoring of blood pressure, by increasing the dose by 5 mg minoxidil (2 tablets of Minoxidil POA Pharma 2.5 mg tablets or ½ tablet of Minoxidil POA Pharma 10 mg tablets) every 6 hours.

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 methods have failed. The data regarding the use of minoxidil in children is very limited, especially in infants and young children. The dosage recommendations can only be considered as a rough guide to treatment at present as this is based on a few published case reports as well as studies involving only a small number of children. The starting dose used based on these reports is 0.2 mg/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 50 mg/day.

Since the 2.5 mg tablet of this product cannot be broken into equal halves, it is not possible to perform paediatric dose titration with sufficient accuracy. For this purpose, other minoxidil-containing products should be used, where the 2.5 mg tablet can be divided into equal halves.

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

Patients with severe renal impairment or dialysis patients

Dosage requirements may be lower in patients with severe renal impairment (creatinine clearance < 30 ml/min) or in dialysis patients.

Minoxidil should be taken either after or at least two hours before dialysis.

Patients with hepatic impairment

Dose adjustment should be considered in patients with hepatic impairment. Therapy can be initiated with a reduced dose once daily and then titrated up, until the desired therapeutic effect is achieved with the lowest effective dose (see section 5.2).

Concomitant therapy

It is recommended to establish a therapy with a beta-adrenergic blocking agent and a diuretic before minoxidil treatment is started. If another sympatholytic – i.e. Labetalol - or if methyldopa or clonidine are used, the initial dose of minoxidil should be smaller.

In general, the additional administration of diuretics is not necessary for dialysis patients. In children under 12 years of age and in patients with heart failure not adequately compensated despite glycoside administration, the administration of a sympatholytic agent may be omitted.

Diuretics

Therapy with minoxidil must be supported by adequate diuretic treatment to maintain salt and water balance in all non-dialysis patients.

Examples of the daily dosages of diuretics when starting therapy with minoxidil:

Hydrochlorothiazide 50 mg: twice a day

Chlortalidone 50 to 100 mg: once a day

Furosemide 40 mg: twice a day

If excessive water retention with a weight gain of more than 2 kg occurs despite the use of thiazide diuretics or chlortalidone, spironolactone should be added or diuretic therapy should be changed to furosemide. Diuretic dosage in children should be in accordance with body weight.

Sympatholytic drugs

Most patients will require a beta-sympatholytic agent at the beginning of therapy with minoxidil to limit a minoxidil-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 patients pre-treated with beta-blockers have an increase in heart rate exceeding 20 beats per minute or when simultaneous initiation of therapy with minoxidil and beta-blockers causes an increase exceeding 10 beats per minute. When beta-blockers are contra-indicated, methyldopa (250 to 750 mg twice daily) or clonidine (0.1 to 0.2 mg twice daily) may be used instead. However, therapy with these agents should be started 24 hours prior to first administration of minoxidil.

Method of administration

Oral administration.

Minoxidil POA Pharma tablets should be taken with water.

Dose adjustments of minoxidil should be done in a special outpatient department or clinic.

Regular monitoring must be guaranteed.

The diuretic must be titrated in such way that no weight gain due to water retention can occur.

There is no special limitation on the duration of use. Treatment-free intervals should not exceed 72 hours.

4.3 Contraindications

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

-Pulmonary hypertension due to mitral valve stenosis.

-Phaeochromocytoma, because minoxidil may stimulate secretion of catecholamines from the tumour through its antihypertensive action.

4.4 Special warnings and precautions for use

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 and possibly angina pectoris may occur. It is therefore necessary to use minoxidil in combination with beta-adrenergic blocking agents or other sympathetic nervous system suppressants to blunt or prevent such a response.

Minoxidil should be used with caution in patients with angina pectoris.

ECG alterations

Shortly after starting minoxidil therapy, approximately 60 % of patients exhibit ECG alterations (direction and magnitude of the T wave) which can also affect the ST interval. Large changes may encroach on the ST segment, unaccompanied by evidence of ischaemia.

These asymptomatic changes usually disappear with prolonged minoxidil treatment and are reversible when minoxidil is discontinued.

Pericarditis, Pericardial Effusion and Pericardial Tamponade

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

Pericardial effusion (occasionally with tamponade), has been observed in about 3 % - 5 % of minoxidil treated patients, who were not on dialysis. Pericardial effusion mainly occurred in patients with insufficient or impaired renal function. In many cases pericardial effusion could be ascribed to the following factors: connective tissue diseases, uraemia, decompensated heart failure or massive volume retention. However, there have been cases in which these potential causes of effusion were not present. Patients should be therefore monitored closely for signs of pericardial effusion and pericarditis. Increased diuretic treatment, dialysis, pericardiocentesis, possibly with echocardiography, or other surgical measures 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.

Unstable or mild hypertension

Minoxidil is not recommended for the treatment of unstable or mild hypertension.

Salt and water retention

If used alone, minoxidil can cause salt and water retention leading to physical signs such as oedema, swelling of the face, eyelids or hands and to clinical deterioration of heart failure in some patients. Additional diuretic treatment, if necessary in combination with restricted salt intake is, therefore, required for 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 and should be documented on a regular basis.

Salt and water retention in excess of 1 to 1.5 kg may diminish the effectiveness of minoxidil. Therefore, patients should 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.

Patients with renal impairment or dialysis patients may need lower doses of minoxidil.

Hypertrichosis

Hypertrichosis occurs in most patients treated with minoxidil and all patients should be advised of the possible occurrence of this side effect before starting therapy. Most patients will experience an elongation, thickening and enhanced pigmentation of fine body hair. A hormonal disorder is not associated with it. Usually these signs will initially emerge in the face 3 to 6 weeks after starting treatment, and they may slightly subside with continued treatment. However, hypertrichosis was severe or intolerable in less than 10 % of minoxidil-treated patients. Reversal to the pre-treatment state can be expected one to six months after cessation of therapy.

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 in patients with significant renal impairment. The development of peripheral oedema or any signs suggestive of decompensated heart failure or of pericardial or pleural effusion should be carefully monitored. Renal function, body weight and urine volume should be monitored.

Regular follow up must be ensured during treatment with minoxidil.

Before starting treatment, parents and health personnel should be advised of the likely occurrence of hypertrichosis.

Minoxidil POA Pharma 2.5 mg, 10 mg Tablets contain lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Sympathetic-blocking agents

The effect of minoxidil may be additive to concurrently administered antihypertensive agents. The interaction of minoxidil with sympatholytic agents such as guanethidine or betanidine may produce excessive blood pressure reduction and/or orthostatic hypotension. If possible, guanethidine should be discontinued before treatment with minoxidil. If this is not feasible, minoxidil therapy should be initiated in the hospital and the patient monitored carefully for orthostatic incidents.

Neuroleptics

An increased antihypertensive effect has been observed when minoxidil and neuroleptics were taken concomitantly.

Diuretics

Minoxidil-induced salt and water retention can usually be effectively reduced with diuretics.

Beta blockers

Beta-blockers (e.g. propranolol) suppress the reflex-induced tachycardia, as well as the increased plasma renin activity and aldosterone secretion that occur with minoxidil.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are 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 of 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 breastfeeding or to discontinue/abstain from minoxidil therapy.

The benefit of breast-feeding for the child and the benefit of therapy for the woman must be weighed.

Fertility

In a fertility study with male and female rats, a dose-dependent reduction of the conception rate was found. In the treated rats, the NOAEL (No Observed Adverse Effect Level) was 1 mg/kg body weight daily.

Teratogenicity has been shown in rats at doses above 80 mg/kg/day. After oral administration to rabbits, indications of increased foetal resorption were observed at doses associated with maternal toxicity. No teratogenicity was found in rabbits.

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 dependent on the individual response to treatment, particularly at the start of therapy.

4.8 Undesirable effects

Most patients receiving minoxidil experience a diminution of pre-existing side-effects attributable to their disease or previous therapy. New side-effects may occur.

Adverse effects have been ranked under headings of frequency using the following convention: 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 the available data).

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)**	**Not known: (cannot be established from the available data)**
Blood and lymphatic system disorders				Leucopenia, thrombocytopenia, individual cases of haemolytic anaemia		

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)	Not known: (cannot be established from the available data)
Immune system disorders				Allergic reactions, antinuclear antibodies		
Metabolism and nutrition disorders		Salt and fluid retention, oedema		Glucose intolerance		
Cardiac disorders	Tachycardia, pericarditis	Pericardial effusion, cardiac tamponade		Angina pectoris, hypotension associated with previous or simultaneous administration of guanethidine		
Vascular disease						Dizziness, drowsiness, fatigue (possibly due to hypotension or hypertension; consider dose adjustment)
Respiratory, thoracic and mediastinal disorders			Pleural effusion	Pulmonary infiltrates		Increased difficulty breathing, especially when lying down (possibly resulting from oedema formation or insufficiently controlled blood pressure)
Gastrointestinal disorders		Gastrointestinal intolerance		Nausea		
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	Gynecomastia		
General disorders and administration site conditions						Peripheral oedema with or without weight gain
Investigations	ECG abnormal			Hepatic enzymes increased		Blood creatinine increased, blood urea increased, haematocrit decreased, haemoglobin decreased

Paediatric population

A post-authorisation analysis of 50 case reports of patients on oral minoxidil identified one case involving a two-year-old female with a history of chronic renal failure and peritoneal dialysis, who developed pericardial effusion, from which she recovered after treatment.

In addition, the estimated total exposure (based on only nine months of data) was about 17,000 patient-years, however, without appreciable data from 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 the national reporting system listed in ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

Symptoms of intoxication

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).

Occasional oliguria development.

Treatment of intoxications

Recommended treatment is intravenous administration of normal saline to maintain blood pressure and to facilitate urination. Sympathomimetic drugs, such as adrenaline (epinephrine) and noradrenaline (norepinephrine) should be avoided due to their excessive cardiac-stimulating action. Phenylephrine, angiotensin II, dopamine and vasopressin, which reverse the antihypertensive 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: Antihypertensives, 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.

Further 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 and 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 only limited information is available from the published literature. Data available in children younger than 10 years of age is only very limited; it involves approximately 40 patients, eight of whom were under one year of age.

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 metabolized in the liver. The primary metabolite in humans is the minoxidil O-glucuronide. In addition, some more polar metabolites are formed. The known metabolites have a weaker antihypertensive effect than the active substance itself.

Elimination

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

Bioavailability

Studies comparing the bioavailability of tablet and oral solution formulations (5 mg of minoxidil each) in hypertensive patients indicated bioequivalent behaviour with regard to the average area under the serum concentration-time curve (AUC), maximum serum concentration, time to reach maximum serum concentration (approximately 40 minutes), and the type of effect (antihypertensive). In comparison with a single dose, the chronic oral administration of minoxidil does not lead to accumulation or to an altered bioavailability.

Hepatic impairment

The pharmacokinetics of minoxidil has not been studied in patients with moderate to severe hepatic impairment.

In a pharmacokinetic study on patients with mild liver cirrhosis, 8 patients with biopsy-documented mild cirrhosis and 8 healthy volunteers received 5 mg of minoxidil. The elimination rate of minoxidil was significantly reduced by approximately 21 % in cirrhotic patients. Although not statistically significant, the AUC in cirrhotic patients increased by 50 % compared to the healthy control group. Dose adjustment should be considered in patients with hepatic impairment. Therapy can be initiated with a reduced dose once daily and then titrated up, until the desired therapeutic effect is achieved with the lowest effective dose.

Paediatric population

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

5.3 Preclinical safety data

In preclinical studies in a variety of species, minoxidil induced several types of cardiac lesions including necrotic and haemorrhagic lesions of the myocardium and papillary muscle, as well as cardiac hypertrophy and dilation. These changes occur only in the context of pronounced hypotension and tachycardia and point to haemodynamic and/or hypoxic stress rather than direct cytotoxicity. As extensive experience with the drug has accumulated by now, it has become apparent that these cardiac lesions do not occur in humans treated with minoxidil.

Carcinogenicity

In the carcinogenicity studies deemed most relevant for orally administered minoxidil, with oral administration to rats and mice, no carcinogenicity potential could be determined in the rats, while the tumours observed in the mice were classified as incidental.

In a carcinogenicity study with topical application in mice, there was an increased frequency of hormone-dependent tumours that were not considered relevant for humans.

Mutagenicity

Minoxidil was not found to be mutagenic in any of the tests for mutagenic potential.

Reproductive toxicity

In a fertility study with male and female rats, a dose-dependent reduction of the conception rate was found. The no observed adverse effect level (NOAEL) was 1 mg/kg per day in treated rats.

Teratogenicity has been demonstrated in rats at doses above 80 mg/kg/day. Oral administration of minoxidil to rabbits has been associated with evidence of increased foetal resorption at doses associated with maternal toxicity. No teratogenicity was observed in rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose, microcrystalline (E460)
Maize starch
Silica, colloidal anhydrous
Magnesium stearate (E572)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Minoxidil POA Pharma Tablets are packed in opaque PVC/PVDC/ALU blisters. Each blister contains 10 tablets.

Pack sizes: 30 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

POA Pharma Scandinavia AB
Hyllie Stationstorg 31, vån 5,
215 32 Malmö
Sweden

8 MARKETING AUTHORISATION NUMBER(S)

MA1531/00101 (2.5mg tablets)

MA1531/00102 (10mg tablets)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17th November 2022

10 DATE OF REVISION OF THE TEXT

3rd August 2023