

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Minoxidil 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5mg minoxidil.

Excipients with known effect:

One tablet contains 47.75mg of lactose monohydrate.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

White colored, round shaped (about 6mm), uncoated tablet debossed “5” on one side and ‘M’ on scoring side.

The score line is not intended for breaking the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Minoxidil is indicated for the treatment of severe hypertension.

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 beta-adrenergic 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 basing 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.

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 minoxidil 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 minoxidil 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 failure or 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 minoxidil either after or at least two hours before dialysis.

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 minoxidil 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 minoxidil 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, minoxidil 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 minoxidil 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 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 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 contra-indicated, alternatives such as methyl dopa may be used instead and should be started 24 hours prior to minoxidil.

Method of Administration

Oral administration

4.3 Contraindications

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

Minoxidil is contra-indicated 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 leucopenia

Thrombocytopenia and leucopenia 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.

This medicine contains lactose

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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 hirsutism 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 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

There are no fertility data from the use of minoxidil in humans. In a fertility study with male and female rats, a dose-dependent reduction of the conception rate was found. The dose corresponded to one to five times the maximum dose used in humans to treat hypertension.

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-existing side-effects attributable to their disease or previous therapy. New events or side-effects likely to increase are included in the following table:

Very common	($\geq 1/10$)
Common	($\geq 1/100$ to $< 1/10$)
Uncommon	($\geq 1/1,000$ to $< 1/100$)
Rare	($\geq 1/10,000$ to $< 1/1,000$)
Very rare	($< 1/10,000$)
Not known	(cannot be estimated from the available data).

MedDRA System Organ Class	Frequency	Undesirable Effects
Blood and Lymphatic System Disorders	Rare	Leucopenia, thrombocytopenia
Metabolism and Nutrition Disorders	Common	Fluid retention, oedema
Cardiac Disorders	Very Common	Tachycardia, pericarditis
	Common	Pericardial effusion, cardiac tamponade
	Not Known	Angina pectoris
Respiratory, Thoracic and Mediastinal Disorders	Not Known	Pleural effusion
Gastrointestinal Disorders	Not known	Gastrointestinal disorder
Skin and Subcutaneous Tissue Disorders	Very Common	Hypertrichosis, hair colour changes
	Rare	Stevens-Johnson syndrome, dermatitis bullous, rash,
Reproductive System and Breast Disorders	Not known	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.

Post authorisation experience has shown that, in a particular study, out of 50 patients on oral minoxidil, one case involved 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 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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: C02 DC01

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

Absorption and distribution

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.

Based on results from a relative bioavailability study, tablet and oral solution formulations have similar values in 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). There is no accumulation following chronic administration of oral tablets compared with single dose.

Minoxidil is not bound to plasma proteins.

Minoxidil does not cross the blood-brain barrier.

Metabolism

At least 90% of the administered minoxidil is metabolized 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 4hours. 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.

Paediatric population

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

Hepatic impairment

No data are available.

5.3 Preclinical safety data

Cardiac lesions in animals

In non-clinical studies in a variety of species, minoxidil induces several types of cardiac lesions 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 carcinogenicity studies in rats and mice dosed via oral or dermal routes of administration no findings considered relevant to humans were found.

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) for this finding was 1 mg/kg per day in treated rats.

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

No data regarding juvenile animal toxicity studies is currently available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate

Maize StarchB (E1401)

Microcrystalline cellulose (E460)

Colloidal Silicon Dioxide (E551)

Magnesium stearate (E572)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Tablets are packed in a blister made up of PVC-PVDC film & aluminium foil.

60 tablets.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

DAWA Limited

5 Sandridge Close

Harrow

Middlesex

HA1 1XD

United Kingdom

8 MARKETING AUTHORISATION NUMBER

PL 30684/0383

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