Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Minoxidil 5 mg Tablets
Minoxidil 10 mg Tablets

minoxidil

PL 49255/0024-0025

Cygnus Pharma Limited

LAY SUMMARY

Minoxidil 5 mg & 10 mg Tablets
minoxidil

This is a summary of the Public Assessment Report (PAR) for Minoxidil 5 mg & 10 mg Tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Minoxidil Tablets in this lay summary for ease of reading.

For practical information about using Minoxidil Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Minoxidil Tablets and what are they used for?
These products are generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised, called Loniten 10 mg Tablets.

Minoxidil Tablets are used to treat very high blood pressure (severe hypertension).

How do Minoxidil Tablets work?
This medicine contains minoxidil, which is one of a group of medicines called 'vasodilators'. It works by relaxing blood vessels so that blood passes through them more easily. This helps to lower blood pressure.

How are Minoxidil Tablets used?
The pharmaceutical form of these medicines is a tablet and the route of administration is oral (taken by mouth).

Minoxidil tablets should be swallowed whole with water.
The 10mg tablets can be divided into equal doses.
The score line is not intended for breaking the 5mg tablet into equal doses.

Adults and children over the age of 12
The patient's doctor might change the patients' daily dose gradually to get the best results. There should be at least three days between each change of dose. The patient should not wait until their tablets are finished before seeing their doctor.

The usual starting dose of Minoxidil tablets for adults and children aged over 12 years is 5 mg each day. The dose can be increased to 20 mg and then 40 mg as single or divided doses if required for optimum blood pressure control. It is unusual to need more than 50 mg a day in adults and children aged over 12 years. In very rare instances the patient's doctor can decide to use up to a maximum of 100 mg.

Elderly
For adults over 65, the usual starting dose is 2.5 mg each day.

Use in children 12 years and under
For children of 12 and under, the dose depends on their weight but they should not be given more than 1 mg per kilogram of body weight each day. The starting dose is normally 0.2 mg each day for each kilogram of their weight.
During treatment with minoxidil tablet the child should be under specialist supervision. The daily dose of minoxidil will be determined by the specialist and it may be adjusted according to the child's needs. During treatment the child will be additionally treated with other medicines as decided by the specialist to prevent rapid heart-beat and accumulation of fluid in the body.
The child's parent/carer should contact the doctor if the child has any of the following: a very rapid heart-beat, rapid breathing, swelling of the legs, rapid weight gain, and reduced urine. While on treatment with minoxidil the child will need to be regularly seen by the doctor.

Patients on dialysis
If a patient is on dialysis they may need a lower dose, even though dialysis can remove minoxidil from the patient's blood. Patients should not take their tablets in the two hours before their dialysis session. The patient should take them after the dialysis, or more than two hours before.

Rapid reduction of blood pressure
Minoxidil Tablets may also be given to a patient in hospital to reduce their blood pressure very quickly. It would be given by a doctor or nurse under strictly monitored conditions at increasing doses of 5 mg every six hours until the patient's blood pressure is normal.

For further information on how Minoxidil Tablets are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of Minoxidil Tablets have been shown in studies?
Because Minoxidil Tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Minoxidil Tablets?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By

reporting side effects, patients can help provide more information on the safety of this medicine.

Because Minoxidil Tablets are generic medicines and are bioequivalent to the reference medicines, their benefits and possible side effects are considered to be the same as the reference medicines.

Why were Minoxidil Tablets approved?
It was concluded that, Minoxidil Tablets has been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Minoxidil Tablets?
As for all newly-authorised medicines, an Risk Management Plan (RMP) has been developed for Minoxidil Tablets. The RMP details the important risks of Minoxidil Tablets, how these risks can be minimised, any uncertainties about Minoxidil Tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Minoxidil Tablets:

Summary of safety concens	
Important identified risks	• Sodium and water retention • Cardiovascular disorders (including palpitations, heart rate increased and chest pain) • Pericarditis, pericardial effusion and tamponade
Important potential risks	• None
Missing Information	• Safety and efficacy during pregnancy and lactation • Safety and efficacy in off-label use in treatment of alopecia

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Minoxidil Tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Minoxidil Tablets
Marketing Authorisations for Minoxidil Tablets were granted in the United Kingdom (UK) on 05 April 2023.

The full PAR for Minoxidil Tablets follows this summary.

This summary was last updated in October 2023.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Minoxidil 5 mg & 10 mg Tablets (PL 49255/0024-0025) could be approved.

The products are indicated for the treatment of severe hypertension.

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.

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Loniten 10 mg Tablets that has been licensed for suitable time, in line with the legal requirements.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is for generic medicinal product of suitable reference product. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing Authorisations for Minoxidil Tablets were granted in the United Kingdom (UK) on 05 April 2023.

II QUALITY ASPECTS

II.1 Introduction

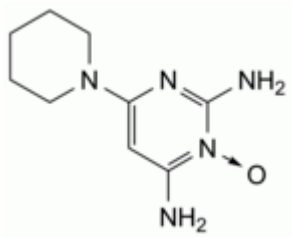
The active substance is minoxidil. Each tablet contains either 5 mg or 10 mg minoxidil. In addition to minoxidil, these products also contain the excipients lactose monohydrate, microcrystalline cellulose (E460), maize starch, colloidal silicon dioxide and magnesium stearate.

The finished products are packaged in a blister made up of PVC-PVDC film and aluminium foil in a pack size of 60 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: minoxidil
Chemical Name: 6-(Piperidin-1-yl)pyrimidine-2,4-diamine 3-oxide
Molecular Formula: $C_9H_{15}N_5O$



Chemical Structure:
Molecular Weight: 209.3 g/mol
Appearance: White or almost white, crystalline powder
Solubility: Slightly soluble in water, soluble in methanol and in propylene glycol.

Minoxidil is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 36 months, with the storage conditions store below 25°C and store in the original package in order to protect from moisture, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of minoxidil are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification was provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the marketing authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects

The grant of marketing authorisations was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of minoxidil are well-known. With the exception of data from one bioequivalence study undertaken (886-19), no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

Study 1:
In support of the application, the applicant submitted the following study 886-19.

This study was an open label, randomized, balanced, two treatment, two period, two sequence, two way crossover, single dose oral bioequivalence study comparing the test product Minoxidil 10 mg Tablets versus the reference products Loniten 10 mg Tablets in healthy, adult, human subjects under fasting conditions.

A single dose of either the test or reference product was administered after an overnight fast of at least 10 hours, in each study period. Blood samples were taken pre-dose and up to 24 hours post dose, with a washout period of 3 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Parameters (units)	Least Square Means		Geometric Least Square Means		Ratio (%) (T Vs R)	90% Confidence Intervals (%)	Intra Subject CV (%)	Power (T Vs R) (%)
	T	R	T	R				
Ln (C_{max}) (ng/ml)	4.5335	4.5854	93.082	98.046	94.94	87.04 - 103.55	23.96	99.42
Ln (AUC_{0-t}) (hr *ng/ml)	5.0076	5.0309	149.545	153.068	97.70	95.00 - 100.48	7.64	100.00

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional strength (5 mg) of the product met the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the product strength can be extrapolated to the other strengths.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted for these applications and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of marketing authorisations was recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with minoxidil is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**