IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Minoxidil for men 5% w/v cutaneous solution
Minoxidil
PA22753/001/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Minoxidil for men 5% w/v cutaneous solution from Careforsons Ireland Limited on 30th April 2021 for the treatment of moderate androgenetic alopecia in men aged 18 – 65 years. This public assessment report concerns the MR-procedure IE/H/1206/001/MR for Minoxidil for men 5% w/v cutaneous solution, with Ireland acting as Reference Member State and Germany as the only Concerned Member State.

This is a well - established use application in accordance with Article 10 (a), bibliographic data supporting 10 years of use of 5% minoxidil solution in men.

Product not subject to medical prescription.

The Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Minoxidil for men 5% w/v cutaneous solution.
Name(s) of the active substance(s) (INN)	Minoxidil
Pharmacotherapeutic classification (ATC code)	D11AX01-minoxidil
Pharmaceutical form and strength(s)	50 milligram(s)/millilitre
Marketing Authorisation Number(s) in Ireland (PA)	PA22753/001/001
Marketing Authorisation Holder	Careforsons Ireland Limited
MRP/DCP No.	IE/H/1206/001/MR

II. QUALITY ASPECTS

II.1. Introduction

This application is for Minoxidil for men 5% w/v cutaneous solution.

II.2 Drug substance

The active substance is minoxidil, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition
The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European and ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for liquid preparations for cutaneous application, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.7 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.8 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Minoxidil for men 5% w/v cutaneous solution.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of minoxidil are well known. As minoxidil is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

Minoxidil for men 5% w/v cutaneous solution is indicated for the treatment of moderate androgenetic alopecia.

Compliance with GLP

No new non-clinical studies have been conducted by the applicant in support of this application. Reference is made to the published scientific literature in the Non-Clinical Overview but the GLP status of these studies cannot be assumed or verified.

III.2 Pharmacology

Cutaneous application of Minoxidil has an anti-alopecic effect. Literature references highlight that minoxidil stimulates the growth of keratinocytes in vitro and in vivo together with hair growth in some patients with androgenic alopecia.

The mode of action of minoxidil on hair growth is not well clarified. In animal studies it has shown that it shortens the telogenic phase, causing a advance in the entrance of the hair follicles in the anagenic phase; it also prolongs the anagenic phase and increases the size of the hair. The hypotensive effect of minoxidil through action of its active metabolite, the minoxidil sulphate, which relaxes the smooth vascular musculature, was derived from the opening of the ATP-dependent K^+ channels; this effect

on the K^+ channels also seems to participate in the stimulation of capillary growth. Other effects with possible participation on hair growth includes stimulation of the cellular proliferation, the inhibition of the collagen synthesis, stimulation of the vascular endothelium growth factor and of the prostaglandin synthesis and activation in the dermal papilla cells the β-catenin, ERK and Akt activity and the increase, also in dermal papilla cells, of the ratio of Bcl-2/Bax.

III.3 Pharmacokinetics

The pharmacokinetics of minoxidil indicates that the percutaneous absorption seems to be minimal after topical application in intact skin. In animal studies, however, this absorption is very variable, oscillating between 5% in monkeys and 48% in mice.

The minoxidil distribution follows patterns similar in all the species after oral, SC and topical administration; it is rapid and includes the liver, kidneys, intestine, bladder and aorta.

There is a first-step phenomenon in evident in all the species tested and 8 metabolites have been characterised. In the case of topical administration, in the application site, 70-80% of the radioactivity corresponded to the drug without modification and there were qualitative differences in the metabolic profile observed regarding that obtained after oral administration.

The majority is eliminated through the urinary tract, with a small fraction through faeces.

III.4 Toxicology

In acute toxicity studies of minoxidil using systemic administration routes, very high LD50 were obtained while in acute toxicity studies after topical administration, no abnormal findings were noted.

In studies of multiple toxicity, after topical administration, the presence of irritation in the application site and cardiovascular changes were highlighted. In the toxicity studies by systemic channels, the most outstanding were hydroelectrolytical renal tubular retention, arterial dilation, tachycardia and hypotension.

The genotoxicity studies showed the absence of a mutagen effect for minoxidil.

The dermal carcinogenicity studies lasting 2 years showed an increase in the incidence of mammary adenomas and adenocarcinomas in female mice, pheochromocytomas in male and female rats and preputial adenomas in male rats. All these neoplasias are not considered clearly related to the use of minoxidil, for which reason it is deemed that they do not affect the safety of its use.

Studies on reproduction have shown the absence of teratogenicity and only the appearance of an increase in foetal resorption and a reduction of dose-dependent conceptions have been shown. The appearance of skeletal abnormalities, an increase in embryonic/foetal mortality and a decrease in the foetal body weight as well as maternal toxicity was only observed with doses of 120 mg/kg/day (132 times the maximum recommended dose in humans).

Regarding local tolerance, it is noted that adverse events of minoxidil cutaneous solutions in stumptailed macaques were occasional nonspecific producing mild inflammatory changes and occurred with the minoxidil solution and also with the vehicle.

III.5 Ecotoxicity/environmental risk assessment

The applicant has provided a full environmental risk assessment (ERA) in accordance with the guideline (CHMP/SWP/4447/00). Minoxidil is not a PBT substance. Considering the data provided, Minoxidil for men 5% w/v cutaneous solution is not expected to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects

The use of minoxidil is well established. As minoxidil is a widely used, well-known active substances, the applicant has not provided additional non-clinical studies to avoid the need for repetitive tests on animals. The submitted overview of the available non-clinical pharmacodynamic, pharmacokinetic and toxicological data is acceptable.

IV. CLINICAL ASPECTS

This application for marketing authorization is presented in bibliographical format under Article 10 a of Directive 2001/83/CE. This document justifies that the applicant doesn´t have to provide the results of further toxicological or pharmacological tests, if it can be clearly demonstrated from the existing literature that the components of the medicinal product in question have an established and extensively medical use for more than a 10-year period, that their efficacy is recognised, and that they are acceptably safe.

This application for marketing authorization is presented in bibliographical format under Article 10 a of Directive 2001/83/CE.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Minoxidil is a vasodilator which when used systematically causes a distinct drop in blood pressure. Minoxidil was first used orally for the treatment of high blood pressure in early 1969. One of the side effects of this medication was hypertrichosis. Starting in 1972, studies began on the topical absorption of minoxidil, and it was later confirmed to be an efficient topical stimulant of hair growth in the treatment of androgenetic alopecia.
Androgenic alopecia is the most prevalent type of hair loss in males, comprising more than 90% of all hair growth dysfunctions. Topical application of minoxidil leads to stimulation of hair growth in patients with androgenetic alopecia. Hair growth can be expected at the earliest after 4 months, excessive hair loss can be stopped after a few weeks following regular application

IV.3 Pharmacodynamics

No new data on primary and secondary pharmacodynamics are included in the present application.

The mechanism by which it promotes hair growth is not fully understood. A number of possible mechanisms have been postulated. Minoxidil promotes regrowth in diseases as alopecia areata and alopecia androgenetica, which suggests that it acts on the hair follicles per se or it may be indicative of a more widespread mechanism such as a direct effect on cellular function. Minoxidil is a potassium channel opener, causing hyperpolarization of cell membranes and it is also a vasodilator. Minoxidil is assumed to stimulate the growth of keratinocytes.

IV.4 Clinical Efficacy

Minoxidil 50 mg/ml is indicated for the treatment of moderate androgenetic alopecia, in men aged 18 – 65 years. The use of minoxidil in this indication is authorized in many products being marketed for more than 10 years and is commonly used in the medical practice
The applicant provided a detailed clinical overview listing worldwide scientific bibliography for Minoxidil cutaneous solution, active principle of Minoxidil 50 mg/ml cutaneous solution, and its ingredients demonstrating that the active substance and the formula have a very well established medical use with recognized efficacy

IV.5 Clinical Safety

The applicant provided a detailed clinical overview demonstrating that the active substance and the formula have a very well established safety profile
No new safety concerns were found in the safety data submitted in support of the present application.
Minoxidil cutaneous solution is indicated for use in men only and should not be used by women. It should not be used if you are pregnant or breast-feeding.

Please see the product information for the full prescribing safety information.

Risk Management Plan
The applicant has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Minoxidil for men 5% w/v cutaneous solution.
The RMP (version 1.1, signed 24/09/21) is acceptable. Routine pharmacovigilance and routine risk minimisation activities are considered sufficient.

Safety specification

Important identified risks	• None
Important potential risks	• None
Missing information	• None

The applicant is requested to ensure it maintains the RMP in line with the latest SmPC and maintains regular reviews.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:
• PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
• For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
• In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

The applicant has submitted sufficient published scientific literature results to support 10 years of use of 5% minoxidil cutaneous solution in men for this well -established use application

V. OVERALL CONCLUSIONS

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that Minoxidil for men 5% w/v cutaneous solution demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

29.04.2026