

Public Assessment Report

Scientific discussion

**Minoxidil Xiromed 20 mg/ml and 50 mg/ml
cutaneous solution**

(minoxidil)

NL/H/3629/001-002/DC

Date: 16 April 2019

This module reflects the scientific discussion for the approval of Minoxidil Xiromed 20 mg/ml and 50 mg/ml cutaneous solution. The procedure was finalised on 7 February 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Minoxidil Xiromed 20 mg/ml and 50 mg/ml cutaneous solution from Medical Valley Invest AB.

The product is indicated for treatment of androgenetic alopecia in men and women.

Minoxidil Xiromed 50 mg/ml must not be used in women, due to the possible appearance of hypertrichosis in other parts of the body (see SmPC section 4.4).

A comprehensive description of the indications and posology is given in the SmPC.

Minoxidil 20 mg/ml topical solution is used since 1987 in France, Belgium, Spain, and Ireland for the treatment of androgenetic alopecia in men. Minoxidil 50 mg/ml solution is authorised in several EU countries (Germany, France, Finland, Ireland, Italy, Portugal, Poland, Sweden, UK, Spain, Austria, Belgium, Croatia, Czech Republic, and Estonia). In Finland, Sweden, and the UK this strength is available since 2000 as an over-the-counter product for the treatment of androgenetic alopecia in men.

The concerned member states (CMS) involved in this procedure were the Czech Republic (only the 50 mg/ml strength), Germany, Poland and Slovakia (only the 50 mg/ml strength).

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, a so called bibliographic application based on the well-established medicinal use of minoxidil.

II. QUALITY ASPECTS

II.1 Introduction

Minoxidil Xiromed is a cutaneous solution. The solution is transparent and colourless to slightly yellowish with an alcohol aroma.

The solution is packed in an HDPE bottle with PP screw cap, PP metering pump and PP push-button, which contains 60 ml, 120 ml (two bottles of 60 ml) and 240 ml (four bottles of 60 ml) of cutaneous solution. Minoxidil Xiromed is administered by the screw-on pump (10 pulsations/sprays are equivalent to 1 ml) with a PP push-button. Each ml of Minoxidil Xiromed contains 20 mg or 50 mg of minoxidil.

The excipients are ethanol 96%, propylene glycol and purified water.

II.2 Drug Substance

The active substance is minoxidil, a well established active substance described in the European Pharmacopoeia (Ph.Eur.). Minoxidil is a white to almost white crystalline powder, slightly soluble in water, and soluble in methanol and propylene glycol. As the drug substance is dissolved in propylene glycol and ethanol during the manufacturing process, particle size and polymorphic form of the drug substance were evaluated of not having an effect on the drug product performance.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance

The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The excipients are well known. Dosing accuracy and uniformity comply with the Ph.Eur. The drug product Minoxidil Xiromed 50 mg/ml cutaneous solution was developed in analogy to other minoxidil-containing products on the European market. The existing drug products were investigated with respect to their qualitative and quantitative composition, as well as physicochemical parameters. All products share the same excipients, together with the same ratio of ethanol/propylene glycol. Furthermore, all products are of the same pH (7.8) and density.

In line with the data provided for the development of the 50 mg/ml product, the MAH has tested samples of approved 20 mg/ml products from the EU market regarding the qualitative and quantitative composition (assay, nature and ratio of solvents, pH, and density) in relation to the proposed 20 mg/ml minoxidil formulation. Due to differences in the propylene glycol content of the test and reference 20 mg/ml formulations, a comparative *in vitro* absorption/permeation study in Franz diffusion cells was performed. However, the Franz diffusion cell is not a clinically validated method for this type of product and the relevance of the generated data could not be judged.

To support that there is no difference in efficacy and safety, the MAH provided several references on minoxidil containing products of different pharmaceutical forms (i.e. gel, solutions, ointment and lotion) as well as with different compositions (% PG: 10-50; % alcohol: 30-70). Based on these references and without the notable difference in efficacy and safety, it is concluded that the literature can be used for bridging. Pharmaceutical development has been adequately performed.

Manufacturing process

The manufacturing process is a preparation of a non-sterile bulk solution, followed by filling of the solution into the plastic bottles. It is considered a standard process. The implemented in-process controls are sufficient for this type of pharmaceutical form. Initially, the manufacturing processes of the two formulations were validated in 2004 and 2005, respectively, according to an older set of release specifications. With a change to the drug product specifications, the process was revalidated on three full scale batches for both formulations. All parameters and attributes were found to be within acceptable ranges and according to acceptance criteria.

Microbiological attributes

The MAH performed preservative efficacy test in-line with Ph.Eur. 5.1.3 with batches of the 2% and 5% formulation near the end of the shelf-life. The antimicrobial preservation system reaches both acceptance criteria in terms of the log reduction in the number of viable micro-organisms at the different time points against the value obtained for the inoculum.

Control of excipients

All excipients are frequently used in topical products. They are controlled according to their respective current monograph in the Ph.Eur. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, hermeticity, pH, density, minimum filling, identification of active, assay, related substances, functionality of the pump and microbiological

quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data for each concentration (20 mg/ml: five batches, 50 mg/ml: four batches) from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

For the 20 mg/ml formulation, batches in the stability programme are all of commercial size. The MAH submitted long term stability data up to 36 months for the 20 mg/ml solution and 60 months for the 50 mg/ml strength, together with up to 36 months intermediate and six months accelerated conditions for both concentrations. No trends are observed over time. The weight loss study has not been fully executed according to ICH requirements, however, the results under controlled conditions are considered acceptable for preliminary estimations. A commitment has been provided to performed weight loss studies according to NfG *on Stability testing of existing active ingredients and related finished products*. A photostability study was conducted according to ICHQ1B and the drug product did not show signs of degradation after exposure to light.

In view of the provided stability data, the MAH proposes 36 months shelf-life with no special storage conditions for the finished product of both concentrations. Based on the observed general stability of the drug product under all storage conditions, this shelf-life is considered acceptable.

The drug product is stable after first opening of the bottle over the course of the intended application duration of 30 days.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Minoxidil Xiromed has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

The mechanism by which the topical application of minoxidil and/or its metabolite stimulate capillary regrowth in androgenetic alopecia and other forms of alopecia has not been completely clarified but it is likely that it has a primary effect on cell function (Messenger and Rundegren, 2004). Vasodilatory, angiogenic, and enhanced cell proliferative effects of minoxidil are thought to be responsible. Minoxidil is an adenosine-triphosphate-sensitive potassium channel opener reported to stimulate the production of vascular endothelial growth factor, a possible promoter of hair growth. Also minoxidil seems to exercise a favourable effect of hair growth by acting preferably on the cellular cycle prolonging duration of anagen of the hair cycle and increases miniaturised hair follicle size in addition to its significant ability to maintain and thicken pre-existing hair (Shamsaldeen et al., 2013; Messenger and Rundegren, 2004) although it also seems to increase the diameter of the hair.

III.2 Pharmacokinetics

The percutaneous absorption of minoxidil seems to be minimal after topical application in intact skin. However, the systemic absorption of topical minoxidil is variable and depends on several factors, including the vehicle used in the formulation, the area of application, the condition of the skin and the inter-individual variability of the amount of absorption. As previously mentioned minoxidil cutaneous solution contains ethanol, water, and propylene glycol as vehicle. Both alcohol and propylene glycol

induce the drug's uptake. Experimental studies show that the increase in the alcohol percentage increases better minoxidil uptake. This means that propylene glycol is important for minoxidil uptake in the tissues (Rossi et al., 2012).

The minoxidil distribution followed similar patterns after oral, subcutaneous (SC) and topical administration; it is rapid and includes the liver, kidneys, intestine, bladder and aorta. The absorption patterns and distribution after administering minoxidil by SC route during 21 days did not show bioaccumulation in rats. The distribution patterns after multiple doses of radiolabelled minoxidil were similar to those of a single dose but the levels of radioactivity were much higher (in general, 2-9 times higher and 17 times in the skin). Without cerebral radioactivity and presence of radioactivity in the foetus, in the case of topical administration, the majority of the radioactivity was observed in the site of the application. The levels of radioactivity in females compared to males were doubled (FDA-CDER, 1997).

Eight metabolites of radiolabelled minoxidil were characterised 3 minutes after the SC administration of 0.9 mg/kg in rats. The majority of radioactivity remained unaltered (50%), followed by the carboxy-minoxidil. In the monkey, a glucuronide conjugate represented 50% of the radioactivity followed the unaltered drug. The majority of the minoxidil metabolites were also identified in other organs of the rat. 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 with respect to that obtained after oral administration (FDA-CDER, 1997).

The elimination of the absorbed minoxidil from its topical application is shown to be primarily through the urinary passage, approximately 95% before 4 days after the end of the topical application of the product. A significant portion of the topical dose seemed to be eliminated unnoticed from the surface of the hair through contact with hands or clothing, volatilisation, displacement by air currents and other non-systemic forms (AHFS, 2005).

The minoxidil excretion in the breast milk of women is not known, although it has been detected in the breast milk of nursing mothers (AHFS, 2005).

III.3 Toxicology

The administration of minoxidil in the toxicity studies with animals at high doses was not associated with toxicity of any principal organ. The doses to which toxicity was shown are very high in comparison with the doses and the plasmatic level that could be reached through topical administration. Minoxidil did not result either mutagenic or genotoxic. Nor did it show a carcinogenic potential. The administration of minoxidil in the studies on the reproductive function, embryo/foetal and perinatal toxicity in animals did not show toxicity in any of the parameters studied (Technical sheet, 2005).

III.4 Ecotoxicity/environmental risk assessment (ERA)

Minoxidil is a well-known and used active substance. Moreover, other medicinal products containing minoxidil are already marketed in countries where Minoxidil Xiromed cutaneous solution will be marketed. For this reason, it will replace formulations of other medicinal products with the same active ingredient for the same therapeutic indications, and in consequence will not lead to an increased exposure to the environment.

III.5 Discussion on the non-clinical aspects

The application for Minoxidil Xiromed 20 mg/ml and 50 mg/ml cutaneous solution is based on well-established use. This is endorsed, since minoxidil has been registered for this indication for a long time and the dose is not increased. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Minoxidil is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

The MAH demonstrated that the substances included in current minoxidil products are in line with the Ph.Eur. and that the chemical composition of the Minoxidil Xiromed cutaneous solution of 50 mg/ml is quali-quantitatively equivalent to that of currently marketed minoxidil cutaneous solutions of 50 mg/ml within the European Union. The MAH's literature overview of pharmacokinetics, describing absorption, distribution, metabolism and elimination is adequate.

IV.3 Pharmacodynamics

The pharmacodynamic properties of minoxidil for topical application are considered well known and the clinical experience of the compound as topical agent in the treatment of androgenic alopecia is considered extensive. Minoxidil is converted in its active form minoxidil sulphate by the enzyme sulfotransferase. Conversion into active minoxidil sulphate is required to optimise the agent's hypotensive effect and to stimulate hair follicles. Effects of minoxidil sulphate appear to be mediated by potassium-ATP channels.

IV.4 Clinical efficacy

In clinical studies, minoxidil 50 mg/ml solution was more often effective than minoxidil 20 mg/ml solution both in men and women. In a European treatment guideline, for male patients, minoxidil 50 mg/ml solution is preferred above minoxidil 20 mg/ml solution, because of the larger efficacy (Blumeyer et al., 2011). For female patients however, only minoxidil 20 mg/ml solution (twice daily) is recommended, due to limited scientific evidence with respect to application of minoxidil 50 mg/ml in women (Blumeyer et al., 2011). Hence, twice daily application of minoxidil solution for androgenetic alopecia is supported both by the submitted documentation and also by a systematic review, meta-analysis, and a European treatment guideline.

Upon prolonged minoxidil treatment, treatment effects remain constant with time. However, after discontinuation of minoxidil treatment, treatment effects disappear rapidly.

IV.5 Clinical safety

Occurrence of adverse events with respect to minoxidil solutions at concentrations of 20 and 50 mg/ml is low. In addition, occurrence of adverse events is comparable for both solutions. Hence, the safety profile of minoxidil solutions at concentrations of 20 and 50 mg/ml is considered similar. Most frequently observed adverse events upon cutaneous application of minoxidil solutions concern topical dermatological adverse events (e.g. pruritus, erythema, and paraesthesia).

IV.6 Risk Management Plan

The MAH 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 Xiromed.

Summary table of safety concerns as approved in RMP:

Important identified risks	<ul style="list-style-type: none"> • Cardiovascular disorders (including palpitations, heart rate increased and chest pain) • Orthostatic hypotension due to interaction with
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	<ul style="list-style-type: none"> peripheral vasodilators and hypertensive drugs • Hypersensitivity reactions including angioedema
Important potential risks	None
Missing information	<ul style="list-style-type: none"> • Safety and efficacy in elderly • Safety and efficacy during pregnancy and lactation

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

Minoxidil Xiromed 20 mg/ml and 50 mg/ml cutaneous solution is considered widely established. For this authorisation, reference is made to clinical studies and experience with minoxidil. Minoxidil has been shown to be effective in the treatment of treatment of androgenic alopecia. The provided clinical overview is sufficient. No new clinical studies were conducted. This is accepted.

V. USER CONSULTATION

The 50 mg/ml package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with four participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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.

A user consultation with target patient groups on the 20 mg/ml PL has been performed on the basis of a bridging report making reference to 50 mg/ml strength PL. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Minoxidil Xiromed 20 mg/ml and 50 mg/ml cutaneous solution has a proven chemical-pharmaceutical quality. Minoxidil Xiromed is an effective drug, which is considered widely established.

The application was discussed in the Board meeting of 2 February 2017. Questions were raised regarding the appropriate use of the 20 mg/ml strength for woman, the side effects of the 50 mg/ml strength, and the prescription status of the product. Sufficient data were provided regarding the use of the 20 mg/ml strength by women. Side effects for the 50 mg/ml strength were considered similar to the side effects for the 20 mg/ml strength. Also it was concluded that the product information should be adjusted in order to comply with the product's prescription status. Overall, the Board concluded that the benefit-risk balance for this medicinal product is positive.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well-established use has been demonstrated for Minoxidil Xiromed with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 February 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the product name. Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	NL/H/3629/I B/001/G	IB	14-1-2019	13-2-2019	Approved	--
Other changes to a test procedure (including replacement or addition)	NL/H/3629/I B/001/G	IB	7-5-2019	6-6-2019	Approved	--

References

Messenger A.G., Rundegren J. Minoxidil: mechanisms of action on hair growth. *Br J Dermatol* 2004; 150(2): 186-94.

Shamsaldeen O.S., Al Mubki T., Shapiro J. Topical agents for hair growth promotion: what is pout there? *Skin Therapy Letter.com* 2013;18(4):5-7.

Rossi A. et al. Minoxidil use in dermatology, side effects and recent patents. *Recent Patents on Inflammation & Allergy Drug Discovery*. 2012 May;6(2):130-136.

FDA-CDER Summary basis of approval. Pharmacology reviews. Rogaine Extra Strength for Men (5% minoxidil topical solution) (NDA 20-834). NDA Approval date: 9/19/1997. Available in: http://www.fda.gov/cder/foi/nda/97/20834_chemr_phrmr_statr_bioeqr.pdf.

AHFS: American Hospital Formulary Service Drug Information 2004. Minoxidil. American Society of Hospital Pharmacists, Bethesda, MD, 2005.

Technical sheet of Minoxidil Viñas 5% skin solution (Laboratorios Viñas, S.A). Agencia Española del Medicamento y Productos Sanitarios. Ministerio de Sanidad y Consumo. Date of authorisation: September 2005. Available in: <http://sinaem.agemed.es:83/presentacion/principal.asp>.

Blumeyer et al. Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and in men. *Journal of the German Society of Dermatology*. 2011 (Suppl. 6) S1-S57.