LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Minoxidil ABECE/ Minoxidil ABECE Forte (minoxidil)

Asp no: 2019-0034-5

This module reflects the scientific discussion for the approval of Minoxidil ABECE Forte, Minoxidil ABECE. The procedure was finalised on 2019-12-05. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Evolan Pharma AB has applied for a marketing authorisation for,
Minoxidil ABECE, cutaneous solution, 20 mg/ml,
Minoxidil ABECE Forte, cutaneous solution 50 mg/ml

The active substance is minoxidil (is used for topical treatment of thinning hair in both men and women (only the 20 mg/ml cutaneous solution).

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.
For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Minoxidil is a widely used, well-known active substance. It is already approved and marketed as 2% and 5% topical solution. The primary pharmacodynamic properties of minoxidil are well documented in the literature, but the mechanism of action has not been clearly defined. A number of possible mechanisms have been postulated. However, as minoxidil is a widely used, well-known active substance, no further studies are required, and the Applicant provides none. Overview based on literature review is, thus, appropriate.
The non-clinical overview has been written by Dr. Paul Draga, M.D and drug safety and pharmacovigilance consultant and is dated 19 December 2018. The report refers 31 documents up to year 2014.

III.2 Pharmacokinetics

The pharmacokinetics section provided is acceptable. The Applicant has provided data from studies in mice and in human volunteers. Overall, the human pharmacokinetics of minoxidil is considered well-known after dermal administration.

III.3 Toxicology

Minoxidil is widely used and the toxicological properties are well known. Overall, the data provided with in the overview is considered adequate and enough to support the Application.

III.4 Ecotoxicity/environmental risk assessment

The Applicant has not provided with an ERA for minoxidil, with the justification that the present Application is proposed for marketing Minoxidil solution 2% (20 ml/mg) and Minoxidil solution 5% (50 ml/mg) which are hybrid products that will be interchangeably with other similar products that are already marketed in European targeted markets for this application. This is considered acceptable.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

No pharmacokinetic studies have been performed for this product, the applicant proposed a waiver to provide equivalence data. The minoxidil product in this application is for topical application intended to act at the site of application. For locally applied, locally active products, bioequivalence is generally not a suitable way to show therapeutic equivalence since plasma levels are not relevant for local efficacy, although they may play a role with regard to safety. However, since the product is a topical solution, a waiver of the need to provide equivalence data may be acceptable according to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) provided that the test product is of the same type of solution and contains the same concentration of the same active substance as the reference product. Minor differences in excipients may be acceptable if the relevant pharmaceutical properties are identical or essentially similar.

For the lower strength, 20 mg/ml, the pharmaceutical composition is assessed as essentially similar to the reference product and the absence of pharmacokinetic studies is acceptable. Therapeutic equivalence can be concluded based on quality data.

The higher strength, 50 mg/ml (forte), has been reformulated during the procedure and the new pharmaceutical composition is assessed as essentially similar to the reference product and the

absence of pharmacokinetic studies is acceptable. Therapeutic equivalence can be concluded based on quality data.

IV.2 Pharmacodynamics

The exact mechanism of action of minoxidil in the treatment of androgenetic alopecia is not known. Minoxidil is via sulfotransferase converted to the active metabolite, minoxidil sulphate. The effects of minoxidil on hair regrowth are possibly mediated by this active metabolite. In clinical studies, no correlation was established between serum or tissue minoxidil concentrations and hair regrowth.

Minoxidil has hemodynamic effects that also do not correlate with serum levels of minoxidil.

IV.3 Clinical efficacy

The clinical efficacy of topical minoxidil in the treatment of thinning hair in men and women has briefly been summarised by the Applicant. Most available data on clinical efficacy are obtained in men with androgenetic alopecia with the minoxidil topical 2% solution.

A temporary hair loss may occur upon initiation of therapy; this increase in shedding generally occurs 2 – 6 weeks after the beginning of treatment and subsides within a few weeks. This shedding upon initiation of therapy is due to hair shifting from resting phase (telogen) to growth phase (anagen). After treatment initiation of twice daily treatments with the 2% minoxidil solution, the time to response differs greatly between individuals. In general, it takes at least 4 months of twice daily applications until a response is evident.

After 4 months of treatment, 26% of individuals reported moderate (defined as new individual hairs that covered all or some of the thinning areas but not as close together as hairs on the rest of the head) to dense hair regrowth (new hairs that cover or almost completely cover the thinning area and are as close together as hairs on the non-thinning areas of the head). A similar response was obtained in 11% of the subjects using the vehicle control. Clinical efficacy tended to improve following further 8 months of treatment, that is treatment duration of one year.

The effect is maintained only for as long as the product is used. Cessation of treatment will result in loss of the newly regrown hair within about 3 months and progressive hair loss will return.

Clinical efficacy data with topical 5% minoxidil foam was also briefly reviewed, as was efficacy data in women with female pattern hair loss.

IV.4 Clinical safety

In general, topical minoxidil is well tolerated and the majority of side effects are due to skin intolerance of the topical formulation in some patients. The side effects resolve upon discontinuation of the product.

The most frequently encountered adverse effect in clinical trials with minoxidil was mild dermatitis of the scalp. The dermatological events were of a similar type and severity in the 2% and 5% groups, but the incidence was greater in the 5% group.

Most frequently reported adverse reactions with 2% and 5% topical minoxidil in commercial marketing experience are dermatological reactions.

The risk for topical minoxidil to adversely affect either hypertension or hypotension seems marginal, due to low percutaneous absorption of minoxidil. Warnings are included in the SmPC (section 4.4 Warnings and precautions) related to cardiovascular diseases and the necessity of contact with a physician. Moreover, hypotension is labelled in the adverse event section 4.8.

Topical minoxidil is not recommended for use by patients treated for other scalp disorders, or when application is accompanied by stinging and burning.

Pharmacovigilance system
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the MPA considers the Summary acceptable.

IV.5 Risk Management Plans

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 ABECE Cutaneous solution, 20 mg/ml, Minoxidil ABECE Forte, Cutaneous solution 50 mg/ml.

Safety specification
The proposed safety concerns (RMP Part II: Module SVIII)] are;

Summary of safety concerns	
Important Identified Risks	• Cardiovascular disorders (including palpitations, heart rate increased and chest pain)
Important Potential Risks	• None
Missing Information	• None

Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
The proposed risk minimisation measures (RMP Part V.3] presented by the Applicant is;

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		
Cardiovascular disorders (including palpitations, heart rate increased and chest pain)	**Routine risk communication:** **Text in SmPC:** *Section 4.4* - Special warnings and precautions for use: *Section 4.8 – Undesirable effects* **Text in PL:** *Section 2 – What you need to know before you use Minoxidil/ Minoxidil Forte* *Section 4 – Possible side effects* **Additional risk minimisation measures:** *None proposed.*	Only routine pharmacovigilance activities, no additional pharmacovigilance activities.
Important potential risk		
None		
Missing information		
None		

Summary of the RMP
The submitted Risk Management Plan, version 0.2 signed 2 July 2019 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the MPA;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet 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 language used for the purpose of user testing the PIL was Portuguese.
The results show that the package leaflet 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 package information leaflet (PIL) has also been performed on the basis of a bridging report making reference to the layout of Natriumklorid Evolan 500 mg capsules (Asp no 2014-0066, MAno 50769) (for Minoxidil Abece/Evolan/Net) and Ranitidin Apofri 150 mg film-coated tablet (Asp no: 2012-1198, MAno 48746) (for Minoxidil Apofri). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Minoxidil ABECE, cutaneous solution, 20 mg/ml, Minoxidil ABECE Forte, cutaneous solution 50 mg/ml are recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Minoxidil ABECE, cutaneous solution, 20 mg/ml, Minoxidil ABECE Forte, cutaneous solution 50 mg/ml were approved in the national procedure on 2019-12-05.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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