Public Assessment Report
Scientific discussion

Rogaine 50 mg/g cutaneous foam
(minoxidil)

SE/H/1173/01/DC

This module reflects the scientific discussion for the approval of Rogaine. Please note that the marketing authorisation was first approved with the name “Regaine” and therefore this name is used throughout the document. The procedure was finalised 2012-07-04. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

McNeil Sweden AB has applied for a marketing authorisation for Regaine cutaneous foam, 50 mg/g. The active substance is minoxidil. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Regaine is presented in the form of a cutaneous foam containing 50 milligrams of minoxidil per gram.

II.2 Drug Substance

The drug substance minoxidil is a white or almost white powder which exhibits low aqueous solubility. The manufacturer of minoxidil holds a Certificate of Suitability (CEP) certifying that the substance is suitably controlled by the monograph “Minoxidil” no. 937 published in the European Pharmacopeia (Ph. Eur.). The specification for minoxidil complies with the requirement of the CEP and the Ph. Eur.

II.3 Medicinal Product

Regaine is a white to yellowish, creamy, unscented foam for topical use. The formulation is based on ethanol and water as main solvents. The remaining excipients are butylhydroxytoluene, lactic acid, citric acid anhydrous, glycerol, cetyl alcohol, stearyl alcohol and polysorbate 60. In addition, Nitrogen is used to blanket the bulk solution during manufacture. Nitrogen is not a component of the finished product. The inclusion of each excipient has been justified. All of the excipients are controlled in accordance with the relevant monograph published in the Ph. Eur. The propellants propane, butane and iso-butane comply with the requirements of the United States Pharmacopeia. The product is packaged in an aerosol can that is sealed with a non-metered valve assembly.

Sufficient information has been presented regarding the pharmaceutical development work. Critical aspects addressed during development include the solubility of minoxidil, pH optimization, crystallization inhibition, minimization of oxidation and antimicrobial effectiveness.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the release and shelf-life specifications are considered appropriate to control the quality of the finished product in relation to its intended purpose. The specifications comply with the requirements of the Ph. Eur. and the impurity limits have been set in accordance with ICH Topic Q3 B. The analytical procedures are adequately described and the analytical validation data show that the methods are suitable for their intended use.
Stability studies according to ICH standards have been performed. The stability data support the shelf-life claimed in the Summary of Product Characteristics.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology
The pharmacological properties of minoxidil are well known. As minoxidil is a widely used, well-known active substance, no further pharmacological studies are required. Overview based on literature review is, thus, appropriate. In the review of literature a number of studies confirm the known effect of minoxidil to stimulate hair growth. However, the mechanism of action seems still to be unclear. Furthermore, the literature data on the secondary pharmacological effects and safety aspects of minoxidil does not give information that is judged to be of significance for the non-clinical safety profile of minoxidil when used topically.

Nevertheless, a proof of concept study in stump tail macaques has been submitted to support this application. The results show an increased hair growth after topical administration of minoxidil. The mean monthly hair growth was 12.40 mg and 10.65 mg in the 5% minoxidil foam group and 5% minoxidil solution group, respectively. The results support a slightly improved efficacy on hair growth in these animals. A similar improved effect in humans seems possible but has to be shown in clinical studies.

III.2 Pharmacokinetics
The uptake of minoxidil from 5% Minoxidil Foam (M) was studied in the Syrian hamster ear model for evaluating targeted drug delivery to the sebaceous gland associated with hair follicles. The 5% minoxidil foams delivered roughly 5-6% of the applied dose to the sebaceous glands within one hour. Comparable values for the 5% Minoxidil Topical Solution (Rogaine® Extra Strength) and the minoxidil gel formulations were roughly 2%. The increased skin absorption from the foam formulation is in line with the increased effect on hair growth seen in the study in stump tail macaques. The slightly increased absorption from the foam formulation is not judged to have an impact on the safety profile and is not a cause for concern.

Furthermore, the in vitro penetration of human cadaver skin was evaluated for these three 5% minoxidil mousse formulations and the registered Rogaine® Extra Strength product containing 5% minoxidil. The measured permeability coefficients of less than 1 x 10^{-10} cm/sec indicated very low absorption through the whole skin. Consequently, there is no significant systemic delivery of minoxidil anticipated.

Moreover the ADME characteristics of minoxidil are well known and have been assessed for the already approved 5% Minoxidil Topical Solution product.

III.3 Toxicology
The toxicological properties of minoxidil are well known. The new foam formulation contain the same amount of active substance as the already approved 5% Topical solution and the systemic exposure after topical application is expected to be similar. The local tolerance and phototoxicity of the foam formulation have not been studied. However, minoxidil in the topical solution formulation did not induce contact sensitization or IgE-mediated sensitization and was neither phototoxic nor photoallergic. Furthermore, the excipients used in the foam are not a cause for concern.
III.4 Ecotoxicity/environmental risk assessment
An ERA for the already approved 5% Minoxidil topical solution has been provided which is acceptable. The introduction of 5% Minoxidil foam formulation is not expected to result in an increased environmental risk.

III.5 Discussion on the non-clinical aspects
The application is approvable from a non-clinical perspective.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics
Regaine cutaneous foam (5% MTF) is a locally applied, locally acting product. Hence, the pharmacokinetic assessment is mainly aimed at an assessment of clinical safety, related to the extent of systemic absorption of the active substance. Minoxidil is a substance with cardiovascular effects, hence, pharmacokinetic data on systemic exposure are of certain interest since a high degree of absorption can result in cardiovascular AEs. From an efficacy perspective, pharmacokinetic data are of limited use. Two pharmacokinetic studies have been submitted in this dossier.

Study 001 was a single-center, two-arm, randomized, crossover, open-label clinical study with three different treatments for each arm. Male subjects with androgenetic alopecia of the vertex region of the scalp used each of two 5% foam formulations and 5% minoxidil topical solution (MTS) over the course of the 3 phases, BID for 5 days and once on the 6th day. There was a 7-day washout period between each phase. The two foam formulations were identical in composition with the exception of one component (Foam #1 contained glycerin and Foam #2 propylene glycol). The glycerine-containing foam was chosen for further development and marketing.

Repeated topical application of either investigational foam in male subjects showed approximately 50% lower systemic absorption of minoxidil than that demonstrated by the currently marketed 5% MTS. The concentrations obtained with the foam formulation to be marketed (Foam #1 containing glycerin) were somewhat lower compared with Foam #2 containing propylene glycol.

Study 005 had the primary objective to establish the steady-state percutaneous absorption and relative systemic absorption of minoxidil with enhanced volumes of 5% MTF applied twice daily in male subjects. It was a single-center, three-treatment group, randomized, crossover, open-label study performed in male subjects with androgenetic alopecia of the vertex region of the scalp. The dosing regimens were 1 g, 2 g, or 3 g BID of 5% minoxidil foam. The systemic exposure to minoxidil increased with increasing doses of foam. The applicant claims that the exaggerated use of the foam preparation up to 3 times the recommended dose does not produce blood levels associated with systemic effects and it is therefore expected that the foam could be safely used with a non-metered-dose apparatus even if up to 3 times the recommended dose is inadvertently applied.

Some samples with serum levels exceeding 10.00 ng/ml were observed, although the mean Cmax values were low. It is stated that the level associated with any systemic effects is approximately 20 ng/ml.

No specific data on the distribution or elimination of minoxidil have been presented in the dossier. Minoxidil is an active substance already approved in other products and its
pharmacokinetics has previously been characterised. Furthermore, Regaine cutaneous foam is a locally acting product and the systemic absorption is low. Some information is given in section 5.2 of the SmPC. No further data is requested.

Regaine cutaneous foam is intended for long-term treatment. There was no comparison of PK parameters on the first and the last day of administration in either study. The treatment duration is short, considering the intended long-term treatment with Regaine cutaneous foam. However, there is no reason to suspect that the pattern of systemic absorption would change dramatically over time and further data are not deemed necessary. Long-term treatment is studied in the phase 3 efficacy and safety study, including the 1-year open-label extension phase.

No pharmacokinetic studies in special populations or interaction studies have been performed. The lack of such studies is acceptable for this product, being a new topical formulation of a previously well-known active substance.

In conclusion, no major issues were identified from a pharmacokinetic point of view and the questions raised regarding the bioanalytical method and interactions have been resolved.

IV.2 Pharmacodynamics
The exact mechanism of action of minoxidil is not understood but considered of minor importance as the clinical experience with products containing minoxidil is extensive.

IV.3 Clinical efficacy
The efficacy and safety of Regaine cutaneous foam is supported by Study MINOB-9140-006, a double-blind, randomized, placebo-controlled trial in males with androgenetic alopecia. A total of 352 male subjects with androgenetic alopecia were enrolled and subjects were randomized at a ratio of 1:1 to receive either 5% MTF twice daily (BID) or placebo foam BID for 16 weeks. The inclusion and exclusion criteria were appropriate for the aim of the study. The clinical study was performed at 14 different centres in the US, which is accepted although the product is proposed to be marketed in EU. The nature of the condition proposed to be marketed, androgenetic alopecia, is similar and also the treatment options in the EU and US.

Subjects were instructed to dispense the topical foam test product onto their fingertips, not exceeding half a capful. The product was then applied directly to the affected area of the scalp where the foam breaks down to a liquid and dries into the scalp. At the present time there are no commercially available applicators capable of metering an exact dose of foam. It is acknowledged that the dosage of a foam product, like other topical products as gels or creams, can never be as exact as pharmaceutical forms intended for oral administration. The applicant has acknowledged that the product is delivered without a metering device. A PK study with twice and three times the recommended dose was conducted, showing proportionally increasing systemic absorption with increasing doses. The applicant claims that the exaggerated use of the foam preparation up to 3 times the recommended dose does not produce blood levels associated with systemic effects and it is therefore expected that the foam could be safely used with a non-metered-dose apparatus even if up to 3 times the recommended dose is inadvertently applied. Some samples with serum levels exceeding 10.00 ng/ml were observed, although the mean \( C_{max} \) values were low. It is stated that the level associated with any systemic effects is approximately 20 ng/ml.

In the phase 3 study, the calculated daily use of minoxidil 5% foam was 2.0 grams for the overall patient population while the mean actual amount used was 2.2 grams. This difference between calculated and mean actual amount foam used is assessed as minor but could be
different when the product has been launched and is sold without prescription. Therefore, the dosage should be as exact as possible considering that the area to be treated might be different in surface area, and thus the plausibility of either local or systemic adverse events, even if available PK data do not suggest a major concern in terms of plasma levels. The advice given in the SmPC section 4.2 “A dose of 1 g (equivalent to the volume of half a capful) Regaine 50 mg/g, cutaneous foam should be applied to the total affected areas of the scalp twice daily” was not considered to be exact enough and the applicant was asked to suggest another wording.

In the response, the Applicant argues that the cap is a readily available object for direct comparison of the dose to be applied. More descriptive terms such as “the size of a golf ball” or “the size of an egg” were considered and rejected as too variable or open to interpretation. Furthermore, the Applicant argues that the clinical studies have demonstrated that the patient use the product as recommended, an opinion which is endorsed since the dose advice results in use of the product within 110% of the recommended dose. Moreover, the readability test has demonstrated that the consumer understands the posology of the product, which is assessed as important arguments for keeping the posology as previously stated. There is no immediate concerns if the product may be slightly overdosed, which may be the case if larger areas are to be treated, or the patient eager to achieve an effect of the medicinal product. The issue on posology of the foam formulation is therefore considered resolved without any changes to the SmPC.

The primary objective of this study was to evaluate efficacy and the aim was to demonstrate superiority for the minoxidil foam formulation versus its vehicle. The primary efficacy endpoints were:

- Mean change in non-vellus hair count in the target region between Baseline and Week 16, as determined by validated computer-assisted dot-mapping technique.
- Subject rating of treatment benefit via use of global photographs, assessed as an overall change from baseline, collected on a subject questionnaire.

The secondary efficacy endpoints were:

- Expert panel review of hair re-growth when comparing global photographs obtained at Baseline with photographs obtained at Week 16.
- Percent change from baseline in non-vellus hair counts within a pre-specified area of clipped hair.

Other secondary objectives were to evaluate the safety of a topical 5% MTF formulation in males when used daily for the treatment of androgenetic alopecia and to obtain safety data on 5% minoxidil topical foam when used BID for up to 1 year (results relating to this objective were reported separately).

The primary and secondary objectives are assessed as adequate for evaluating the efficacy and safety of the minoxidil foam formulation. The primary analysis population was the intent-to-treat (ITT) population, which included all randomized subjects. All efficacy and safety analyses were based on the ITT population. A PP population was to be used only for the analyses of the primary efficacy variables which included all randomized subjects who completed 16 weeks of treatment with no major protocol violation and for whom change in hair count and subject evaluation of treatment benefit data were available at week 16.

A total of 352 subjects were enrolled. Thirty seven subjects discontinued from the study, 21 (12.2%) and 16 (8.9%) in the placebo and the minoxidil group respectively; early termination
data was obtained from 24 of these subjects (14 in the placebo and 10 in the 5% minoxidil group respectively). The two treatment groups seem generally well balanced with respect to age and patterns of hair loss.

In the primary analyses of change from Baseline Hair Count (ITT Population), the difference in adjusted means between minoxidil and placebo were statistically significant (P<0.0001 at all 3 visits, i.e. weeks 8, 12 and 16). These results were confirmed in the PP population at Week 16 (difference in the adjusted means 16.9; P<0.0001; 95% CI 12.1 to 21.6).

At week 16 (or the early termination visit), subjects rating of treatment benefit based on photographs was made and also in this analysis, a statistically significant difference vs. vehicle was obtained both in the ITT and PP populations.

Superior differences in favour of minoxidil were shown for both the primary variables. The differences were highly statistically significant. Regarding mean change in hair count, the difference seen at week 16/Early withdrawal was slightly smaller than was expected at the planning of the study but is still considered clinically relevant. The results were confirmed in analyses of the secondary efficacy variables.

One single pivotal clinical trial has been performed in support of the present application. With one pivotal study it is usually required that the results are robust and compelling. The results in the present multi-centre study are highly significant and the results show consistency between primary and secondary analyses as well as for analyses of ITT and PP populations. Furthermore, this is a new pharmaceutical formulation in the same strength as an already approved product. Hence, the efficacy data are considered sufficient for approval of the product.

**IV.4 Clinical safety**

Minoxidil 5% solutions applied topically has been marketed and in clinical use as OTC product for many years. The clinical safety profile of the substance is considered well-known.

In support of the present application, safety of the minoxidil 5% foam formulation was assessed in the dermal irritation/sensitization study 004 and in the clinical efficacy and safety trial 006. In the dermal irritation/sensitization study, three different 5% MTF formulations were included and also the placebo, unscented foam vehicle. There was no comparison with the marketed 5% MTS (Rogaine solution) formulation, although such a comparison would have been of interest. The unscented 5% MTF formulation is the formulation to be marketed and it showed mostly no or mild irritant reactions and no indications of a sensitization potential.

The number of patients exposed to Regaine cutaneous foam in the pivotal efficacy and safety study 006 is 180 and of these 75 patients were exposed for one year. Considering that Regaine cutaneous foam 50 mg/g is a new formulation with identical strength of a well-known active substance, the extent of exposure is considered sufficient.

The incidence of drug-related AEs was overall low. Twelve placebo subjects (7.0%) and 12 subjects in the 5% minoxidil foam group (6.7%) experienced drug-related AEs. Only headache, pruritus, rash and pain occurred in more than 1% of subjects in either treatment group. The drug-related AEs occurring in more than 1% of subjects in either treatment group were by the Applicant assessed as minor conditions related to pain or to application of study drug to the skin, a view which is shared by the assessor.
Three subjects in the placebo group (accidental injury, grand mal convulsion, acute kidney failure) and two subjects in the 5% minoxidil foam group (cholelithiasis, pancreatitis) had serious adverse events (SAEs) during the study. All SAEs resolved except for the acute kidney failure. All the SAEs were considered unlikely to be related to study treatment by the Applicant, a view which is shared by the assessor.

Five subjects, two placebo subjects and three minoxidil subjects withdrew from the study because of AEs. The AEs in the minoxidil group were headache, alopecia and rash which are included in the proposed SPC section 4.8 adverse events.

No changes were noted in laboratory findings as can be expected considering the low systemic absorption of minoxidil.

A group of 75 subjects in the minoxidil group was included the 1-year open-label extension phase. These subjects were monitored for local adverse events and the data suggest similar incidence of local skin adverse reactions as observed in the 16-week study.

The adverse events noted with the foam formulation seem rather similar in extent and magnitude as with minoxidil 5% solution. However, no direct comparison has been made, either in phase 3 study or in the dermal safety study. Hence, no claims can be made with respect to a potentially less irritation potential for the foam vs. the solution formulation.

IV.5 Discussion on the clinical aspects
The target population for Regaine cutaneous foam 50 mg/g is the same as for Regaine cutaneous solution 50 mg/ml, i.e. males with androgenetic alopecia. It is not expected that the introduction of a new formulation would result in new concerns in comparison with Regaine cutaneous solution. However, no direct comparison has been made and no claims can be made with respect to a potentially less irritation potential for the foam vs. the solution formulation. The presented data demonstrate a benign safety profile for the new topical minoxidil foam formulation.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

From a clinical point of view, pharmacokinetic studies support a low systemic absorption of minoxidil from the foam formulation. A study investigating exaggerated use of the foam preparation up to 3 times the recommended dose did not produce blood levels associated with systemic effects.

Efficacy of the new foam formulation is supported by the clinical phase 3 double-blind, randomized, placebo-controlled trial comparing 5% Minoxidil Foam with its vehicle in the treatment of androgenetic alopecia in males. Superior efficacy is shown vs. the vehicle in this study. No active comparator, e.g. minoxidil topical solution, was included. However, since this is a complete stand-alone application, such a comparison is not deemed necessary since efficacy is clearly demonstrated vs. the foam vehicle. In a non-clinical study in stump tail macaques, both 5% minoxidil foam and 5% minoxidil solution were included and the results showed similar effects on mean monthly hair growth with both products.

From a safety perspective, the adverse events noted with the foam formulation seem rather similar in extent and magnitude as with minoxidil 5% solution. However, no direct comparison has been made, either in phase 3 study or in the dermal safety study. Hence, no claims can be made with respect to a potentially less irritation potential for the foam vs. the solution formulation.
formulation. The target population for Regaine cutaneous foam 50 mg/g is the same as for Regaine cutaneous solution 50 mg/ml, i.e. males with androgenetic alopecia. It is not expected that the introduction of a new formulation would result in new concerns in comparison with Regaine cutaneous solution. Adequate information is included in the SmPC, e.g. related to possible cardiovascular effects. The presented data demonstrate a benign safety profile for the new topical minoxidil foam formulation.

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 English.
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.

The risk/benefit ratio is considered positive and Regaine 50 mg/g cutaneous foam is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Regaine cutaneous foam, 50 mg/g was successfully finalised 2012-07-04.
Public Assessment Report – Update

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