Public Assessment Report
Scientific discussion

Roquinna 50 mg/g, Kutant skum
minoxidil

SE/H/1503/01/DC

This module reflects the scientific discussion for the approval of Roquinna 50 mg/g. The procedure was finalised on 2015-12-14. 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 Roquinna, 50 mg/g cutaneous foam. The active substance is minoxidil which has been developed for topical treatment of androgenetic alopecia (Female Hair Loss Pattern) in women, in adult patients 18 years of age and older.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8.3 of Directive 2001/83/EC.

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 and 5% foam. The primary pharmacodynamic properties of
minoxidil, based on literature review, are well documented. However, the mechanism of action has not been clearly defined. In the review of literature a number of studies confirm the known effect of minoxidil to stimulate hair growth. Also, a proof of concept study in stump tail macaques demonstrates increased hair growth after topical administration of minoxidil foam and solution formulations compared to a gel formulation. No control group was used in the study. 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.

The major secondary pharmacological effect of minoxidil is its long-acting hypotensive activity, which is due to rapid relaxation of vascular smooth muscle by its sulphated metabolite. Other secondary pharmacodynamic effects have also been investigated in recent years. These effects are due to the $K_{\text{ATP}}$ channel-activity of minoxidil. They are not considered relevant for the current application, which concerns topical administration with negligible systemic exposure.

Minoxidil caused cardiovascular toxicity in dogs. These effects have been addressed in several studies, and most likely result from an exaggerated pharmacodynamic activity of minoxidil. Available human data indicate that no similar effects occur in humans treated topically with minoxidil.

### III.2 Pharmacokinetics

The absorption of minoxidil following oral administration in various animal species, including human, has been found to be rapid and complete. Percutaneous minoxidil absorption following topical administration showed great variability among species. The mean levels of absorption from dermal application for each species were as follows: mouse 48%; rat 32%; dog 39%; and monkey 5%. In contrast, the average minoxidil dermal absorption in humans was 1.7%.

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 mousses 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 considered 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 $1 \times 10^{-10}$ cm/sec indicated low absorption through the whole skin. Consequently, there is no significant systemic delivery of minoxidil expected.

Following absorption, the drug was rapidly and extensively distributed throughout the body in a similar way following oral, subcutaneous and topical administration. Minoxidil was extensively metabolized following administration to animals and human. All of the examined species excreted substantially the same metabolites but in relatively different amounts. The principal excretory route of minoxidil and drug-related materials in all species was in urine, with minor amounts excreted into the feces.
III.3 Toxicology

Minoxidil is widely used and the toxicological properties of minoxidil are well known.

The foam formulation contains the same amount of active substance as the 5% topical solution and the systemic exposure after topical application is expected to be similar. The local tolerance and phototoxicity of the foam formulation has 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 formulation are not a cause for concern.

The genotoxicity of minoxidil was tested in various assays, both in vivo and in vitro. No evidence of genotoxic properties was found.

Minoxidil was tested for carcinogenic effects in several studies in mice and rats by dermal and oral administration. Increased incidences for some tumors were observed with minoxidil treatment in the dermal carcinogenicity studies, which were suggested to be caused by a hormonal imbalance. Due to differences between rodents and humans with regard to prolactin regulation, these tumours are not considered relevant for humans.

Minoxidil exposure at dose-levels between 3 and 80 mg/kg/day exhibited some adverse effects on fertility. In one study, the NOEL for effects on fertility was determined at 9 mg/kg/day subcutaneously. According to the Applicant, animal reproductive toxicity studies have shown a risk to the fetus at exposure levels that are very high in comparison to levels obtained in humans (doses ranging from 569- to 1,139-fold anticipated human exposures), and give some indication of maternal toxicity (i.e. doses ≥ 80 mg/kg/day).

In view of the new indication in women, it is of importance to more closely assess the reproduction and developmental toxicity studies. The Applicant was asked to submit the pivotal study reports, together with a discussion on main findings and their potential clinical relevance as a point for clarification. The Applicant has submitted pivotal study NDA 20-834 and a thorough discussion of the main findings. However, Study NDA 20-834 is a fertility study and as a consequence does not cover the discussion about embryotoxicity and perinatal toxicity put forth by the applicant and the proposed changes in the SmPC (see non-clinical AR).

An ERA has been submitted by the applicant. Several points for clarification were raised regarding the studies in the ERA. While some of the points have been adequately addressed by the applicant, there are remaining issues that will be handled as a FUM (see list of commitments).

III.4 Ecotoxicity/environmental risk assessment

An ERA has been submitted by the applicant. Several points for clarification were raised regarding the studies in the ERA. While some of the points have been adequately addressed by the applicant, there are remaining issues that will be handled as a FUM (see list of commitments).

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The pharmacokinetic profile of minoxidil after topical administration to the scalp has been previously described. The previously available pharmacokinetic data have shown that the systemic absorption of topically applied minoxidil is low, with a bioavailability from the
solution (MTS) of 1-2%. In men, the systemic absorption of minoxidil from a 5% Foam formulation (MTF) was about half that of the absorption from a 5% MTS. Distribution volume of minoxidil after intravenous administration is estimated to 70 L. Glucuronidation is the primary elimination pathway. About 60% of bioavailable minoxidil is metabolised to minoxidil glucuronide. Minoxidil and its metabolites are excreted almost exclusively in the urine. The proposed and the previously approved SmPC:s contain no specific recommendations for patients with renal or hepatic impairment. No risks for systemic pharmacokinetic interactions have been identified. The SmPC mentions that percutaneous absorption of minoxidil may be enhanced by tretinoin and dithranol.

Minoxodil is intended to act locally, and pharmacokinetic data on systemic absorption is primarily important from a safety perspective. There is no new pharmacokinetic data specifically for this application. However, one pharmacokinetic study (from year 2003) was submitted in support of the MTF, comparing bioavailability of the MTS and the MTF in men and women, respectively. The mean steady state Cmax and AUC\textsubscript{0-24} after once daily application of the 5% MTF to women was 1.25 ng/ml and 12.0 ng/ml*hr, respectively. The maximum individual values were 6.65 ng/ml and 36.1 ng/ml*hr, respectively. A direct comparison between men and women of the bioavailability of minoxidil after topical administration to the scalp is not possible from this study. However, the available data does not give raise to any concern regarding the systemic absorption of minoxidil to women from the currently applied formulation, as compared with what has been seen for previously approved formulations.

IV.2 Pharmacodynamics
No new data on primary and secondary pharmacodynamics are included in the present application.

The mechanism by which minoxidil stimulates hair growth is not fully understood, but some effects of minoxidil include increasing the diameter of the hair shaft, stimulation of anagen growth, and prolongation of the anagen growth phase, and stimulation of transition of hair follicles from the resting phase (telogen) to the growth phase (anagen).

IV.3 Clinical efficacy
Rogaine is approved for topical treatment of androgenetic alopecia in men and women since several decades. The clinical experience of topical minoxidil is assessed as extensive. A foam formulation with 5% minoxidil indicated in men, was approved in 2012 with Sweden as RMS (SE/H/1173/01/DC). The present application concerns foam with identical strength, but with a slightly different composition, in order to decrease application site adverse events and hence increase compliance to treatment.

Design and conduct of clinical studies

The efficacy of Rogaine for Women is supported by two phase 3 studies, (MINAL 03004 and MINAL 03005), performed in women with female pattern hair loss (FPHL). The studies are multicentre, parallel design clinical trials performed in Canada, the US and in different EU countries.

The phase 3 studies enrolled female patients 18 years of age and above presenting with FPHL. There is no European guideline available for products indicated for treatment of FPHL. Hence, efficacy end-points to be used are not clearly established.
Study MINAL 03004 is an active controlled study with MTF 5% OD tested against MTS 2% BD, while study MINAL 03005 is a vehicle control study with MTF 5% OD tested against the vehicle foam. The primary efficacy end-point in study MINAL 03004 was change from Baseline in the target area hair count (TAHC) as measured by macrophotography at Week 24. In study MINAL 03005, the primary efficacy end-points were change from baseline in TAHC and subject assessment of scalp coverage as measured by the change from Baseline at Week 24 on a 7-point scale.

In study MINAL 03004, the secondary efficacy endpoint was the change from Baseline in TAHC as measured by macrophotography at Week 12. Further endpoints were expert panel review of hair re-growth based on global photographs as measured as the change from Baseline at Week 24 and Week 52 on a 7-point scale, change from baseline in TAHC as measured by macrophotography at Week 40 and Week 52 and change from baseline in total unit area density (TUAD) as measured by macrophotography at Week 12, Week 24, Week 40, and Week 52. Secondary and further efficacy end-points in study MINAL 03005 was the change from Baseline in TAHC at Week 12. Other endpoints for exploratory purposes included the following expert panel review (EPR) of hair re-growth week 24 and change from baseline in TUAD at Week 12 and Week 24.

Overall, the end-points used in the phase 3 studies are considered relevant.

Approximately 300 female subjects were in study MINAL 03004 randomized in a 1:1 ratio to use either 5% MTF OD or 2% MTS BID for 52 weeks. In MINAL 03005, approximately 400 female subjects were randomly randomized in a 1:1 ratio to use either 5% MTF OD or foam vehicle OD for 24 weeks. Block randomization was employed for assigning subjects to treatment groups in both studies. This study was blinded, which was not the case in MINAL 03004, where blinding was not possible due to different dosages and formulations.

The statistical methods used in both the phase 3 studies are standard and straight forward.
Efficacy data and additional analyses

Demographic data were overall similar in the two clinical studies; the mean age was $\geq 50$ in both studies with subjects included from 18 to 87 years of age. The majority of women were postmenopausal and white. In study MINAL 03005, Black or African American women constituted approximately one fourth of the women. The subjects included in the studies had duration of hair loss for 9-10 years, the pattern of hair loss according to Savin female hair loss scale was for the majority of subjects D3 and D4.

Study MINAL 03004

Primary end-point

The results showed that after 24 weeks of treatment, both treatment groups, minoxidil 5% foam OD and minoxidil 2% solution BD, re-grew 24 hairs/cm².

Table. Change from Baseline in TAHC (hairs/cm²) at Week 24 (ITT Population with Original Data)

<table>
<thead>
<tr>
<th>Visit</th>
<th>2% MTS (N=161)</th>
<th></th>
<th>5% MTF (N=161)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hair Counts</td>
<td>Change</td>
<td>Percent Change</td>
<td>Hair Counts</td>
</tr>
<tr>
<td>Baseline</td>
<td>160</td>
<td></td>
<td></td>
<td>156</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>167.3 (55.0)</td>
<td>169.7 (58.6)</td>
<td>Median</td>
</tr>
<tr>
<td></td>
<td>Min-Max</td>
<td>28 - 346</td>
<td>54 - 338</td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>139</td>
<td>138</td>
<td>138</td>
<td>134</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>192.8 (57.0)</td>
<td>23.8 (24.7)</td>
<td>194.4 (64.7)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>189.0</td>
<td>18.5</td>
<td>188.5</td>
</tr>
<tr>
<td></td>
<td>Min-Max</td>
<td>39 - 342</td>
<td>-31 - 125</td>
<td>71 - 404</td>
</tr>
</tbody>
</table>

| Adjusted Mean (SE) | 24.2 (2.1) | 23.9 (2.1) |
| Difference (5% MTF - 2% MTS) | -0.3 | P-value$^a$ | 0.9170 |
| 95% confidence interval | -6.0, 5.4 |

SD = standard deviation, SE = standard error
$^a$ P-value is from ANCOVA model with treatment and center as factors and Baseline hair count as a covariate.

Source: Statistical Tables 14.2.1 and 14.2.2

The magnitude of efficacy observed in this study is overall very similar to the result observed with minoxidil topical foam in men. The sample size calculation seems to have been based on an assumed superiority for the 5% MTF OD over 2% MTS BID of 3 hairs/cm². With an equal efficacy, the power for showing non-inferiority would have been considerably lower. The non-inferiority margin was set to -5, and the lower limit of the confidence interval was -6 for the primary analysis. Hence, formally the study failed on its primary objective to show non-inferiority. It is assessed however that -5 is needlessly strict, and a non-inferiority margin of -6 for the primary analysis is considered acceptable.

The subject’s age and menopausal status had no notable impact on the efficacy results.

The two treatment groups had similar efficacy for all sensitivity analyses.
Secondary end-points
The secondary efficacy endpoint was the change from Baseline in target area hair count at Week 12. The adjusted means of re-grown hairs were 24 hairs/cm² and 22 hairs/cm² for the 5% MTF and the 2% MTS groups, respectively. The treatment difference was 2 hairs/cm².

Table. Change from Baseline in TAHC (hairs/cm²) at Week 12 (ITT Population with Original Data)

<table>
<thead>
<tr>
<th>Visit</th>
<th>2% MTS (N=161)</th>
<th>5% MTF (N=161)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hair Counts</td>
<td>Change</td>
</tr>
<tr>
<td>Baseline</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD) 167.3 (55.0)</td>
<td>169.7 (58.6)</td>
</tr>
<tr>
<td></td>
<td>Median 163.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min-Max 28 - 346</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>141</td>
<td>22.5 (22.8)</td>
</tr>
<tr>
<td></td>
<td>Mean (SD) 190.7 (56.9)</td>
<td>184.0</td>
</tr>
<tr>
<td></td>
<td>Median 184.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min-Max 35 - 354</td>
<td>-118 - 84</td>
</tr>
<tr>
<td>Adjusted Mean (SE)</td>
<td>22.2 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Difference (5% MTF − 2% MTS)</td>
<td>2.4</td>
<td>p-valuea</td>
</tr>
</tbody>
</table>

SD = standard deviation; SE = standard error
a P-value is from ANCOVA model with treatment and center as factors and Baseline hair count as a covariate.

Source: Statistical Tables 14.2.1 and 14.2.2

In the ancillary analysis, the total area hair count at Week 40 and Week 52 was between 18-20 hairs/cm² for both treatment groups. The total unit area density was measured at Week 12, Week 24, Week 40, and Week 52 which demonstrated that both 5% MTF and 2% MTS increased the total non-vellus hair diameters at all measuring time points. When analyzed by an expert panel review, improved scalp coverage was observed in both the 5% MTF and 2% MTS groups.

Overall, the secondary endpoints and the ancillary analysis support the conclusions from the primary endpoint.

Study MINAL 03005
The vehicle control study MINAL 03005 enrolled 400 patients with female pattern hair loss.

Primary end-point
The aim of the study, to show superiority of the MTF formulation over foam vehicle was fulfilled regarding the co-primary endpoint Change from baseline in target area hair count at Week 24. The MTF group re-grew 13.4 hairs/cm² and the foam vehicle group re-grew 4.3 hairs/cm². The treatment difference was 9.1 hairs/cm², which is statistically significant. The level of efficacy is somewhat lower than could be expected but is accepted as clinically relevant.
The subject’s age and menopausal status had no notable impact on the efficacy results.

Hair counts were measured based on macrophotographs of the target area. Of all randomized subjects, 314 subjects (77.7%) had all hair count data at all 3 visits and 90 subjects (22.3%) had at least 1 missing hair count data. All sensitivity analyses show robust benefit on hair regrowth compared to foam vehicle, indicating that missing data had little or no effect on the efficacy conclusion based on the hair count measurement.

The secondary co-primary endpoint Subject assessment of scalp coverage as measured by the change from Baseline at Week 24 on a 7-point scale demonstrated an increased level of scalp coverage compared to the foam vehicle group. No measurement of subject rating of treatment benefit was made which had been of interest.

The results of the sensitivity analyses showed robust benefit in improving the scalp coverage compared to foam vehicle, indicating that missing data had little or no effect on the efficacy conclusion based on the subject assessment of scalp coverage.

Seventy-five (75) subjects identified “no difference” between the 2 photos for the subject assessment score (the score was set to zero) and 7 subjects were not able to differentiate which photo was better (the score were set to missing). It is not understood why ”no difference” and ”not able to differentiate” is handled in such different ways. It seems reasonable that also the 7 subjects not able to differentiate which photo was better should have had the score set to zero. However, the number of affected subjects is small and the impact of the efficacy result is therefore assessed as minor and not a cause for concern.

Secondary end-points
The secondary efficacy endpoint was the change from Baseline in target area hair count at Week 12. The adjusted means of re-grown hairs were 5 hairs/cm² and 16 hairs/cm² for the foam vehicle and the 5% MTF groups, respectively. The treatment difference was 11 hairs/cm².

Table. Change from Baseline in TAHC at Week 12 (ITT Population with Original Data)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Foam Vehicle (N=197)</th>
<th>5% MTF (N=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hair Counts</td>
<td>Change</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>197</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>152.7 (59.7)</td>
<td>158.6 (61.6)</td>
</tr>
<tr>
<td>Median</td>
<td>150.0</td>
<td></td>
</tr>
<tr>
<td>Min-Max</td>
<td>21 - 365</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>168</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>163.3 (63.2)</td>
<td>178.1 (66.4)</td>
</tr>
<tr>
<td>Median</td>
<td>159.5</td>
<td></td>
</tr>
<tr>
<td>Min-Max</td>
<td>22 - 375</td>
<td></td>
</tr>
<tr>
<td>Adjusted Mean (SE)</td>
<td>5.3 (1.4)</td>
<td>16.2 (1.4)</td>
</tr>
<tr>
<td>Difference (5% MTF – foam vehicle)</td>
<td>10.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>7.0, 14.7</td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation; SE = standard error

a P-value is from ANCOVA model with treatment and center as factors and Baseline hair count as a covariate.

Source. Statistical Tables 14.2.1 and 14.2.2

In the ancillary analysis, the total unit area density was measured at Week 12 and Week 24 which demonstrated that 5% MTF increased the total non-vellus hair diameters at all measuring time points more than foam vehicle. When analyzed by an expert panel review, improved scalp coverage was observed in the 5% MTF group.

Overall, the secondary endpoints and the ancillary analysis support the conclusions from the primary endpoints.

IV.4 Clinical safety

Short term risks

Overall, 394 patients were exposed to Rogaine 5% MTF OD, the formulation proposed for marketing in the clinical development program. 161 patients were exposed to 2% MTC BID and 201 patients were exposed to foam vehicle. In the Phase 1 dermal sensitization study, 519 healthy volunteers were exposed to MTF 5% and 173 to foam vehicle. In the Phase 2 pharmacology study, 60 patients were exposed to 5% MTF and 31 were exposed to 2% MTS. The mean treatment duration in the pivotal studies was 325 days in MINAL03004 and 157 days in MINAL03005. The safety database for the proposed product is considered sufficient, also when considering the extensive clinical experience of 5% minoxidil formulations in men.

The safety documentation submitted in support of this application is overall considered adequate.
In MINALO3004, treatment-emergent AEs in the 5% MTF group with an incidence $\geq 2.0\%$ greater than in the 2% MTS BID group included weight increased (12.4% versus 8.7%), upper respiratory tract infection (9.9% versus 4.3%), urinary tract infection (5.0% versus 1.9%), bronchitis (5.0% versus 1.2%), and oropharyngeal pain (2.5% versus 0%). Treatment-emergent AEs in the 2% MTS BID group with an incidence $\geq 2.0\%$ greater than in the 5% MTF OD group included abdominal pain upper (2.5% versus 0%) and headache (9.9% versus 5.6%).

In MINALO3005, the only treatment-emergent AE in the 5% MTF group with an incidence $\geq 2.0\%$ greater than in the foam vehicle group was gastroenteritis (3.0% versus <1%), and the only treatment-emergent AE in the foam vehicle group with an incidence $\geq 2.0\%$ greater than in the 5% MTF OD group was nasopharyngitis (6.5% versus 4.4%).

No new or unexpected adverse events were seen in the two pivotal clinical studies compared to the labelled AE profile of 5% MTF and 5% MTS in males.

Drug related AEs were observed to a similar frequency in the 5% MTF group and the 2% MTS group. In study MINAL03004, the most commonly ($\geq 1.0\%$ of subjects) experienced drug-related treatment emergent AEs in the 5% MTF OD group were pruritus (2.5%), alopecia (2.5%), and hypertrichosis (1.9%). In MINALO3005, the percentage of subjects with at least 1 drug-related treatment-emergent AE was 8.9% in the 5% MTF group and 4.5% in the foam vehicle group. The most commonly ($\geq 1.0\%$ of subjects) experienced drug-related treatment emergent AEs in the 5% MTF and foam vehicle groups were pruritus (1.5% and 1.5%, respectively) and weight increased (1.5% and 2.0%, respectively).

One aim of the present drug development was to gain a product with less scalp irritation and low incidence of hypertrichosis. A low incidence of scalp irritation and hypertrichosis was noted in both pivotal clinical trials, with no notable differences between 5% MTF and 2% MTS (MINALO3004) or between 5% MTF OD and foam vehicle (MINALO3005). It can therefore be concluded that one of the aims with the drug development has been fulfilled.

When treatment-emergent AEs that were reported in $\geq 1.0\%$ of the subjects in descending order of frequency were pooled for the four studies included in the submission, pruritus was noted in 14% subjects, weight increased and headache in 9% and 7%, respectively.

A variety of AE’s caused subjects to withdraw from the studies. Of these pruritus and headache are the most common reasons for withdrawal. Overall, the percentage of subjects discontinuing due to treatment-emergent AEs was low across the studies.

The dermal local tolerance studies that has been evaluated in 2011 during the marketing authorisation procedure for minoxidil 5% foam for men (SE/H/1173/01/DC), showed no or mild irritant reactions under normal use conditions. However, the proposed formulation proposed for marketing has not been tested. Since clinical safety data are available, the absence of dermal local tolerance data can be accepted.

The Applicant has not conducted any clinical photosafety testing which is considered acceptable since the clinical experience with topical minoxidil is extensive and no adverse reactions due to sun exposure are labelled.

In conclusion on short term risks, no other than adverse events already known from treatment of men with minoxidil 5% are to be anticipated at the recommended use of Rogaine 5% MTF OD for women.
Potential long term risks

Minoxidil has a well-known safety profile from extensive clinical use in men in concentrations between 2 and 5%, and in women, where minoxidil is approved in a 2% solution. According to the Applicant, there is off-label use of 5% minoxidil formulations by women who experience FPHL.

No systemic adverse events were reported in any of the performed clinical studies and are not anticipated at the proposed use of the product.

No adverse effects on cardiovascular parameters were observed which are not to be expected considering the low systemic exposure of minoxidil. However, if minoxidil would be applied on very large areas or ingested orally, pharmacodynamic related adverse events from the cardiovascular system would be anticipated. This a well known risk, the proposed SmPC contains relevant warnings in analogy with other approved minoxidil formulations.

The most common local adverse events associated with topical use of minoxidil are pruritus, alopecia and hypertrichosis (see above). The incidence of TEAEs was essentially similar when compared to the 2% minoxidil solution and no marked difference was noted versus vehicle foam. Overall, the local adverse events of the product proposed for marketing are considered benign.

Subpopulations

No specific subgroup analyses were conducted to explore the potential differences of common TEAEs within a subgroup (age and race) compared with the entire study population. Available data do not indicate that subjects ≥65 years of age have an increased risk of adverse events when compared to subjects 18 to 64 years of age. There was no difference in the TEAE profiles based on race, however, based on the very low number of Non-Caucasian participants, conclusions on AEs based on race are difficult to make.

At very high systemic exposure compared to therapeutic level humans, animal studies have shown signs of maternal toxicity and a risk to the fetus. Question has been raised in the Non-clinical AR on data on reproduction toxicity. After assessment of the Applicant response, a SmPC text will be suggested.

In conclusion on potential long term risks, no risks due to systemic uptake of minoxidil are to be anticipated at the proposed clinical use if the product.

IV.5 Risk Management Plans

The MAH has submitted RMP version 6.0, dated 22 October 2015. The summary of safety concerns has been updated in response to questions.

The summary of safety concerns is as follows:
Routine pharmacovigilance and routine risk minimisation measures are considered adequate to handle the risks.

The RMP is approved.

**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.

- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

**V. USER CONSULTATION**

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Rogaine 50 mg/g cutaneous foam, SE/H/1173/01/E01. The bridging report regarding content and layout submitted by the applicant has been found acceptable.

**VI. BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**
Statistically significant efficacy of the minoxidil foam proposed to be marketed for women with female pattern hair loss has been demonstrated both in a comparative study with minoxidil solution and in a vehicle control study. The studies submitted and the results obtained are in line with earlier experience and extensive clinical experience of topical treatment with minoxidil in androgenetic alopecia.

The safety profile for topical use of minoxidil is in general considered benign, and well known from extensive clinical use of topical minoxidil. No new safety concerns were found in the safety data base submitted in support of the present application. No systemic adverse events were reported in any of the performed studies and are not to be expected at the proposed clinical use.

The benefit risk of Rogaine 5% foam for women is considered positive.

VII. APPROVAL

The Decentralised procedure for Roquinna, 50 mg/g, cutaneous foam, was positively finalised on 2015-12-14.
# Public Assessment Report – Update

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<th>Product Information affected</th>
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<th>Date of end of procedure</th>
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