Swiss Summary of the Risk Management Plan for Soolantra (ivermectin cream 10mg/g)

Galderma International

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Summary of the Risk Management Plan (RMP)

This Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP contains information of the medicine's safety profile and explains the measures that are taking in order to further investigate and follow the risks as well as to prevent or minimize them. The RMP summary of Soolantra is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation" approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss marketing authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Soolantra in Switzerland is the "Arzneimittelinformation" (see www.swissmedicinfo.ch) approved and authorized by Swismedic. Galderma International is fully responsible for the accuracy and correctness of the content of the here published summary RMP of Soolantra.

Overview of disease epidemiology

Soolantra cream is indicated for the cutaneous treatment of inflammatory lesions of rosacea (papulopustular rosacea) in adult patients.

Rosacea is a chronic dermatological disease of unknown aetiology, characterised by flushing, central facial erythema, recurrent papules and pustules most notably in the central convex areas of the face, superficial telangiectasia (dilations of previously existing small blood vessels) and by remission and exacerbations of symptoms.

Genetic and environmental factors have been identified which contribute to rosacea's pathology. These aetiologic factors include enhanced vasomotor liability resulting in erythema, immune system and sebaceous gland abnormalities (but not sebum production) resulting in lesions, and greater susceptibility to heat and ultraviolet light. There also appears to be a hereditary component to the disease. The disease has been categorised by the US National Rosacea Society (NRS) into four main subtypes based on the combination of signs and symptoms present in predominantly adult patients: erythematous-teleangiectatic rosacea, papulopustular rosacea, phymatous rosacea, and ocular rosacea.

Few data are available on the incidence of rosacea. Rosacea is one of the most common chronic dermatological diseases; the prevalence statistics published in Europe and the United States are highly variable, ranging from less than 1% to more than 20% of the adult population.

The majority of patients affected by rosacea are aged between 30 to 60 years of age and prevalence does increase with age. However, the disorder may uncommonly be seen in young individuals before the age of 30 years. Rosacea classically predominates in females.
Summary of treatment benefits

The beneficial effect of Soolantra 1% cream has been observed in two identical clinical studies conducted in the USA and Canada. In total, 1371 subjects were allocated randomly to either Soolantra 1% Cream or a dummy medication which contained only the cream constituents (vehicle cream) without the active ingredient (ivermectin). In order to assess the efficacy of Soolantra 1% cream, treatments were applied once daily for 12 weeks. Beneficial effects were measured using an Investigator Global Assessment scale, which ranged from a score 0 (Clear - No inflammatory lesions present, no erythema) to a score 4 (Severe- Numerous small and/or large papules/pustules, severe erythema,). Assessment was also performed by counting the number of inflammatory lesions (papules and pustules) observed on the face.

Per protocol at the start of the study, all patients had a score of 3 or 4. After 12 weeks of treatment, 173 of 451 subjects (38%) treated with Soolantra 1% cream achieved a success in the first study compared to 27 of 232 (12%) treated with the vehicle cream. The mean number of inflammatory lesions reduced from 31 to 11 with Soolantra 1% cream and from 30 to 18 with the vehicle cream. Results from the second study were similar with 184 of 459 subjects (40%) achieving a success with Soolantra 1% cream compared to 43 of 229 (19%) with the vehicle cream; the number of inflammatory lesions reducing from 33 to 11 and 32 to 19 for Soolantra 1% cream and vehicle cream respectively.

Treatment with Soolantra 1% cream was continued for a further 40 weeks in both studies and showed that the number of successfully treated subjects continued to increase. After a total of 52 weeks treatment, success rates in the groups of subjects treated with Soolantra 1% cream were 71% and 76% in the two studies.

The effect of Soolantra 1% cream was also assessed compared to a marketed cutaneous treatment of rosacea (metronidazole 0.75% cream) in an additional clinical study. Nine hundred and sixty two subjects (962) were treated for 16 weeks with Soolantra 1% cream or metronidazole 0.75% cream. In the group of subjects treated with Soolantra 1% cream, a higher decrease in the mean percent change in inflammatory lesions from baseline to week 16 was observed compared to the subjects in the metronidazole 0.75% cream group (83% versus 74% respectively).

Unknowns relative to treatment benefits

In the main and supporting studies, most subjects were of white/caucasian origin with moderate to severe rosacea. There is no evidence to suggest that the results would have been any different in other ethnicities, although rosacea mainly occurs in white subjects. It is not known how effective the treatment would be in subjects with complicated forms of rosacea. Although not studied, treatment beneficial effects would be expected in subjects with mild disease. Experience and safety in subjects exposed for very long periods (more than one year) is limited.
### Important identified risks

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<tr>
<th>Risk</th>
<th>What is known</th>
<th>Preventability</th>
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<tbody>
<tr>
<td>Hypersensitivity- Contact dermatitis (allergic or irritant)</td>
<td>Clinical trials: 3 subjects out of more than 2000 included in clinical studies reported adverse reactions suggestive of a localised skin allergy, although it was not completely known if these were definitely due to Soolantra Cream. Animal studies suggest that the active ingredient, ivermectin, has a low likelihood of causing allergic reactions. Post-marketing experience: 47 cases reported diagnosis terms of dermatitis allergic, dermatitis contact, hypersensitivity, eczema, application site eczema, urticaria. 1 case with positive patch test to parabens. 66 additional cases with symptoms which can be suggestive of allergy including 15 cases associating several symptoms.</td>
<td>The information about this risk is included in sections 4.3, 4.4, and 4.8 of the product labelling. Skin sensitization is idiosyncratic and unpredictable and therefore not preventable. Identification and withdrawal of the &quot;trigger&quot; medication is required to prevent worsening of the reaction and for any progression to system hypersensitivity.</td>
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### Important potential risks

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<tr>
<th>Risk</th>
<th>What is known (including reason why it is considered a potential risk)</th>
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<tr>
<td>Systemic Allergic reactions</td>
<td>No case observed in clinical program. One serious case and 10 non-serious cases in post marketing. Out of 237 cases from post-marketing experience and 13 cases from clinical trials regarding hypersensitivity, only one case was reported with a clear diagnosis of anaphylactic reaction, serious and medically confirmed, but no patch test performed to confirm the allergy to the ingredients of the product. It is maintain as an important potential risk to be closely monitored. Hypersensitivity is already described in the labeling of the product in the section &quot;Contraindications&quot;.</td>
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<td>Accidental oral ingestion</td>
<td>All medications intended for external use have the potential to be accidentally ingested, particularly by children. For Soolantra, the product is protected by a Child Proof Lock to minimise this risk. Ivermectin has been used as an oral medication. Whilst it is unlikely that oral ingestion of the cream would result in harm, there is limited information available at the present time. Up to now, in clinical trials one patient accidentally ingested the product but no adverse events were reported, except for bad taste on the mouth. In post-marketing, two cases were reported without adverse events associated to the ingestion of the product. Accidental oral ingestion is maintained as an important potential risk to be closely monitored, even if up to know, no safety concern has been identified after the analysis of safety data.</td>
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<td>Potential interaction with CYP3A4 and p-glycoprotein</td>
<td>No information about these interactions is available for topical route. This important potential risk has been requested by the local Regulatory Authorities in Switzerland.</td>
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