Swiss Summary of the Risk Management Plan (RMP)

for Soolantra (Ivermectin)

Based on the EU RMP Soolantra ver2.0 dated 07-May-2021, with Data Lock Point 22-Jan-2021

Active substance(s) (INN or common name):	Ivermectin
Product(s) concerned (brand name(s)):	SOOLANTRA®
Name of Marketing Authorisation Holder or Applicant:	GALDERMA SA Zählerweg 10, 6300 Zug, Switzerland
Swiss Summary RMP Version	2.0
Date of document:	17-Jun-2021

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The Swiss RMP summary of Soolantra® (ivermectin) 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 / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Soolantra® (ivermectin) in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Galderma SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of Soolantra®.

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Part VI: Summary of the risk management plan

This is a summary of the Risk Management Plan (RMP) for Soolantra®. The RMP details important risks of Soolantra®, how these risks can be minimised and how more information will be obtained about the risks and uncertainties (missing information). Soolantra®s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how the product should be used.

I. The medicine and what it is used for

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

Soolantra® contains Ivermectin as active substance and it is for cutaneous use only.

Overview of disease epidemiology

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 aetiological 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:

- Erythemato-telangiectatic rosacea,

- Papulopustular rosacea,

- Phymatous rosacea,

- 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. ln 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).
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 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. ln 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

ln 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. lt 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.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Soolantra -cream 10mg/g, together with measures to minimise such risks are outlined below.
Measures to minimise the risks identified for medicinal products can be:

• Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals,

• The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

• The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures. In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary.

These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Soolantra® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Soolantra®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long term use of the medicine).

Summary of safety concerns	
Important identified risks	Contact dermatitis (allergic or irritant)
Important potential risks	Systemic Allergic Reactions Accidental oral ingestion Potential interaction with CYP3A4 and p-glycoprotein
Missing information	Exposure during pregnancy Exposure during lactation Use longer than one year Use with concomitant topical treatments Off-label use Use with laser or UV radiation

II.B Summary of important risks

Important Identified risk: Contact dermatitis (allergic or irritant)	
Evidence for linking the risk to the medicine	Evidence reported during clinical trials and post-marketing experience. Skin sensitization is idiosyncratic and unpredictable and therefore not preventable. Identification and withdrawal of the "trigger" medication is required to prevent worsening of the reaction and for any potential of progression to system hypersensitivity.
Risk minimisation measures	Routine risk minimization measures Product labeling in SmPC and PIL Known hypersensitivity to active substance or excipients included in Section 4.3 of SmPC. Section 4.4 warns that excipients may cause allergic reactions (possibly delayed) and skin irritation. Section 4.8 Contact dermatitis (allergic or irritant) with frequency Not known.
Additional pharmacovigilance activities	None
Important Potential risk: Systemic Allergic Reactions	
Evidence for linking the risk to the medicine	Evidence reported in post-marketing. It is maintained as an important potential risk to be closely monitored.
Risk minimisation measures	Routine risk minimization measures Product labeling in SmPC and PIL Known hypersensitivity to active substance or excipients included in Section 4.3 of SmPC. Section 4.4 warns that excipients may cause allergic reactions (possibly delayed) and skin irritation.
Additional pharmacovigilance activities	None
Important Potential risk: Accidental oral ingestion	
Evidence for linking the risk to the medicine	Evidence reported during clinical trials and post-marketing experience. 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. 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.

Risk minimisation measures	Routine risk minimization measures Product labelling in SmPC and PIL SmPC text in Section 4.9 describes possible consequences of oral ingestion and treatment of overdose. Product packaging with Child Proof Lock is described.
Additional pharmacovigilance activities	None
Important Potential risk: Potential interaction with CYP3A4 and p-glycoprotein	
Evidence for linking the risk to the medicine	No formal interaction studies have been performed with ivermectin administered topically.
Risk minimisation measures	Routine risk minimization measures Product labelling in the Swiss Product Information (SmPC) and Patient Information (PIL). The Section "Warnings and precautions" of the Swiss Product Information (SmPC) describes that Ivermectin should not be used with strong inhibitors of P-glycoprotein (P-gp) and CYP3A4 (e.g., itraconazole, voriconazole, posaconazole, clarithromycin, cobicistat) because this may lead to a significant increase in ivermectin levels. When Soolantra is used together with moderate inhibitors of P-gp and moderate CYP3A4 inhibitors, caution is advised as ivermectin exposure may be significantly increased. Ivermectin is a potent P-gp inhibitor and may lead to a significant increase in plasma concentrations of P-gp substrates. It should therefore not be used with substances with a narrow therapeutic range whose excretion depends significantly on P-gp (e.g. digoxin, ciclosporin). The Section "Interactions" of the Swiss Product Information describes the Influence of other medicinal products on the pharmacokinetics of ivermectin, as well as the influence of ivermectin on the pharmacokinetics of other drugs. The Swiss Patient Information (PIL) advises that caution should be taken when using Soolantra. The patient should inform in advance the physician, whenever using other medicines like ketoconazole, digoxin or ciclosporin, since these may influence the effect of Soolantra or may be influenced in the effect by Soolantra.
Additional pharmacovigilance activities	None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of ivermectin.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for ivermectin.