Summary of the Risk Management Plan (RMP) for Elidel® (Pimecrolimus)

1% Crème

Marketing Authorisation Holder: MEDA Pharma GmbH

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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 RMP summary of Elidel 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 Elidel in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. MEDA Pharma GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Elidel.

Summary of risk management plan for Elidel® 1% / Elidel Cream 10 mg/g (Pimecrolimus 1% Cream)

This is a summary of the risk management plan (RMP) for Elidel® 1% / Elidel Cream 10 mg/g. The RMP details important risks of pimecrolimus 1% cream and how these risks can be minimised.

Elidel® 1% / Elidel Cream 10 mg/g's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how it should be used.

I. The medicine and what it is used for

Elidel® 1% / Elidel Cream 10 mg/g is authorised for the treatment of patients aged 3 months and older with mild or moderate atopic dermatitis (AD) where treatment with TCS (topical corticosteroid) is either inadvisable or not possible, for example:

- Intolerance to TCS
- Lack of effect of TCS
- Use on the face and neck where prolonged intermittent treatment with TCS may be inappropriate.

It contains pimecrolimus as the active substance and it is given by cream, for dermal application.

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

Important risks of Elidel® 1% / Elidel Cream 10 mg/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;
- Important advice on the medicine's packaging;
- 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 public (e.g. with or without prescription) can help to minimises its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

In the case of Elidel® 1% / Elidel Cream 10 mg/g, these routine measures are supplemented with additional risk minimisation measures, mentioned under relevant risks below.

II.A List of important risks and missing information

Important risks of Elidel® 1% / Elidel Cream 10 mg/g are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered to patients. 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 Elidel® 1% / Elidel Cream 10 mg/g. 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/use in special patient populations etc.).

Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Off-label use for other indications than AD (Use of pimecrolimus in other indication that AD)
Important potential risks	• Skin malignancies (skin cancer) • Lymphoma (systemic immunosuppression) (Cancer of lymphocytes in immunocompromised patients) • Other malignancies (non-lymphoma, non-skin) (Other neoplasms (non-lymphoma, non-cutaneous)

Summary of safety concerns	
Missing information	• None

II.B Summary of important risks

Important Identified Risk: Off-label use in other indications than AD	
Evidence for linking the risk to the medicine	Analysis of off label use case in indications other than AD in the company safety database and Eudravigilance database. Implementation of educational material for the prescribers. Based on data derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature and due to the possible undesirable clinical outcomes related to it, this safety concern has been classified as an important identified risk.
Risk factors and risk groups	Not applicable
Risk minimisation measures	Routine risk minimisation measures Additional risk minimisation measures: Educational material (only for countries with high off-label use) for the prescribers.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Monitoring of Off-label use for other indications than AD in PSURs.

Important Potential Risk: Skin malignancies	
Evidence for linking the risk to the medicine	Based on data derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature and due to the possible undesirable clinical outcomes

Important Potential Risk: Skin malignancies	
	related to it, this safety concern has been classified as an important potential risk.
Risk factors and risk groups	Immunocompromised patients, patients with acute cutaneous viral infections, patients with Netherton's syndrome, patients with severely inflamed or damaged skin (e.g. erythroderma), patients with potentially malignant or pre-malignant skin lesions.
Risk minimisation measures	Routine risk minimisation measures Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Initially (from 2006) bi-annual, from 2012 onwards annual assessment of all available safety data by an independent Elidel Global DSMB were performed based on FAR of RMP #7. During the reporting interval, During the reporting interval, it was proposed to change the frequency of the regular DSMB meetings to triennial, if the count of the malignancy cases being reported with pimecrolimus under suspect drugs does not exceed two cases per a calendar year. However, the Viatris team should provide the DSMB with a short annual report on update on the cases and summary of the recent literature. • Biannual assessment of all available safety data by PEER DSMB.

Important Potential Risk: Lymphoma (systemic immunosuppression)	
Evidence for linking the risk to the medicine	Based on data derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published

Important Potential Risk: Lymphoma (systemic immunosuppression)	
	literature and due to the possible undesirable clinical outcomes related to it, this safety concern has been classified as an important potential risk. Although animal studies have shown evidence of carcinogenicity (lymphoma) after oral application of calcineurin inhibitors, there is no evidence of systemic immunosuppression in humans when these agents are used topically (Spergel and Leung 2006). Although blood levels of pimecrolimus following topical application of the 1% cream formulation are very low (maximum 2.6 ng/ml in registration program), a potential risk for systemic immunosuppression and malignancies cannot be excluded, based on the mechanism of action of the drug in vitro and experience with this class of drugs (TCIs) when given systemically in transplantation. Consequently, the risk of lymphoma (especially immunosuppression related Epstein-Barr virus positive B-cell lymphoma) is closely monitored in post-marketing surveillance. However, most importantly, a re-evaluation of the oral monkey toxicity study 0370001 and re-assessment of spleen and lymph node exposure (DMPK R1000544) revealed that a safety margin could be established for humans: a safety margin of 33-fold regarding the systemic exposure which is substantial. In conclusion, topical administration of Pimecrolimus Cream 1% does not cause high pimecrolimus levels in local (draining) lymph nodes nor in other potential target tissues. The tissue exposure pattern after dermal administration is fundamentally different from that after oral treatment with high doses. Consequently, the potential lymphoma risk following topical application of Pimecrolimus Cream 1% must be classified much lower than thought at the time when the first RMP was established (2006 by Novartis). This is

Important Potential Risk: Lymphoma (systemic immunosuppression)	
	supported by the results from epidemiological studies in which topical pimecrolimus administration is not associated by an increased risk of lymphoma in AD patients (Arellano et al 2005, Arellano et al 2007, Arana et al 2010). In fact, epidemiological studies indicate an increased risk of lymphoma in association with AD itself, especially with severe AD (Arana et al 2010, Vajdic et al 2009).
Risk factors and risk groups	Patients who are immunocompromised (e.g. AIDS) or who have existing pre-malignant skin lesions (e.g. cutaneous T-cell lymphoma).
Risk minimisation measures	Routine risk minimisation measures Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Initially (from 2006) bi-annual, from 2012 onwards annual assessment of all available safety data by an independent Elidel Global DSMB were performed based on FAR of RMP #7. During the reporting interval, it was proposed to change the frequency of the regular DSMB meetings to triennial, if the count of the malignancy cases being reported with pimecrolimus under suspect drugs does not exceed two cases per a calendar year. However, the Viatris team should provide the DSMB with a short annual report on update on the cases and summary of the recent literature. • Biannual assessment of all available safety data by PEER DSMB • Study ASM981C2311 Pediatric Eczema Elective Registry (Partner's (Bausch) study).

Important Potential Risk: Other malignancies (non-lymphoma, non-skin)	
Evidence for linking the risk to the medicine	Based on data derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature and due to the possible undesirable clinical outcomes related to it, this safety concern has been classified as an important potential risk. Most importantly, a re-evaluation of the oral monkey toxicity study 0370001 and reassessment of spleen and lymph node exposure (DMPK R1000544) revealed that a safety margin could be established for humans: a safety margin of 33-fold regarding the systemic exposure which is substantial. In conclusion, topical administration of Pimecrolimus Cream 1% does not cause high pimecrolimus levels in local (draining) lymph nodes nor in other potential target tissues. The tissue exposure pattern after dermal administration is fundamentally different from that after oral treatment with high doses. Consequently, the potential malignancy risk following topical application of Pimecrolimus Cream 1% must be classified much lower than thought at the time when the first RMP was established (2006 by Novartis).
Risk factors and risk groups	Immunocompromised patients.
Risk minimisation measures	Routine risk minimisation measures Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Initially (from 2006) bi-annual, from 2012 onwards annual assessment of all available safety data by an independent

Important Potential Risk: Other malignancies (non-lymphoma, non-skin)	
	Elidel Global DSMB were performed based on FAR of RMP #7. During the reporting interval, it was proposed to change the frequency of the regular DSMB meetings to triennial, if the count of the malignancy cases being reported with pimecrolimus under suspect drugs does not exceed two cases per a calendar year. However, the Viatris team should provide the DSMB with a short annual on update on the cases and summary of the recent literature. • Biannual assessment of all available safety data by PEER DSMB • Study ASM981C2311 Pediatric Eczema Elective Registry (Partner's (Bausch) study).
Risk minimisation measures	Routine risk minimisation measures Additional risk minimisation measures Educational material for the prescribers in several countries
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

II.C Post-authorisation development plan

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

The following study is condition of the marketing authorisation:

Pediatric Eczema Elective Registry (PEER, study code: ASM981C2311)

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

There are no studies required for Elidel/ Elidel Cream 10 mg/g.