## PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

### Summary of risk management plan for Elidel® 1% / Elidel Cream 10 mg/g /Aregen 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, how these risks can be minimised, and how more information will be obtained about pimecrolimus 1% cream's risks and uncertainties (missing information).

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 mild or moderate atopic dermatitis (AD) where treatment with TCS 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 /Aregen 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.

If important information that may affect the safe use of Elidel® 1% / Elidel Cream 10 mg/g is not yet available, it is listed under 'missing information' below.

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 /Aregen 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 /Aregen 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.).

Table 21 Part VI: Summary of safety concerns

| **Summary of safety concerns** | |
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| 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) |

| **Summary of safety concerns** | |
|---|---|
| | • Lymphoma (systemic immunosuppression) (Cancer of lymphocytes in immunocompromised patients)<br>• Other malignancies (non-lymphoma, non-skin) (Other neoplasms (non-lymphoma, non-cutaneous) |
| Missing information | • Application of pimecrolimus in children <2 years of age (Use in paediatric less than 2 years of age) |

## II.B Summary of important risks

| **Important Identified Risk: Off-label use in other indications than AD** | |
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| Evidence for linking the risk to the medicine | Analysis of off label use case in indications other than AD and children < 2 years in the company safety database and Eudravigilance database. Implementation of educational material for the prescribers.<br><br>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<br><br>Additional risk minimisation measures:<br>Educational material and DHPC (only for countries with high off-label use in children) for the prescribers in several countries. |

| **Important Identified Risk: Off-label use in other indications than AD** | |
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| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>Monitoring of Off-label use for other indications than AD in PSURs. |

| **Important Potential Risk: Skin malignancies** | |
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| 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. |
| 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<br><br>Additional risk minimisation measures<br>Not applicable as there are no additional risk minimisation measures for this safety concern |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• 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 Mylan team should provide the DSMB with |

| **Important Potential Risk: Skin malignancies** | |
|---|---|
| | a short annual report on update on the cases and summary of the recent literature.<br>• Biannual assessment of all available safety data by PEER DSMB.<br>• Study V01-ELDA-401 (Partner's (Bausch) study) (former study code ASM981C2308S1): Adult NMSC study. The study will be initiated upon the endorsement of study protocol by FDA.<br>• Study V01-ELDA-402 (Partner's (Bausch) study) (former study code ASM981C2324): Adult MSC study. The study will be initiated upon the endorsement of study. |

| **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 literature and due to the possible undesirable clinical outcomes related to it, this safety concern has been classified as an important potential risk.<br><br>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).<br><br>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 |

| **Important Potential Risk: Lymphoma (systemic immunosuppression)** | |
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| | 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 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<br><br>Additional risk minimisation measures: |

| **Important Potential Risk: Lymphoma (systemic immunosuppression)** | |
|---|---|
| | Not applicable as there are no additional risk minimisation measures for this safety concern |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• 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 Mylan team should provide the DSMB with a short annual report on update on the cases and summary of the recent literature.<br>• Biannual assessment of all available safety data by PEER DSMB<br>• 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.<br><br>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 |

| **Important Potential Risk: Other malignancies (non-lymphoma, non-skin)** | |
|---|---|
| | 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<br><br>Additional risk minimisation measures<br>Not applicable as there are no additional risk minimisation measures for this safety concern |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• 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 Mylan team should provide the DSMB with a short annual on update on the cases and summary of the recent literature.<br>• Biannual assessment of all available safety data by PEER DSMB |

| **Important Potential Risk: Other malignancies (non-lymphoma, non-skin)** | |
|---|---|
| | • Study ASM981C2311 Pediatric Eczema Elective Registry (Partner's (Bausch) study). |
| Risk minimisation measures | Routine risk minimisation measures<br><br>Additional risk minimisation measures<br>Educational material for the prescribers in several countries |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>Monitoring of Off-label use in children < 2 years of age in PSURs by analysing cases in children < 2 years of age from company safety database and EudraVigilance. |

| **Missing information: Application of pimecrolimus in children < 2 years of age** | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures<br><br>Additional risk minimisation measures<br>Educational material and DHPC (only for countries with high off-label use in children) for the prescribers in several countries |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>Monitoring of Off-label use in children < 2 years of age in PSURs by analysing cases in children < 2 years of age from company safety database and EudraVigilance. |

## 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.