## VI.2 Elements for a Public Summary

### *VI.2.1 Overview of disease epidemiology*

Eczema mainly affects children and it occurs more commonly in urban areas than in rural areas. Male and female patients are equally affected. The occurrence of eczema appears mainly to be related to an individual's genetic make-up. In other words a person inherits a tendency to develop these conditions. Other factors, such as stress, dry environments, contact with irritants on the skin and infection such as colds may provoke atopic eczema.

Elidel Cream specifically treats an inflammation of the skin called atopic dermatitis (eczema). It works in the cells in the skin that cause the inflammation and characteristic redness and itching of eczema.

The cream is used to treat signs and symptoms of mild or moderate eczema (e.g. redness and itch) in children (2-11 years), adolescents (12-17 years) and adults. When used to treat first signs and symptoms it can prevent progression to severe flare-ups.

### *VI.2.2 Summary of treatment benefits*

- Three 6-week, vehicle-controlled trials were conducted including 589 paediatric patients (3 months-17 years; treated twice daily with Elidel). Significant improvement in pruritus was observed within the first week of treatment in 44-70% of patients.
- Two double-blind studies of long-term management of atopic dermatitis (AD) were undertaken in 964 paediatric patients (3 months-17 years). Elidel was used at first signs of itching / redness. In case of a flare of severe disease not controlled by Elidel, treatment with topical corticosteroids (TCS) was initiated. Studies showed a significant reduction in the incidence of flares ($p<0.001$) in favour of Elidel treatment. Elidel had a sparing effect on TCS use.
- A 6-month randomized, double-blind, parallel group, vehicle-controlled study was performed in 192 adults with AD. TCS were more often used in the control group than in the Elidel group ($p<0.001$). In the Elidel group 26% less patients experienced flares compared to the control group.
- A 5-year, multicenter, open-label, randomized study was performed in more than 2,400 infants (3 −< 12 months of age). Treatment success and diseases improvement were similar between Elidel and TCS treatment groups, however, there was a marked steroid sparing effect in patients treated with Elidel.

### *VI.2.3 Unknowns relating to treatment benefits (1 short paragraph per indication of 50 words maximum)*

Patients in clinical trials were treated with Elidel to improve symptoms of AD. In the majority of studies children and adolescents have been included. No studies were performed concerning organ impairment, polymorphism or racial origin. Lack of data is not considered relevant due to topical application and low systemic exposure.

### *VI.2.4 Summary of safety concerns*

**Important identified risks**

| Risk | What is known | Preventability |
|---|---|---|
| *Local immunosuppression (skin infections)* | Approximately 1-≤10% of patients treated with Elidel will experience skin infections (folliculitis).<br>Approximately 0.1-≤1% of patients treated with Elidel will experience skin infection comprising furuncle, impetigo, herpes simplex, herpes zoster, herpes simplex dermatitis, skin papilloma | Yes, by special warnings and precautions for use (Section 4.4 of SmPC):<br>Use in immunocompromised patients, patients with Netherton's syndrome, patients with severely inflamed or damaged skin (e.g. erythroderma), patients with potentially malignant or pre-malignant skin lesions is not recommended. |
| *Off-label use for other indications than AD* | Extent of off-label use for other indication than AD varies from one country to another. | Yes, by clarifying the approved indication of Elidel in the SmPC and PIL:<br>Treatment of patients aged 2 years and over with mild or moderate atopic dermatitis where treatment with topical corticosteroids is either inadvisable or not possible.<br><br>Additionally, the off-label use is tracked by country and educational material is provided to health care professionals when deemed necessary, as was done in Austria, Finland, Greece, Italy, Portugal, the UK,the Netherlands and Czech Republic. In Spain, educational material in local language was submitted to Spanish Authority. Furthermore, the MAH plans to newly implement educational material in Poland. |
| *Medication error* | Known medication error e.g. comprise accidental exposure, administration at inappropriate site or application of expired product.<br>Related to the high number of Elidel | Correct use of Pimecrolimus Cream 1% according to SmPC sections 4.2 and 4.4:<br><br>Elidel should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis. |

| Risk | What is known | Preventability |
|---|---|---|
| | prescriptions, the number of medication errors is very low (< 0.01%). | Elidel should only be applied to areas affected with atopic dermatitis.<br>Elidel may be used on all skin areas, including the head and face, neck and intertriginous areas, except on mucous membranes.<br>Care should be taken to avoid contact with eyes and mucous membranes. If accidentally applied to these areas, the cream should be thoroughly wiped off and/or rinsed off with water.<br><br>Correct storage of Pimecrolimus Cream 1% according to PIL section 5:<br><br>Keep out of the reach and sight of children.<br>Do not store above 25 C. Do not freeze. Store in the original package.<br>Keep the tube tightly closed.<br>Do not use this medicine after the expiry date which is stated on the carton and tube. The expiry date refers to the last day of that month.<br>Once opened, the tube should be used within 12 months. You may find it helpful to write the date you opened the tube in the space provided on the carton. |

**Important potential risks**

| Risk | What is known (Including reason why it is considered a potential risk) |
|---|---|
| *Skin malignancies* | Patients treated with Elidel may be at an increased risk of developing new skin cancers. There are theoretical considerations due to the mode of action of Elidel (immunosuppressive effect, including inhibition of DNA repair in the skin).<br>However, the results of a case-control study provided no evidence of an increased risk of non-melanoma skin cancer in association with Elidel. |
| *Lymphoma (systemic immunosuppression)* | Although blood levels of pimecrolimus (active ingredient of Elidel) following topical application of Elidel are very low, a potential risk for systemic immunosuppression and cancers cannot be excluded, based on the mode of action of the drug in vitro and experience with this class of drugs when given systemically in transplant patients.<br>Although animal studies have shown evidence of lymphoma after oral application of pimecrolimus, there is no evidence of systemic immunosuppression in humans when these agents are applied topically. |
| *Other malignancies (non-lymphoma, non-skin)* | Immunocompromised patients have a greater risk to develop cancers. Although blood levels of pimecrolimus (active ingredient of Elidel) following topical application of Elidel are very low, a potential risk for systemic immunosuppression cannot be excluded.<br>At the moment, there is no evidence of systemic immuno-suppression in humans when these agents are applied topically. Furthermore, no causal relationship between topical Elidel application and development of non-lymphoma or non-skin cancers could be confirmed, yet. |
| *Herpes zoster* | Immunocompromised patients have a greater risk to develop herpes zoster infections. Although blood levels of pimecrolimus (active ingredient of Elidel) following topical application of Elidel are very low, a potential risk for systemic immunosuppression cannot be excluded.<br>However, no causal relationship between topical Elidel application and development of herpes zoster infections could be confirmed, yet. |
| *Pneumonia* | Immunocompromised patients have a greater risk to develop pneumonia. Although blood levels of pimecrolimus (active ingredient of Elidel) following topical application of Elidel are very low, a potential risk for systemic immunosuppression cannot be excluded.<br>However, no causal relationship between topical Elidel application and development of pneumonia could be confirmed, |

| Risk | What is known (Including reason why it is considered a potential risk) |
|---|---|
| | yet. |
| *Asthma/bronchospasm* | Given the propensity of development of asthma in children with AD, the finding asthma and bronchospasm in patients treated with Elidel is not unexpected. The risk for asthma in patients with AD has been shown to correlate with the severity of AD. Furthermore, no causal relationship between topical Elidel application and development of asthma/bronchospasm could be confirmed, yet. |
| *Hair abnormality* | There have been several case reports of hair abnormality in patients treated with Elidel.<br>However, no causal relationship between topical Elidel application and development of hair abnormalities could be confirmed, yet. |

**Missing information**

| Risk | What is known |
|---|---|
| *Application of pimecrolimus in children <2 years of age* | Atopic Dermatitis (eczema) is mainly observed in younger patients, therefore, the main study population (about two third of total study population) consists of children and adolescents. However, in patients under 2 years of age the use of Elidel is not recommended until further data become available. |

### *VI.2.5 Summary of risk minimisation measures by safety concern*

For the following safety concerns, only routine risk minimisation measures, including special warning in the SmPC, CCDS or PIL, are applied:

- Important identified risk: Local immunosuppression (skin infections)
- Important identified risk: Medication error
- Important potential risk: Skin malignancies
- Important potential risk: Lymphoma (systemic immunosuppression)
- Important potential risk: Other malignancies (non-lymphoma, non-skin)
- Important potential risk: Herpes zoster
- Important potential risk: Pneumonia
- Important potential risk: Asthma/bronchospasm
- Important potential risk: Hair abnormality

Additional risk minimisation measures are applied for the following safety concerns:

**Important identified risk: Elidel use for other indications than AD (Off-label use)**

| **Risk minimisation measure** |
|---|
| Objective and rationale:<br>• Monitoring of Elidel use for other indications than AD<br>• To ensure Elidel is used according to the approved indication |
| • Summary description of main additional risk minimisation measures:<br>– Providing of educational material to health care professionals |
| Based on the country-specific evaluation of the extent of Elidel use in indications other than AD educational material was provided to health care professionals in Austria, Finland, Greece, Italy, Portugal, the UK, the Netherlands, Czech Republic, Spain and was recently implemented in Poland.<br><br>Based on careful analysis of data from the current reporting period, the MAH draws the following conclusion: the MAH comits to further monitor off-label use of the product under review and to analyze carefully the effectiveness of this risk minimization measure. However, the MAH would also like to suggest prolonging the time period for analyzing prescription data from 1 year to 3 years in order to obtain more profound data. |

**Missing information: Elidel use in children < 2 years of age (Off-label use)**

| **Risk minimisation measure(s)** |
|---|
| Objective and rationale<br>• Monitoring of Elidel use in children <2 years of age<br>• To ensure Elidel is used in the approved population |
| • Summary description of main additional risk minimisation measures<br>– Providing of educational material to health care professionals |
| Based on the country-specific evaluation of the extent of Elidel use in children < 2 years of age educational material was provided to health care professionals in Austria, Finland, Greece, Italy, Portugal, the UK, the Netherlands, Czech Republic, Spain and was recently implemented in Poland.<br><br>The MAH has carefully re-evaluated the effectiveness of the measures undertaken to date. Generally, off-label use in children < 2 years of age was unchanged.<br>Based on careful analysis of data from the current reporting period, the MAH draws the following conclusion: the MAH comits to further monitor off-label use of the product under review and to analyze carefully the effectiveness of this risk minimization measure. However, the MAH would also like to suggest prolonging the time period for analyzing prescription data from 1 year to 3 years in order to obtain more profound data. |

### *VI.2.6 Planned post authorisation development plan*

**List of studies in post authorisation development plan**

| Study/activity (including study number) | Objectives | Safety concerns /efficacy issue addressed | Status | Planned date for submission of (interim and) final results |
|---|---|---|---|---|
| Pediatric Eczema Elective Registry (PEER)<br>Study code: ASM981C2311 | To investigate the risk of cancer in paediatric patients with AD who have used Elidel for at least 6 weeks. | Non-skin cancer | Ongoing | Interim reports planned 2022;<br>Final study report planned 2027 |
| V01-ELDA-401 (former study code ASM981C2308S1)<br>Database cohort study | To investigate the risk non-melanoma skin cancer in adult patients with AD who have used topical calcineurin inhibitors (including Elidel). | Non-melanoma skin cancer | Ongoing (study code adapted to MEDA partner Valeant's numbering) | The final study report is expected in 2019. |
| V01-ELDA-402 (former study code ASM981C2324)<br>Database cohort study | To investigate the risk melanoma skin cancer in adult patients with AD who have used topical calcineurin inhibitors (including Elidel). | Melanoma skin cancer | Ongoing (study code adapted to MEDA partner Valeant's numbering) | The final study report is expected in 2019. |

**Studies which are a condition of the marketing authorisation**

The Pediatric Eczema Elective Registry (PEER, study code: ASM981C2311) is a condition of the marketing authorisation.

### *VI.2.7 Summary of changes to the Risk Management Plan over time*

Major changes to the Risk Management Plan over time

| Version | Date (sign off date of RMP) | Safety Concerns | Comment |
|---|---|---|---|
| 9 | 28/05/2013 | No new safety concerns.<br><br>The following safety concerns are included in | Adaptation to the new format<br>Adaption of post- |

| Version | Date (sign off date of RMP) | Safety Concerns | Comment |
|---|---|---|---|
| | | the RMP:<br><br>Important identified risk<br>• Local immunosuppression (skin infections)<br>• Off-label use for other indications than AD<br>• Medication error<br><br>Important potential risk<br>• Skin malignancies<br>• Lymphoma (systemic immunosuppression)<br>• Other malignacies<br>• Herpes zoster<br>• Pneumonia<br>• Asthma/bronchospasm<br>• Hair abnormality<br><br>Missing information<br>• Application of pimecrolimus in children < 2 years of age | marketing experience |
| 10.0 | 05/06/2014 | The following safety concerns are included in the RMP:<br><br>Important identified risk<br>• Off-label use for other indications than AD<br>• Medication error<br><br>Important potential risk<br>• Skin malignancies<br>• Lymphoma (systemic immunosuppression)<br>• Other malignancies<br>• Hair abnormality<br><br>Missing information<br>• Application of pimecrolimus in children < 2 years of age | The MAH suggested to discontinue certain risks. This was rejected by P-RMS and a new RMP version with re-inclusion of all previous risks was requested. |
| 10.1 | 31/10/2014 | The following safety concerns are included in the RMP:<br><br>IImportant identified risk<br>• Local immunosuppression (skin infections)<br>• Off-label use for other indications than AD<br>• Medication error<br><br>Important potential risk<br>• Skin malignancies | Version prepared as response to P-RMS request and was endorsed on 16 Feb 2015. |

| Version | Date (sign off date of RMP) | Safety Concerns | Comment |
|---|---|---|---|
| | | • Lymphoma (systemic immunosuppression)<br>• Other malignacies<br>• Herpes zoster<br>• Pneumonia<br>• Asthma/bronchospasm<br>• Hair abnormality<br><br>Missing information<br>• Application of pimecrolimus in children < 2 years of age | |
| 11.0 | 26/05/2015 | The following safety concerns are included in the RMP:<br><br>Important identified risk<br>• Local immunosuppression (skin infections)<br>• Off-label use for other indications than AD<br>• Medication error<br><br>Important potential risk<br>• Skin malignancies<br>• Lymphoma (systemic immunosuppression)<br>• Other malignacies<br>• Herpes zoster<br>• Pneumonia<br>• Asthma/bronchospasm<br>• Hair abnormality<br><br>Missing information<br>Application of pimecrolimus in children < 2 years of age | General update |
| 12.0 | 03/06/2016 | The following safety concerns are included in the RMP:<br><br>Important identified risk<br>• Local immunosuppression (skin infections)<br>• Off-label use for other indications than AD<br>• Medication error<br><br>Important potential risk<br>• Skin malignancies<br>• Lymphoma (systemic immunosuppression)<br>• Other malignacies<br>• Herpes zoster<br>• Pneumonia<br>• Asthma/bronchospasm | General update |

| Version | Date (sign off date of RMP) | Safety Concerns | Comment |
|---|---|---|---|
| | | • Hair abnormality<br><br>Missing information<br>Application of pimecrolimus in children < 2 years of age | |
| 13.0 | Xx/06/2017 | The following safety concerns are included in the RMP:<br><br>Important identified risk<br>• Local immunosuppression (skin infections)<br>• Off-label use for other indications than AD<br>• Medication error<br><br>Important potential risk<br>• Skin malignancies<br>• Lymphoma (systemic immunosuppression)<br>• Other malignacies<br>• Herpes zoster<br>• Pneumonia<br>• Asthma/bronchospasm<br>• Hair abnormality<br><br>Missing information<br>Application of pimecrolimus in children < 2 years of age | General update |