PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Elidel (pimecrolimus cream 1%)

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

Elidel's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how it should be used.

Important new concerns or changes to the current ones will be included in updates of Elidel's RMP.

I. The Medicine and What it is Used For

Elidel is authorised for the treatment of patients aged 3 months and older with 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 1% cream for dermal application.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Elidel, 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.

II.A List of Important Risks and Missing Information

Important risks of Elidel 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. 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 25: Part VI.1- Summary of safety concerns

List of Important Risks and Missing Information	
Important Identified Risks	1. Off-label use for other indications than AD
Important Potential Risks	1. Skin malignancies 2. Lymphoma (systemic immunosuppression) 3. Other malignancies (non-lymphoma, non-skin
Missing Information	None

II.B Summary of Important Risks

Table 26: Part VI.2- Important Identified Risk: Off-label use in other indications than AD

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 identified risk.
Risk Factors and Risk Groups	Unknown
Risk Minimisation Measures	Routine risk minimisation measures - SmPC section 4.1 - PIL section 1 and 2 Additional risk minimisation measures - None
Additional Pharmacovigilance Activities	Additional pharmacovigilance activities: - Monitoring of off-label use of pimecrolimus for indications other than AD in future RMPs

Table 27: Part VI.3 - 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 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 - SmPC section 4.4 and 4.8 - PIL sections 2 and 4

	Additional risk minimisation measures - None
Additional Pharmacovigilance Activities	Additional pharmacovigilance activities: - Assessment of all available safety data by partner Bausch PEER (non-interventional study ASM981C2311 sponsored by the partner) DSMB meetings.

Table 28: Part VI.4- 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, Global DSMB meeting minutes 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 & 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 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., 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 - SmPC section 4.4 and 4.8 - PIL sections 2 and 4 Additional risk minimisation measures - None
Additional Pharmacovigilance Activities	Additional pharmacovigilance activities: - Assessment of all available safety data by partner Bausch PEER (non-interventional study ASM981C2311 sponsored by the partner) DSMB meetings.

Table 29: Part VI.5 - 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 and the Global DSMB meeting minutes, 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 - SmPC section 4.4 and 4.8 - PIL sections 2 and 4 Additional risk minimisation measures - None
Additional Pharmacovigilance Activities	Additional pharmacovigilance activities: - Assessment of all available safety data by partner Bausch PEER (non-interventional study ASM981C2311 sponsored by the partner) DSMB meetings

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

The following study is conditions of the marketing authorisation for the business partner Bausch Health:

A prospective 10-year observational registry of paediatric subjects aged 2 to 17 years (at enrolment) with atopic dermatitis (AD) who have used Elidel for the treatment of AD - Pediatric Eczema Elective Registry [PEER], Study code: ASM981C2311)

Purpose of the study: to investigate the long-term malignancy risk of paediatric subjects with atopic dermatitis using pimecrolimus.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Elidel in the EEA-region and UK.