ANNEX I

LIST OF THE INVENTED NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION AND MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration
Austria	Novartis Pharma GmbH, Brunnerstraße 59, 1235 Wien, Austria	Elidel	1%	Cream	Cutaneous use
Belgium	Novartis Pharma N.V.Medialaan 40 B-1800 Vilvoorde Belgium	Elidel 1%	10 mg/g	Cream	Cutaneous use
Belgium	Novartis Pharma N.V.Medialaan 40 B-1800 Vilvoorde Belgium	Isaplic 1%	10 mg/g	Cream	Cutaneous use
Czech Republic	Novartis s.r.o Praha Nagano III U Nákladového Nádraží 10 130 00 Praha 3 Czech Republic	Elidel 1% Krém	1%	Cream	Cutaneous use
Cyprus	Demetriades & Papaellinas Ltd 21 Kassou street P.O. Box 23490 Acropolis 1683 Lefkosia Cyprus	Elidel cream 1%	1%	Cream 15 g	Cutaneous use
Cyprus	Demetriades & Papaellinas Ltd 21 Kassou street P.O. Box 23490 Acropolis 1683 Lefkosia Cyprus	Elidel cream 1%	1%	Cream 30 g	Cutaneous use

Denmark	Novartis Healthcare A/S, Lyngbyvej 172, 2100 København Ø Denmark	Elidel	1%	Cream	Cutaneous use
Denmark	Novartis Healthcare A/S, Lyngbyvej 172, 2100 København Ø Denmark	Aregen	1%	Cream	Cutaneous use
Denmark	Novartis Healthcare A/S, Lyngbyvej 172, 2100 København Ø Denmark	Velov	1%	Cream	Cutaneous use
Estonia	Novartis Finland Oy, Metsänneidonkuja 10, 02130 Espoo, Finland	Elidel	1% cream	Cream	Cutaneous use
Finland	Novartis Finland Oy, Metsänneidonkuja 10, 02130 Espoo, Finland	Elidel	1%	Cream	Cutaneous use
France	Novartis Pharma 2-4, rue Lionel Terray 92500 Rueil-Malmaison France	Elidel	1%	Cream 15 g	Cutaneous use
France	Novartis Pharma 2-4, rue Lionel Terray 92500 Rueil-Malmaison France	Elidel	1%	Cream 30 g	Cutaneous use
France	Novartis Pharma 2-4, rue Lionel Terray 92500 Rueil-Malmaison France	Elidel	1%	Cream 60 g	Cutaneous use

France	Novartis Pharma 2-4, rue Lionel Terray 92500 Rueil-Malmaison France	Elidel	1%	Cream 100 g	Cutaneous use
Germany	Novartis Pharma GmbH Roonstraße 25 D-90429 Nürnberg Germany	Elidel 1 % Creme	10 mg/ 1g	Cream	Cutaneous use
Germany	3M Medica Zweigniederlassung der 3M Deutschland GmbH Hammfelddamm 11 D-41460 Neuss Germany	Douglan 1 % Creme	10 mg/ 1g	Cream	Cutaneous use
Germany	Novartis Pharma GmbH Roonstraße 25 D-90429 Nürnberg Germany	Velov 1 % Crème	10 mg/ 1g	Cream	Cutaneous use
Greece	Novartis (Hellas) AEBE 12km Athens-Lamia Metamorfosi GR-14451 Athens Greece	Elidel	1%	Cream	Cutaneous use
Greece	Novartis (Hellas) AEBE 12km Athens-Lamia Metamorfosi GR-14451 Athens Greece	Aregen	1%	Cream	Cutaneous use
Hungary	Novartis Hungária Kft. Pharma 1114 Budapest, Bartók Béla út 43-47. Bartók-Ház, V. em. Hungary	Elidel 1% krém	1% (10mg/g)	Cream	Cutaneous use

Iceland	Novaris Healthcare A/S, Lyngbyvej 172 DK-2100 København Ø, Denmark	Elidel cream 1%	1%	Cream	Cutaneous use
Italy	Novartis Farma S.p.A. Via Umberto Boccioni, 1 21040 Origgio, Varese Italy	Elidel	1%	Cream	Cutaneous use
Italy	L.P.B. Istituto Farmaceutico S.p.A Via Umberto Boccioni, 1 21040 Origgio, Varese Italy	Ombex	1%	Cream	Cutaneous use
Latvia	Novartis Finland Oy Metsänneidonkuja 10 FI – 02130 Espoo Finland	Elidel	1%	Cream	Cutaneous use
Lithuania	Novartis Finland Oy Metsänneidonkuja 10 FI – 02130 Espoo Finland	Elidel	10 mg/g	Cream	Cutaneous use
Luxembourg	Novartis Pharma GmbH Roonstraße 25 D-90429 Nürnberg Germany	Elidel	1%	Cream	Cutaneous use
Malta	Novartis Pharmaceuticals UK Ltd. Frimley Business Park, Frimley, Camberley, Surrey GUI6 7SR, United Kingdom	Elidel	1% w/w	Cream	Cutaneous use

Norway	Novartis Norge AS Postboks 237 Økern 0510 Oslo Norway	Elidel	1%	Cream	Cutaneous use
Poland	Novartis Pharma GmbH Roonstraße 25 D-90429 Nürnberg Germany	Elidel	10 mg/g	Cream	Cutaneous use
Portugal	Laboratório Normal - Produtos Farmacêuticos, S.A Rua do Centro Empresarial, Edifício 8 Quinta da Beloura 2710-444 Sintra Portugal	Aregen	10 mg/g	Cream	Cutaneous use
Portugal	Novartis Farma - Produtos Farmacêuticos, S.A Rua do Centro Empresarial, Edifício 8 Quinta da Beloura 2710-444 Sintra Portugal	Elidel	10 mg/g	Cream	Cutaneous use
Slovak Republic	Novartis s.r.o. U nákladového nádraží 10 130 00 Praha 3 Czech republic	Elidel 1%	10mg in 1g (1%)	Cream	Cutaneous use
Slovenia	Novartis Pharma GmbH Roonstraße 25 D-90429 Nürnberg Germany	Elidel	1%	Cream	Cutaneous use
Spain	Novartis Farmaceutica, S.A Gran Via de les Corts Catalanes, 764 08013 Barcelona Spain	Elidel 1 % cream	1 %	Cream	Cutaneous use

Spain	Novartis Farmaceutica, S.A Gran Via de les Corts Catalanes, 764 08013 Barcelona Spain	Pimecrolimus Novartis 1 % cream	1 %	Cream	Cutaneous use
Spain	Novartis Farmaceutica, S.A Gran Via de les Corts Catalanes, 764 08013 Barcelona Spain	Rizan 1 % cream	1 %	Cream	Cutaneous use
Sweden	Novartis Sverige AB Box 1150 183 11 Täby Sweden	Elidel	1% cream	Cream	Cutaneous use
The Netherlands	Novartis Pharma B.V., Arnhem, P.O.Box 241, 6800 LZ The Netherlands	Elidel, crème 10 mg/g	10 mg per g	Cream	Cutaneous use
United Kingdom	Novartis Pharmaceuticals UK Limited, Frimley Business Park, Frimley, Camberley, Surrey GU16 7SR, UK	Elidel 1% Cream	1% w/w	Cream	Cutaneous use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLETS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF MEDICINAL PRODUCTS CONTAINING PIMECROLIMUS (see Annex I)

Pimecrolimus is a calcineurin inhibitor approved as cream formulation at a 1% concentration. Pimecrolimus was initially approved for the use in patients with mild to moderate atopic dermatitis (AD) aged 2 years and over for short-term treatment of signs and symptoms and intermittent long-term treatment for prevention of progression to flares.

Denmark requested the CHMP to give its opinion on the benefit/risk profile of pimecrolimus considering efficacy and safety concerns with regards to the potential risk of cancer. Following this request, the CHMP reviewed data on efficacy and the available data on the mentioned safety issue, including post-marketing reports, data from non-clinical studies, clinical trials and epidemiological studies.

With regard to efficacy, pimecrolimus is less effective than the primary treatment for AD (topical corticosteroids). Therefore, the CHMP recommended the restriction of the therapeutic indications to these patients where treatment with topical corticosteroids is either inadvisable or not possible. This may include intolerance to topical corticosteroids, lack of effect of topical corticosteroids and use on the face and neck where prolonged intermittent treatment with topical corticosteroids may be inappropriate.

Prolonged systemic exposure to intense immunosuppression in transplant patients following systemic administration of calcineurin inhibitors has been associated with an increased risk of developing lymphomas and skin malignancies. Systemic exposure is limited with the topical use of pimecrolimus. However a local immunosuppressive effect in the skin cannot be excluded.

Case reports of malignancies (including cutaneous T-Cell lymphoma (CTCL) and skin cancer) have been received during the clinical development and post-marketing experience in association with the use of topical pimecrolimus. The malignancies reported were very diverse in their origin and location. The duration of the exposure to pimecrolimus cream until the diagnosis of malignancy was also different in all cases, and it was not possible to detect any specific trend. The CHMP agreed that these skin malignancies may mimic AD and that their diagnosis can be difficult. However, having reviewed the available data, the CHMP concluded that a potential association with the use of pimecrolimus could not be ruled out.

The CHMP also considered the available data from clinical trials and epidemiological studies. At the present stage, the CHMP considered that the data produced from reported epidemiological studies do not allow conclusions to be drawn regarding the potential risk of malignacies. In general, these data are not conclusive and the studies have weaknesses which limit their interpretation. The main reasons include too short lengths of exposure, too short durations of follow-up and methodological shortcomings. Some amendments of study designs have to be undertaken and further time is needed in order for pimecrolimus to be used by more subjects who can be observed for a sufficient length of time.

In view of the available data so far, the CHMP concluded that the long term safety of pimecrolimus needs to be further established. The MAH has already put in place a safety-monitoring plan to further evaluate the long-term safety of pimecrolimus, including a registry in paediatric patients.

The CHMP also expressed concerns about the degree of use of topical pimecrolimus in children under the age of 2 (not approved) when the immune system is still developing. Therefore the CHMP requested that the MAH should take the appropriate measures in order to ensure that Elidel is not used in this age group.

The Committee also concluded that the product information should include warnings regarding the potential risk of malignancies and reflect the second line use.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLETS

Whereas

- The Committee considered the referral made under article 31 of Directive 2001/83/EC, as amended, for medicinal products containing topical pimecrolimus.

- The Committee considered that pimecrolimus cream is effective in the treatment of mild or moderate atopic dermatitis; however the CHMP considered that the therapeutic indications should be restricted for patients where treatment with topical corticosteroids is either inadvisable or not possible.

- The Committee acknowledged that cases of malignancy (including skin cancer and lymphoma) have been reported in patients treated with pimecrolimus cream. In view of the available data (including pre-clinical, clinical and epidemiological) the CHMP concluded that a potential association with the use of pimecrolimus cannot be ruled out and therefore further data are needed to ensure an acceptable long term safety profile.

- The Committee, as a consequence, considered the benefit/risk balance of medicinal products containing pimecrolimus cream to be favourable in the "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. This may include intolerance to topical corticosteroids, lack of effect of topical corticosteroids and use on the face and neck where prolonged intermittent treatment with topical corticosteroids may be inappropriate". Furthermore the CHMP concluded that the following information should be included in the Summaries of Product Characteristics and relevant sections of the Package Leaflets:

    - The treatment with pimecrolimus cream should only be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis.

    - The treatment should be intermittent and not continuous.

    - A statement to highlight that pimecrolimus should not be applied to lesions, which are considered to be potentially malignant or pre-malignant.

    - Pimecrolimus cream should not be used in immunocompromised adults or children.

    - A statement that pimecrolimus cream should not be used in children under 2 years.

    - A statement reflecting the cases of malignancies reported in the post-marketing

As a consequence, the CHMP has recommended the maintenance of the Marketing Authorisations for the medicinal products referred to in Annex I for which the amendments to the relevant sections of the Summaries of Product Characteristics and Package Leaflets are set out in Annex III.

ANNEX III

Note: This Annex III (Summary of Product Characteristics, Labelling and Package Leaflet) is the one that was Annexed to the Commission Decision on this Article 31 referral for pimecrolimus containing medicinal products.
The text was valid at that time.

After the Commission Decision, the Member State competent authorities will update Annex III as required. Therefore, Annex III may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<<Invented Name>>

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of cream contains 10 mg of pimecrolimus.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Cream.

Whitish and homogeneous.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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. This may include:

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

4.2 Posology and method of administration

<Invented Name> should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis.

<Invented Name> can be used in the short term for the treatment of the signs and symptoms of atopic eczema and intermittently in the long term for the prevention of progression to flares.
<Invented Name> treatment should begin at the first appearance of signs and symptoms of atopic dermatitis. <Invented Name> should only be applied to areas affected with atopic dermatitis.
<Invented Name> should be used for as short period as possible during flares of disease. The patient or caregiver should stop using <Invented Name> when signs and symptoms resolve. Treatment should be intermittent, short-term and not continuous. <Invented Name> should be applied thinly to the affected areas twice daily.

Data from clinical studies support intermittent treatment with <Invented Name> for up to 12 months.

If no improvement occurs after 6 weeks, or in case of disease exacerbation, <Invented Name> should be stopped. The diagnosis of atopic dermatitis should be re-evaluated and further therapeutic options considered.

Adults
Apply a thin layer of <Invented Name> to the affected skin twice daily and rub in gently and completely. Each affected region of the skin should be treated with <Invented Name> until clearance occurs and then treatment should be discontinued.

<Invented Name> may be used on all skin areas, including the head and face, neck and intertriginous areas, except on mucous membranes. <Invented Name> should not be applied under occlusion (see Section 4.4 “Special warnings and precautions for use”).

In the long-term management of atopic dermatitis (eczema), <Invented Name> treatment should begin at first appearance of signs and symptoms of atopic dermatitis to prevent flares of the disease. <Invented Name> should be used twice daily. Emollients can be applied immediately after using <Invented Name>.

Paediatric patients

The use of <Invented Name> in patients under 2 years of age is not recommended until further data become available.
For children (2-11 years) and adolescents (12-17 years) the posology and method of administration are the same as for adults.

Elderly patients

Atopic dermatitis (eczema) is rarely observed in patients aged 65 and over. Clinical studies with <Invented Name> did not include a sufficient number of patients in this age range to determine whether they respond differently from younger patients.

4.3 Contraindications

Hypersensitivity to pimecrolimus, other macrolactams or to any of the excipients. For excipients, see 6.1.

4.4 Special warnings and precautions for use

<Invented Name> cream should not be used in patients with congenital or acquired immunodeficiencies or in patients on therapy that causes immunosuppression.

Long-term effect on the local skin immune response and on the incidence of skin malignancies is unknown. <Invented Name> should not be applied to potentially malignant or pre-malignant skin lesions.

<Invented Name> should not be applied to areas affected by acute cutaneous viral infections (herpes simplex, chicken pox).

<Invented Name> has not been evaluated for its efficacy and safety in the treatment of clinically infected atopic dermatitis. Before commencing treatment with <Invented Name>, clinical infections at treatment sites should be cleared.

While patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi's varicelliform eruption), treatment with <Invented Name> may be associated with an increased risk of skin herpes simplex virus infection, or eczema herpeticum (manifesting as rapid spread of vesicular and erosive lesions). In the presence of herpes simplex skin infection, <Invented Name> treatment at the site of infection should be discontinued until the viral infection has cleared.

Patients with severe atopic dermatitis may have an increased risk of skin bacterial infections (impetigo) during treatment with <Invented Name>.

Use of <Invented Name> may cause mild and transient reactions at the site of application, such as a feeling of warmth and/or burning sensation. If the application site reaction is severe, the risk-benefit of treatment should be re-evaluated.

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.

Physicians should advise patients on appropriate sun protection measures, such as minimisation of the time in the sun, use of sunscreen product and covering the skin with appropriate clothing (see Section 4.5 “Interaction with other medicinal products and other forms of interaction”).

<Invented Name> contains cetyl alcohol and stearyl alcohol which may cause local skin reactions. <Invented Name> also contains propylene glycol, which may cause skin irritation.

<Invented Name> contains the active substance pimecrolimus, a calcineurin inhibitor. In transplant patients, prolonged systemic exposure to intense immunosuppression following systemic administration of calcineurin inhibitors has been associated with an increased risk of developing lymphomas and skin malignancies.
Cases of malignancies, including cutaneous and other types of lymphoma, and skin cancers have been reported in patients using pimecrolimus cream (see section 4.8). However, patients with atopic dermatitis treated with <Invented Name> have not been found to have significant systemic pimecrolimus levels.

Populations with potentially higher risk of systemic exposure.

<Invented Name> has not been studied in patients with Netherton’s syndrome. Due to the potential for increased systemic absorption of pimecrolimus, <Invented Name> is not recommended in patients with Netherton's syndrome.

As the safety of <Invented Name> has not been established in erythrodermic patients, the use of the product in this patient population cannot be recommended.

The use of <Invented Name> under occlusion has not been studied in patients. Occlusive dressings are not recommended.

In patients with severely inflamed and/or damaged skin, the systemic concentrations may be higher.

4.5 Interaction with other medicinal products and other forms of interaction

Potential interactions between <Invented Name> and other medicinal products have not been systematically evaluated. Pimecrolimus is exclusively metabolised by CYP 450 3A4. Based on its minimal extent of absorption, interactions of <Invented Name> with systemically administered medicinal products are unlikely to occur (see Section 5.2 “Pharmacokinetic properties”).

The present data indicate that <Invented Name> can be used simultaneously with antibiotics, antihistamines and corticosteroids (oral/nasal/inhaled).

Based on the minimal extent of absorption, a potential systemic interaction with vaccination is unlikely to occur. However, this interaction has not been studied. Therefore, in patients with extensive disease, it is recommended to administer vaccinations during treatment-free intervals.

There is no experience with concomitant use of immunosuppressive therapies given for atopic eczema such as UVB, UVA, PUVA, azathioprine and cyclosporin A.

<Invented Name> has no photocarcinogenic potential in animals (see section 5.3. “Preclinical Safety Data”). However, since the relevance to man is unknown excessive exposure of the skin to ultraviolet light including light from a solarium, or therapy with PUVA, UVA or UVB should be avoided during treatment with <Invented Name>.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of <Invented Name> in pregnant women. Animal studies using dermal application do not indicate direct or indirect harmful effects with respect to embryonal/fetal development. Studies in animals after oral application have shown reproductive toxicity (see Section 5.3 “Preclinical safety data”). Based on the minimal extent of pimecrolimus absorption after topical application of <Invented Name> (see Section 5.2 “Pharmacokinetic properties”), the potential risk for humans is considered limited. However, <Invented Name> should not be used during pregnancy.

Lactation
Animal studies on milk excretion after topical application were not conducted and the use of <Invented Name> in breastfeeding women has not been studied. It is not known whether pimecrolimus is excreted in the milk after topical application.

However, based on the minimal extent of pimecrolimus absorption after topical application of <Invented Name>, (see Section 5.2 “Pharmacokinetic properties”), the potential risk for humans is considered limited. Caution should be exercised when <Invented Name> is administered to breastfeeding women.

Breastfeeding mothers may use <Invented Name> but should not apply <Invented Name> to the breast in order to avoid unintentional oral uptake by the newborn.

4.7 Effects on ability to drive and use machines

<Invented Name> has no known effect on the ability to drive and use machines.

4.8 Undesirable effects

The most common adverse events were application site reactions which were reported by approximately 19% of the patients treated with <Invented Name> and 16% of patients in the control groups. These reactions generally occurred early in treatment, were mild/moderate and were of short duration.

Frequency estimates: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000, including isolated reports).

- very common: application site burning.
- common: application site reactions (irritation, pruritus and erythema), skin infections (folliculitis).
- uncommon: furuncle, impetigo, herpes simplex, herpes zoster, herpes simplex dermatitis (eczema herpeticum), molluscum contagiosum, skin papilloma, application site disorders such as rash, pain, paraesthesia, desquamation, dryness, oedema, and condition aggravated.
- rare: alcohol intolerance (in most cases, flushing, rash, burning, itching or swelling occurred shortly after the intake of alcohol), allergic skin reactions (e.g.dermatitis, urticaria).

Post marketing: Cases of malignancy, including cutaneous and other types of lymphoma, and skin cancers, have been reported in patients using pimecrolimus cream (See Section 4.4) .

4.9 Overdose

There has been no experience of overdose with <Invented Name>.

No incidents of accidental ingestion have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other dermatologicals, ATC code: D11AX15

Non-clinical pharmacology
Pimecrolimus is a lipophilic anti-inflammatory ascomycin macrolactam derivative and a cell selective inhibitor of the production and release of pro-inflammatory cytokines.
Pimecrolimus binds with high affinity to macrophilin-12 and inhibits the calcium-dependent phosphatase calcineurin. As a consequence, it blocks the synthesis of inflammatory cytokines in T cells.

Pimecrolimus exhibits high anti-inflammatory activity in animal models of skin inflammation after topical and systemic application. In the pig model of allergic contact dermatitis, topical pimecrolimus is as effective as potent corticosteroids. Unlike corticosteroids, pimecrolimus does not cause skin atrophy in pigs and does not affect Langerhans´cells in murine skin.

Pimecrolimus neither impairs the primary immune response nor affects lymph nodes in murine allergic contact dermatitis. Topical pimecrolimus penetrates similarly into, but permeates much less through human skin than corticosteroids, indicating a very low potential of pimecrolimus for systemic absorption.

In conclusion, pimecrolimus has a skin-selective pharmacological profile different from corticosteroids.

Clinical data
The efficacy and safety profile of <Invented Name> has been evaluated in more than 2,000 patients including infants (≥3 months), children, adolescents, and adults enrolled in phase II and III studies. Over 1,500 of these patients were treated with <Invented Name> and over 500 were treated with control treatment i.e. either <Invented Name> vehicle and/or topical corticosteroids.

Short-term (acute) treatment:
Children and adolescents: Two 6-week, vehicle-controlled trials were conducted including a total of 403 paediatric patients aged 2 to 17 years. Patients were treated twice daily with <Invented Name>. The data of both studies were pooled.

Infants: A similar 6-week study was conducted in 186 patients aged 3-23 months.

In these three 6-week studies, the efficacy results at endpoint were as follows:

		Children and adolescents			Infants		
Endpoint	**Criteria**	**<Invented Name> 1% (N=267)**	**Vehicle (N=136)**	**p-value**	**<Invented Name> 1% (N=123)**	**Vehicle (N=63)**	**p-value**
IGA*:	**Clear or almost clear [1]**	**34.8%**	**18.4%**	**<0.001**	**54.5%**	**23.8%**	**<0.001**
IGA*	**Improvement [2]**	**59.9%**	**33%**	**not done**	**68%**	**40%**	**Not done**
Pruritus:	**Absent or mild**	**56.6%**	**33.8%**	**<0.001**	**72.4%**	**33.3%**	**<0.001**
EASI°:	**Overall (mean % change)[3]**	**-43.6**	**-0.7**	**<0.001**	**-61.8**	**+7.35**	**<0.001**
EASI°:	**Head/Neck (mean % change)[3]**	**-61.1**	**+0.6**	**<0.001**	**-74.0**	**+31.48**	**<0.001**

*** Investigators Global Assessment**
° Eczema Area Severity Index (EASI): mean % change in clinical signs (erythema, infiltration, excoriation, lichenification) and body surface area involved
[1]: p-value based on CMH test stratified by centre
[2]Improvement=lower IGA than at baseline
[3]: p-value based on ANCOVA model of EASI at Day 43 endpoint, with centre and treatment as factors and baseline (Day 1) EASI a covariate;

A significant improvement in pruritus was observed within the first week of treatment in 44% of children and adolescents and in 70% of infants.

Adults: <Invented Name> was less effective than 0.1% betamethasone-17-valerate in the short-term treatment (3 weeks) of adults with moderate to severe atopic dermatitis.

Long-term treatment
Two double-blind studies of long-term management of atopic dermatitis were undertaken in 713 children and adolescents (2-17 years) and 251 infants (3-23 months). <Invented Name> was evaluated as foundation therapy.

<Invented Name> was used at first signs of itching and redness to prevent progression to flares of atopic dermatitis. Only in case of a flare of severe disease not controlled by <Invented Name>, treatment with medium potency topical corticosteroids was initiated. When corticosteroid therapy was initiated for the treatment of flares, <Invented Name> therapy was discontinued. The control group received <Invented Name> vehicle in order to maintain blinding.

Both studies showed a significant reduction in the incidence of flares ($p<0.001$) in favour of <Invented Name> treatment; <Invented Name> treatment showed better efficacy in all secondary assessments (Eczema Area Severity Index, Investigators Global Assessment, subject assessment); pruritus was controlled within a week with <Invented Name>. More patients treated with <Invented Name> completed 6 months [children (61% <Invented Name> vs 34% control), infants (70% <Invented Name> vs 33% control)] and 12 months with no flare [children (51% <Invented Name> vs 28% control), infants (57% <Invented Name> vs 28% control)].

<Invented Name> had a sparing effect on the use of topical corticosteroids: more patients treated with <Invented Name> did not use corticosteroids in 12 months [children (57% <Invented Name> vs 32% control), infants (64% <Invented Name> vs 35% control)]. The efficacy of <Invented Name> was maintained over time.

A 6-month randomized, double-blind, parallel group, vehicle-controlled study of similar design was performed in 192 adults with moderate to severe atopic dermatitis. Topical corticosteroid medication was used on 14.2 ± 24.2% of the days of the 24-week treatment period in <Invented Name> group and on 37.2 ± 34.6% of the days in the control group ($p<0.001$). A total of 50.0% of the patients treated

with <Invented Name> did not experience any flare compared with 24.0% of the patients randomized to the control group.

A one year double-blind study in adults with moderate to severe atopic dermatitis was conducted to compare <Invented Name> to 0,1% triamcinolone acetonide cream (for trunk and extremities) plus 1% hydrocortisone acetate cream (for face, neck and intertriginous areas). Both <Invented Name> and topical corticosteroids were used without restrictions. Half of the patients in the control group received topical corticosteroids for more than 95% of study days. <Invented Name> was less effective than 0,1% triamcinolone acetonide cream (for trunk and extremities) plus 1% hydrocortisone acetate cream (for face, neck and intertriginous areas) in the long-term treatment (52 weeks) of adults with moderate to severe atopic dermatitis.

Long-term clinical trials were 1 year in duration. There is no clinical data beyond 1 year of treatment.

Frequency of application greater than twice daily has not been studied.

Special studies

Tolerability studies demonstrated that <Invented Name> has not shown contact sensitising, phototoxic or photosensitising potential, nor did they show any cumulative irritation.

The atrophogenic potential of <Invented Name> in humans was tested in comparison to medium and highly potent topical steroids (betamethasone-17-valerate 0.1% cream, triamcinolone acetonide 0.1% cream) and vehicle in sixteen healthy volunteers treated for 4 weeks. Both topical corticosteroids induced a significant reduction in skin thickness measured by echography, as compared to <Invented Name> and vehicle, which did not induce a reduction of skin thickness.

5.2 Pharmacokinetic properties

Data in animals
The bioavailability of pimecrolimus in mini-pigs following a single dermal dose (applied for 22h under semi-occlusion) was 0.03%. The amount of active substance-related material in the skin at the application site (almost exclusively unchanged pimecrolimus) remained practically constant for 10 days.

Data in humans

Absorption in adults
Systemic exposure to pimecrolimus was investigated in 12 adults with atopic dermatitis who were treated with <Invented Name> twice daily for 3 weeks. The affected body surface area (BSA) ranged from 15-59%. 77.5% of pimecrolimus blood concentrations were below 0.5 ng/ml and 99.8% of the total samples were below 1 ng/ml. The highest pimecrolimus blood concentration was 1.4 ng/ml in one patient.

In 40 adult patients treated for up to 1 year with <Invented Name>, having 14-62% of their BSA affected at baseline, 98% of pimecrolimus blood concentrations were below 0.5 ng/ml. A maximum blood concentration of 0.8 ng/ml was measured in only 2 patients in week 6 of treatment. There was no increase in blood concentration over time in any patient during the 12 months of treatment. In 8 adult atopic dermatitis patients, in which AUC levels could be quantified, the $AUC_{(0\text{-}12h)}$ values ranged from 2.5 to 11.4 ng h/ml.

Absorption in children
Systemic exposure to pimecrolimus was investigated in 58 paediatric patients aged 3 months to 14 years. The affected BSA ranged from 10-92%. These children were treated with <Invented Name> twice daily for 3 weeks and five out of them were treated for up to 1 year on a “as needed” basis.

Pimecrolimus blood concentrations were consistently low regardless of the extent of lesions treated or duration of therapy. They were in a range similar to that measured in adult patients. Around 60% of pimecrolimus blood concentrations were below 0.5 ng/ml and 97% of all samples were below 2 ng/ml. The highest blood concentrations measured in 2 paediatric patients aged 8 months to 14 years were 2.0 ng/ml.

In infants (aged 3 to 23 months), the highest blood concentration measured in one patient was 2.6 ng/ml. In the 5 children treated for 1 year, blood concentrations were consistently low (maximum blood concentration was 1.94 ng/ml in 1 patient). There was no increase in blood concentration over time in any patient during the 12 months of treatment.

In 8 paediatric patients aged 2-14 years, $AUC_{(0\text{-}12h)}$ ranged from 5.4 to 18.8 ng h/ml. AUC ranges observed in patients with <40% BSA affected at baseline were comparable to those in patients with ≥40% BSA.

The maximum body surface area treated was 92% in clinical pharmacology studies and up to 100% in Phase III trials.

Distribution, Metabolism, and Excretion
Consistent with its skin selectivity, after topical application, pimecrolimus blood levels are very low. Therefore pimecrolimus metabolism could not be determined after topical administration.

After single oral administration of radiolabeled pimecrolimus in healthy subjects, unchanged pimecrolimus was the major active substance-related component in blood and there were numerous minor metabolites of moderate polarity that appeared to be products of O-demethylations and oxygenation.

Active substance-related radioactivity was excreted principally via the faeces (78.4%) and only a small fraction (2.5%) was recovered in urine. Total mean recovery of radioactivity was 80.9%. Parent compound was not detected in urine and less than 1% of radioactivity in faeces was accounted for by unchanged pimecrolimus.

No metabolism of pimecrolimus was observed in human skin *in vitro*.

5.3 Preclinical safety data

Conventional studies of repeated dose toxicity, reproductive toxicity and carcinogenicity using oral administration produced effects at exposures sufficiently in excess of those in man to be of negligible clinical significance. Pimecrolimus had no genotoxic, antigenic, phototoxic, photoallergenic or photocarcinogenic potential. Dermal application in embryo/fetal developmental studies in rats and rabbits and in carcinogenicity studies in mice and rats were negative.

Effects on reproductive organs and altered sex hormone functions were seen in male and female rats in repeated dose toxicity studies after oral administration of 10 or 40 mg/kg/day (= 20 to 60 times the maximum human exposure after dermal application). This is reflected by the findings from the fertility study. The No Observed Adverse Effect Level (NOAEL) for female fertility was 10 mg/kg/day (= 20 times the maximum human exposure after dermal application). In the oral embryotoxicity study in rabbits, a higher resorption rate associated with maternal toxicity was observed at 20 mg/kg/day (= 7 times the maximum human exposure after dermal application); the mean number of live fetuses was not affected.

Dose-dependent increases in the incidence of lymphomas were observed at all doses in a 39 week monkey oral toxicity study. Signs of recovery and/or at least partial reversibility of the effects were noted upon cessation of dosages in a few animals. Failure to derive a NOAEL precludes an assessment of the margin of safety between a non-carcinogenic concentration in the monkey and exposures in patients. The systemic exposure at the LOAEL of 15mg/kg/day was 31 times the highest maximum exposure observed in a human (paediatric patient). The risk for humans cannot be completely ruled

out as the potential for local immunosuppression with the long-term use of pimecrolimus cream is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Medium chain triglycerides
Oleyl alcohol
Propylene glycol
Stearyl alcohol
Cetyl alcohol
Mono-and di-glycerides
Sodium cetostearyl sulphate
Benzyl alcohol
Citric acid anhydrous
Sodium hydroxide
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years. After first opening the container: 12 months.

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.

6.5 Nature and contents of container

Aluminium tube with a phenol-epoxy protective inner lacquer and polypropylene screw cap.

Tubes of 15, 30, 60 and 100 grams.

6.6 Instructions for use and handling

Emollients can be applied together with <Invented Name> (see Section 4.2 “Posology and method of administration”).

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

<<Date of revision>>

LABELLING AND PACKAGE LEAFLET

LABELLING

PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>

{NATURE/TYPE}

1. NAME OF THE MEDICINAL PRODUCT

<{(Invented) name strength pharmaceutical form}>

<{(Invented) name and associated names (see Annex I) strength pharmaceutical form}>
<[See Annex I - To be completed nationally]> *[For referral procedures]*

Pimecrolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

3. LIST OF EXCIPIENTS

Medium chain triglycerides, Oleyl alcohol, Propylene glycol, Stearyl alcohol, Cetyl alcohol, Mono- and di-glycerides, Sodium cetostearyl sulphate, Benzyl alcohol, Citric acid anhydrous, Sodium hydroxide, Purified water

4. PHARMACEUTICAL FORM AND CONTENTS

1% Cream

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Topical administration.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

[For terms on Batch number and Expiry date see Appendix IV]

9. SPECIAL STORAGE CONDITIONS

[For storage conditions statements see Appendix III]

<[To be completed nationally]> *[For referral procedures, as appropriate]*

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>
<[See Annex I - To be completed nationally]> *[For referral procedures]*

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

[For terms on Batch number and Expiry date see Appendix IV]

14. GENERAL CLASSIFICATION FOR SUPPLY

<[To be completed nationally]>

<Medicinal product subject to medical prescription.>
<Medicinal product not subject to medical prescription.>

15. INSTRUCTIONS ON USE

Apply a thin layer of <Invented Name> and completely cover the affected skin.

16. INFORMATION IN BRAILLE

<[To be completed nationally]> *[For referral procedures]*

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

<{(Invented) name strength pharmaceutical form}>

<{(Invented) name and associated names (see Annex I) strength pharmaceutical form}>
<[See Annex I - To be completed nationally]> *[For referral procedures]*

{pimecrolimus}

Read all of this leaflet carefully before you start using <Invented Name> cream
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist (chemist).
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours

In this leaflet:

1. What <Invented Name> cream is and what it is used for
2. Before you use <Invented Name> cream
3. How to apply <Invented Name> cream
4. Possible side effects
5. Storing <Invented Name> cream
6. Further information

1. WHAT <INVENTED NAME> CREAM IS AND WHAT IT IS USED FOR

<Invented Name> cream is a white, odourless, non-staining and easily spreadable cream containing 1% by weight pimecrolimus. It does not contain any steroids.

<Invented Name> 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.
<Invented Name> cream is available in tubes of 15 g, 30 g, 60 g and 100 g.
The cream is used to treat signs and symptoms of mild or moderate eczema (e.g. redness and itch) in children (aged 2 years and above), teenagers and adults When used to treat early signs and symptoms it can prevent progression to severe flare-ups.

<Invented Name> Cream is for use only after other prescription medicines or emollients have not worked for you or if your Doctor recommends that other prescription medicines should not be used**.**

2. BEFORE YOU USE <INVENTED NAME> CREAM

Carefully follow all instructions given to you by your doctor.
Read the following information before you use <Invented Name> cream.

Do not use <Invented Name> cream

- If you are hypersensitive (allergic) to pimecrolimus or any of the other ingredients of <Invented Name> cream.
- If you have a weakened immune system (you are immuno-compromised)

Take special care with <Invented Name> cream

<Invented Name> is not approved for children younger than 2 years of age. Therefore it should not be used in this age group. Please consult your doctor.

<Invented Name> Cream is only to be used for atopic dermatitis. Do not use for other skin conditions.
<Invented Name> cream is for external use only. Do not use it in your nose, eyes or mouth.
If accidentally applied to these areas, the cream should be thoroughly wiped off and/or rinsed with water. You should take care not to swallow it, or to accidentally transfer it into your mouth when for example it is applied to the hands.
Do not apply the cream to areas of the skin affected by active viral infection such as cold sores (herpes simplex) or chicken pox.
If your skin is infected, your doctor may ask you to use an appropriate medicine to treat the infection. When the infection at treatment sites is cleared, treatment with <Invented Name> can be started. If your skin becomes infected during treatment with <Invented Name> , you should inform your doctor. Your doctor may ask you to stop using <Invented Name> until the infection has been adequately controlled.
<Invented Name> may be associated with an increased risk of a severe herpes simplex skin infection (eczema herpeticum). Therefore if you develop painful sores anywhere on your body, tell your doctor immediately. Treatment with <Invented Name> should be discontinued until the infection has cleared.
<Invented Name> may cause reactions at the application site such as a feeling of warmth and/or a burning sensation. These reactions are usually mild and last only for a short time. Tell your doctor immediately if you have a severe reaction to <Invented Name> .
If you are using <Invented Name> , do not cover the treated skin with bandages, dressings or wraps. However, you can still wear normal clothing.
Avoid excessive exposure to sunlight, sun lamps and tanning beds during treatment with <Invented Name> . If you are outdoors after applying <Invented Name> , wear loose fitting clothing, use appropriate sunscreen products and minimise the amount of time you spend in the sun.
If you have erythroderma (redness of almost the entire body) or a skin condition called Netherton's syndrome, speak to your doctor before you start using <Invented Name> .
Also speak to your doctor before using <Invented Name> if you have any skin malignancies (tumours) or if you have a weakened immune system (immuno-compromised) whatever the cause.

Pregnancy and breast-feeding

Tell your doctor before starting treatment with <Invented Name> if you are pregnant or think that you may be pregnant. You should not use <Invented Name> if you are pregnant.

Tell your doctor if you are breast-feeding before using <Invented Name> or any other medicines.
It is not known whether the active substance in <Invented Name> passes into the milk after application to the skin. Do not apply <Invented Name> to the breasts if breast-feeding.

Driving and using machines

<Invented Name> has no known effect on the ability to drive or use machines.

Using other medicines

Inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed by a doctor.

If you have extensive eczema, treatment with <Invented Name> may have to be stopped before any vaccinations. Your doctor will be able to tell you if this is necessary.
<Invented Name> should not be used at the same time as ultraviolet light treatments (e.g. UVA, PUVA, UVB) or systemic immunosuppressive medicines (e.g. azathioprine or cyclosporin).

Interactions with other medicines that you take are unlikely to occur.

3. HOW TO APPLY <INVENTED NAME> CREAM

Always use <Invented Name> exactly as your doctor has instructed. Please check with your doctor or pharmacist if you have any questions.
You can use <Invented Name> on all skin areas, including the head, face and neck and in the folds of the skin. Apply the cream as follows:

- Wash and dry your hands.
- Open the tube (the first time you use the tube you will need to break the seal using the spike in the top of the cap).
- Squeeze the cream onto your finger.
- Apply a thin layer of <Invented Name> and completely cover the affected skin.
- Apply only on areas affected with eczema
- Rub in gently and fully.
- Replace the cap on the tube.

The cream should be applied twice daily, for instance once in the morning and once in the evening.
You can use moisturisers (emollients) with <Invented Name> . If you use moisturisers, they should be applied immediately after <Invented Name> .
Do not bath, shower or swim right after applying <Invented Name> . This could wash off the cream.

How long to apply <Invented Name>

Long term treatment should be intermittent and not continuous. Stop <Invented Name> as soon as signs of eczema have disappeared.
Continue using the cream for as long as your doctor advises.
Stop the treatment and consult your doctor if no improvement occurs after 6 weeks or if your eczema gets worse.
In the long-term treatment of eczema, begin using <Invented Name> as soon as you notice signs and symptoms (redness and itch). This helps to prevent progression to severe flare-ups. If signs and symptoms return you should start treatment again.

If you apply more <Invented Name> than you should

If you apply more cream to your skin than you needed to, just wipe it off.

If you forget to use <Invented Name>

If you forget an application of the cream, apply it as soon as possible and then continue your normal dosing routine.

If you accidentally swallow some <Invented Name>
If you or someone else accidentally swallows <Invented Name> , tell your doctor immediately.

4. POSSIBLE SIDE EFFECTS

The most common side effects of <Invented Name> are reactions (e.g. discomfort) at the application site. Such reactions are generally mild/moderate, occur early in treatment and last only for a short time.
Very common side-effects, reported in more than 1 in 10 people include:
A feeling of warmth and/or burning at the application site.
Common side-effects, reported in between 1 in 10 and 1 in 100 people include:
Irritation, itching and reddening of the skin at the application site. Skin infections (e.g. folliculitis).

Uncommon side-effects, reported in between 1 in 100 and 1 in 1000 people include:
Skin infections such as impetigo (a bacterial skin infection), herpes simplex (cold sores), herpes zoster (shingles), herpes simplex dermatitis (eczema herpeticum), molluscum contagiosum (a viral skin infection), warts and furuncles (boils). Application site reactions such as rash, pain, prickling sensation, slight scaling of the skin, dryness, swelling and worsening of eczema symptoms.

Rare side-effects, reported in between 1 in 1000 and 1 in 10,000 people include:
Flushing, rash, burning, itching or swelling shortly after drinking alcohol. Allergic skin reactions (e.g. swelling, itch or redness).

Rarely, cases of malignancy, including lymphomas and skin cancers, have been reported in patients using Elidel . However, a link to the treatment with Elidel Cream has not been confirmed or refuted on the available evidence so far.

If you notice any side effects not mentioned in this leaflet, tell your doctor or pharmacist.

5. STORING <INVENTED NAME> CREAM

Keep out of the reach and sight of children.

Do not store above 25°C.

Do not freeze.

Store in the original package.

Keep the tube tightly closed.

Do not use after the expiry date shown on the carton and tube.

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.

6. FURTHER INFORMATION

If you have any questions or are unsure about anything regarding your medicine please ask your doctor or pharmacist.

Date of last revision: 2 November 2004
<Invented Name> Cream: PL 00101/0659

What <Invented Name> Cream contains

The active substance of <Invented Name> Cream is pimecrolimus.

The other ingredients of <Invented Name> Cream are: medium chain triglycerides, oleyl alcohol, propylene glycol, stearyl alcohol, cetyl alcohol, mono-and di-glycerides, sodium cetostearyl sulphate, benzyl alcohol, citric acid anhydrous, sodium hydroxide, purified water.

What X looks like and contents of the pack

<[To be completed nationally]> *[For referral procedures, as appropriate]*

Marketing Authorisation Holder and Manufacturer

<This medicinal product is authorised in the Member States of the EEA under the following names:>

<{Name of the Member State}> <{Name of the medicinal product}>
<{Name of the Member State}> <{Name of the medicinal product}>

<[See Annex I - To be completed nationally]> *[For referral procedures, as appropriate]*

This leaflet was last approved in {MM/YYYY}.

<[To be completed nationally]>

<This medicine has been authorised under "exceptional circumstances".
This means that <because of the rarity of this disease> <for scientific reasons> <for ethical reasons> it has been impossible to get complete information on this medicine.
{MA/Agency} will review any new information on the medicine every year and this leaflet will be updated as necessary.>

<Detailed information on this medicine is available on the web site of {MA/Agency}>

<----------

<The following information is intended for medical or healthcare professionals only:>

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORIZATION

National Competent Authorities, coordinated by the Reference Member State, shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holders:

1. Communication Plan

The MAHs should implement a comprehensive non-promotional communication plan designed to reach both prescribers and patients in order to highlight the correct use of pimecrolimus according to the approved indication; to provide guidance when to start and to stop and how to administer the cream in relation to the disease extent; and further to discourage off-label use (with regard to age groups and non-approved high risk groups).

The MAHs should provide to the Reference Member State (RMS), as part of the Risk Management Plan, the final copies of the educational materials for the prescribers and patients prior to distribution.

A Dear Healthcare professional letter should be sent to relevant Healthcare professionals on 3 April 2006.

2. Lymphoma study

The MAHs should re-run the lymphoma study in 2009 and report the results to the RMS.

3. Registry Study (C2311)

The MAHs should submit 6-monthly updates to the RMS on the 10-year prospective observational cohort study to assess the risk of systemic cancer in paediatric patients.

4. Study C2308

The MAHs should provide a re-analysis of the data of this case-control study to estimate the risk of non-melanoma skin cancer. The timelines will depend on the scope of the re-analysis, which will be clarified with the RMS.

5. Pharmacological/Mechanistic Studies

The MAHs should report on the results of all planned mechanistic studies, as part of the Risk Management Plan. On the view of these results, the necessity for further studies should be re-discussed with the RMS.

6. Independent DSMB

The MAHs will set up an independent Data Safety Monitoring Board (DSMB) to assess the safety of pimecrolimus every 6 months based on all the available safety information from clinical trials, pharmacoepidemiology and post-marketing surveillance data. The DSMB will be composed of independent physicians with expertise in Dermatology, Pediatric Medicine, Immunology, Epidemiology and Oncology. It will meet twice a year and review all clinical trial, pharmaco-epidemiology and post marketing safety data obtained with pimecrolimus. The DSMB will issue an expert report every 6 months that will be shared with all National Competent Authorities in the EU and attached to the PSUR. The first report will be provided in 2007 and this requirement will be re-evaluated on a regular basis.

7. Patients HIV status, HTLV-1 for T-cell lymphomas and EVB status for B-cell lymphomas

The MAHs should provide, if available, the immune status and serology data when reporting individual tumours to Regulatory Authorities and in the regular PSURs.

8. PSURs

The MAHs should continue the submission of 6-monthly PSURs. This will be re-evaluated on a regular basis.

Cases of tumours and herpes zoster should be kept under review and regular updates should be provided in the PSURs.

9. Risk Management Plan

In accordance with the "Guideline on risk management systems for medicinal products for human use (EMEA/CHMP/96268/2005)", the MAHs should provide a full Risk Management Plan to the RMS.

10. Use of pimecrolimus in the EU vs US

The MAHs should explain the apparent differences in pimecrolimus use in the US vs the EU.

11. Measuring off label use in patients without AD

The MAHs should measure the use of Elidel in patients without AD and report its findings on an annual basis. This should encompass ***all*** age groups including those aged <2 years.

12. Measuring off label use of patients with AD and less than the age of 2

The MAHs should measure the off-label use of pimecrolimus in patients of less than 2 years.