SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Elidel 10 mg/g cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of cream contains 10 mg of pimecrolimus.

For a full list of excipients, see section 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

Posology
Elidel should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis.

Elidel 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.

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

Data from clinical studies support intermittent treatment with Elidel for up to 12 months.

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

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

Elidel may be used on all skin areas, including the head and face, neck and intertriginous areas, except on mucous membranes. Elidel should not be applied under occlusion (see section 4.4).

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

Paediatric population
The use of Elidel 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 Elidel 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 listed in section 6.1.

4.4 Special warnings and precautions for use

Elidel 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. Elidel should not be applied to potentially malignant or pre-malignant skin lesions.

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

Elidel has not been evaluated for its efficacy and safety in the treatment of clinically infected atopic dermatitis. Before commencing treatment with Elidel, 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 Elidel 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, Elidel 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 Elidel.

Use of Elidel 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).

Elidel contains cetyl alcohol and stearyl alcohol which may cause local skin reactions. Elidel also contains propylene glycol, which may cause skin irritation.

Elidel 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 Elidel have not been found to have significant systemic pimecrolimus levels.

In clinical studies, 14/1,544 (0.9%) cases of lymphadenopathy were reported while using Elidel 10 mg/g cream. These cases of lymphadenopathy were usually related to infections and noted to resolve upon appropriate antibiotic therapy. Of these 14 cases, the majority had either a clear etiology or were known to resolve. Patients who receive Elidel 10 mg/g cream and who develop lymphadenopathy should have the etiology of their lymphadenopathy investigated. In the absence of a clear etiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, Elidel 10 mg/g cream should be discountinued. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.

Populations with potentially higher risk of systemic exposure.
Elidel has not been studied in patients with Netherton's syndrome. Due to the potential for increased systemic absorption of pimecrolimus, Elidel is not recommended in patients with Netherton's syndrome.

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

The use of Elidel 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 Elidel 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 Elidel with systemically administered medicinal products are unlikely to occur (see section 5.2).

The present data indicate that Elidel 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.

Application of pimecrolimus to vaccination sites, as long as local reactions persist, was not studied and is therefore not recommended.

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

Elidel has no photocarcinogenic potential in animals (see section 5.3.). 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 Elidel.

Rare cases of flushing, rash, burning, itching or swelling have been observed shortly after the intake of alcohol in patients using pimecrolimus cream (see section 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Elidel 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). Based on the minimal extent of pimecrolimus absorption after topical application of Elidel (see section 5.2), the potential risk for humans is considered limited. However, Elidel should not be used during pregnancy.

Lactation
Animal studies on milk excretion after topical application were not conducted and the use of Elidel 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 Elidel, (see section 5.2), the potential risk for humans is considered limited. Caution should be exercised when Elidel is administered to breastfeeding women.

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

Fertility
There are no clinical data on the effects of pimecrolimus on male or female fertility (see section 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines

Elidel 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 Elidel and 16% of patients in the control groups. These reactions generally occurred early in treatment, were mild/moderate and were of short duration.

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: 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); not known (cannot be estimated from the available data).

Infections and infestations	
Uncommon	Molluscum contagiosum
Immune system disorders	
Very rare	Anaphylactic reactions, including severe forms
Metabolism and nutrition disorders	
Rare	Alcohol intolerance (in most cases, flushing, rash, burning, itching or swelling occurred shortly after the intake of alcohol)
Skin and subcutaneous tissue disorders	
Common	Skin infections (folliculitis)
Uncommon	Furuncle, impetigo, herpes simplex, herpes, zoster, herpes simplex dermatitis (eczema herpeticum), skin papilloma and condition aggravated
Rare	Allergic reactions (e.g. rash, urticaria, angiooedema), skin discoloration (e.g hypopigmentation, hyperpigmentation)
General disorders and administration site conditions	
Very common	Application site burning

Common	Application site reactions (irritation, pruritus and erythema)
Uncommon	Application site disorders (rash, pain, paraesthesia, desquamation, dryness, oedema)

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).
Cases of lymphadenopathy have been reported in post-marketing use and in clinical trials, however a causal relationship with the Elidel treatment has not been established (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

[*For the printed material, please refer to the guidance of the annotated QRD template.]

4.9 Overdose

There has been no experience of overdose with Elidel.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other dermatological preparations. Agents for dermatitis, excluding corticosteroids. ATC code: D11AH02.

Mechanism of action
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.

Pharmacodynamic effects
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 efficacy and safety
The efficacy and safety profile of Elidel 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 Elidel and over 500 were treated with control treatment i.e. either Elidel 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 Elidel. 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**	**Elidel 1% (N=267)**	**Vehicle (N=136)**	**p-value**	**Elidel 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: Elidel 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). Elidel was evaluated as foundation therapy.

Elidel 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 Elidel, treatment with medium potency topical corticosteroids was initiated. When corticosteroid therapy was initiated for the treatment of flares, Elidel therapy was discontinued. The control group received Elidel vehicle in order to maintain blinding.

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

Elidel had a sparing effect on the use of topical corticosteroids: more patients treated with Elidel did not use corticosteroids in 12 months [children (57% Elidel vs 32% control), infants (64% Elidel vs 35% control)]. The efficacy of Elidel 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 Elidel 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 Elidel 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 Elidel to 0,1% triamcinolone acetonide cream (for trunk and extremities) plus 1% hydrocortisone acetate cream (for face, neck and intertriginous areas). Both Elidel 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. Elidel 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 controlled clinical trials were 1 year in duration. There is clinical data in pediatric patients for up to 24 months.

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

Special studies
Tolerability studies demonstrated that Elidel has not shown contact sensitising, phototoxic or photosensitising potential, nor did they show any cumulative irritation.

The atrophogenic potential of Elidel 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 Elidel and vehicle, which did not induce a reduction of skin thickness.

Paediatric population
Results of relevant studies in infants, children and adolescents are detailed above in section 5.1.

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 Elidel 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 Elidel, 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 Elidel 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
Consistent with its skin selectivity, after topical application, pimecrolimus blood levels are very low. Therefore pimecrolimus metabolism could not be determined after topical administration.
In vitro plasma protein binding studies have shown that 99.6% of pimecrolimus in plasma is bound to proteins. The major fraction of pimecrolimus in plasma is bound to different lipoproteins.

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

Elimination
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.

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 5, 15, 30, 60 and 100 grams.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Emollients can be applied together with Elidel (see ection 4.2).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

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

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>

<[To be completed nationally]>