AUSTRALIAN PRODUCT INFORMATION

ELIDEL® (pimecrolimus 1% w/w)

1 NAME OF THE MEDICINE

Pimecrolimus

2 and 3 QUALITATIVE AND QUANTITATIVE COMPOSITION and PHARMACEUTICAL FORM

Elidel (pimecrolimus 1% w/w) cream contains the compound pimecrolimus, the 33-epi-chloro-derivative of the macrolactam ascomycin.

Pimecrolimus is a white to off-white fine crystalline powder. It is very soluble in methanol and ethanol and practically insoluble in water.

Each gram of Elidel cream contains 10 mg of pimecrolimus in a whitish cream base.

For the full list of excipients, see Section 6.1 **LIST OF EXCIPIENTS**.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Elidel cream is indicated for patients 3 months of age and older with atopic dermatitis (eczema) for:

- short term treatment of signs and symptoms
- intermittent long-term treatment of emerging and resolving lesions in atopic dermatitis where the use of a topical corticosteroid is not yet warranted, no longer needed, or is inadvisable (according to the usage restrictions in the respective topical corticosteroid Product Information).

4.2 DOSE AND METHOD OF ADMINISTRATION

Apply a thin layer of Elidel to the affected skin twice daily and rub in gently and completely. Elidel cream may be used on all skin areas, including the head and face, neck and intertriginous areas.

Elidel cream should only be applied to areas of eczema (see Section 4.4 **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**). The amount of cream to apply can be limited by using the fingertip dosing unit: a fingertip unit is the amount of cream expressed from a tube and applied from the distal skin crease to the tip of the palmar aspect of an adult index finger. A fingertip unit of cream is sufficient to cover the surface corresponding to two hand areas of eczema.

Carers should wash their hands after application of Elidel to their children.

Emollients can be applied after using Elidel cream.

Elidel cream should be initiated at the first sign of itching (pruritus), such as persistent scratching or rubbing, and/or persistent redness (erythema), and/or

thickening of the skin (infiltration), to prevent progression to flares of atopic dermatitis. Treatment should be discontinued when there is no longer evidence of the disease apart from dry skin. Treatment should be resumed at the first signs of recurrence.

In short-term clinical trials, Elidel cream was used twice daily for up to 6 weeks, or until resolution of signs and symptoms, if this occurred before 6 weeks. In long-term clinical trials Elidel was used intermittently for up to 12 months in infants and children and 6 months in adults (see Section 5.1 **PHARMACODYNAMIC PROPERTIES - Clinical Trials** for more information on the extent of drug exposure during the long-term trials). Elidel treatment was initiated at the first signs of itching, redness and/or skin thickening. Treatment with a moderately potent topical corticosteroid was initiated if the disease progressed to flares (severe erythema, papulation/infiltration, with or without oozing/ crusting). When topical corticosteroid therapy was initiated for the treatment of flares, Elidel therapy was discontinued. Elidel therapy was recommenced to treat residual disease or if topical corticosteroid therapy was no longer appropriate or inadvisable because of potential risks.

In general, the duration of treatment with Elidel cream for each eczema episode is up to 6 weeks (see **Use in infants (3-23 months)** below). If no improvement in the signs and symptoms occurs after 6 weeks, or in case the condition worsens, Elidel should be stopped and the patient should be re-evaluated.

Long-term continuous usage of Elidel cream is not recommended. Therapy should be intermittent, in conjunction with other therapies (see Section 4.1 **THERAPEUTIC INDICATIONS**).

Use in infants (3-23 months)

In the absence of safety data beyond 12 months, application of Elidel cream in infants (3-23 months) should be limited to the smallest practicable body surface area and treatment of each episode should generally be limited to no more than 3 weeks. Use in babies under 3 months of age has not been evaluated.

Use in the elderly

Clinical studies with Elidel cream did not include a sufficient number of patients in this age range to determine whether they respond differently from younger patients.

Use in renal or hepatic impairment

There is no evidence to suggest the need to alter dosage requirements in this specific patient population (see Section 4.4 **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

4.3 CONTRAINDICATIONS

Elidel cream is contraindicated in individuals with a history of hypersensitivity to pimecrolimus, other macrolactams or any of the components of the cream.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Long-term safety of Elidel cream has not been established.

Pimecrolimus is a calcineurin inhibitor. In transplant patients, prolonged systemic exposure to intense immunosuppression from systemic administration

of calcineurin inhibitors has been associated with an increased risk of developing lymphomas and skin malignancies.

However, patients with atopic dermatitis treated with Elidel have not been found to have significant systemic pimecrolimus levels (see Section 5.2 **PHARMACOKINETIC PROPERTIES**). In patients treated with topical calcineurin inhibitors including Elidel, although a causal relationship has not been established, rare cases of malignancy (e.g. skin and lymphoma) have been reported.

Elidel cream should not be applied to areas affected by cutaneous pre-malignant or potentially malignant changes (e.g. actinic keratoses) as caused, for example, by excessive sun exposure or phototherapy, or to areas where skin cancers have been removed.

The safety of Elidel cream has not been established in patients with Netherton's syndrome and generalised erythroderma. Elidel cream is not recommended in patients with Netherton's syndrome or severely inflamed or damaged skin (e.g. erythroderma) where there is a potential for increased absorption.

The safety and efficacy of Elidel cream in immunocompromised patients have not been studied. The use in immunocompromised patients is therefore not recommended.

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

Patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi's varicelliform eruption). Elidel cream should not be applied to areas affected by acute cutaneous viral infections (e.g. herpes simplex, chicken pox).

Treatment with Elidel may be associated with an increased risk of eczema herpeticum, herpes simplex virus infection or skin bacterial infections (impetigo).

In the presence of a dermatological bacterial or fungal infection, the use of an appropriate antimicrobial agent should be instituted. If resolution of the infection does not occur, Elidel cream should be discontinued until the infection has been adequately controlled.

In the presence of viral infection, discontinuation of treatment with Elidel at the site of infection until the viral infection has cleared should be considered.

Use of Elidel cream 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 benefit-risk of treatment should be re-evaluated.

Pimecrolimus *per se* was neither phototoxic nor photocarcinogenic in animal studies, but the cream base was found to slightly enhance the development of

skin tumours induced by UV radiation in hairless mice. Care should be taken to avoid exposure of skin areas treated with Elidel cream to natural or artificial sunlight (see Section 4.8 **ADVERSE EFFECTS (UNDESIRABLE EFFECTS) – Post-marketing data**). Patients should be advised to wear protective clothing, hats and low irritant sunscreens when Elidel is used. Elidel is to be applied first.

Elidel should not be used in patients who are receiving phototherapy.

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 rinsed off with water.

Occlusive dressings are not recommended as the use of Elidel under occlusion has not been studied in patients.

Use in renal or hepatic impairment

Although no formal studies have been carried out in patients with altered renal or hepatic function, there is no evidence to suggest reduced tolerability or the need to alter dosage requirements in this specific patient population.

Use in the elderly

Atopic dermatitis (eczema) is rarely observed in patients aged 65 and over. Nine (9) patients ≥ 65 years old received Elidel cream in phase III studies. Clinical studies of Elidel did not include sufficient numbers of patients aged 65 and over to assess efficacy and safety.

Paediatric use

Studies on the safety and efficacy of Elidel in paediatric patients below the age of 3 months have not been conducted.

Use in patients with weakened immune systems

Elidel should not be used in children and adults with weakened immune systems.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Potential interactions between Elidel cream and other drugs have not been systematically evaluated. Based on its minimal extent of absorption, interactions of Elidel cream with systemically administered drugs are unlikely to occur.

There is no experience with concomitant use of Elidel with immunosuppressive therapies such as azathioprine or ciclosporin.

A vaccination response survey was conducted in 76 children aged 3-23 months who were treated with pimecrolimus 1% cream for up to 2 years. These children had moderate to severe atopic dermatitis with an average of 27.6% total body surface affected. The results showed that the proportions of children who had protective antibodies titres were in accordance with the seropositivity rates of age-matched children reported in literature. Application of Elidel to vaccination

sites, as long as local reactions persist, was not studied and is therefore not recommended.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no clinical data on the effects of pimecrolimus on male or female fertility. Two oral fertility and embryofoetal developmental studies in rats revealed disturbance of oestrous cycles and post–implantation loss in females at 45 mg/kg/day (associated with blood AUC of $\geq$ 23 times the maximum observed human value during clinical trials). One of the studies also revealed reduced testicular and epididymal weights, reduced testicular sperm counts and motile sperm at 45 mg/kg/day and testicular degeneration and oligospermia of the epididymis at 10 and at 45 mg/kg/day in males (associated with blood AUC of $\geq$ 24 times the maximum observed human value), and decreased fertility rate, corpora lutea and implantations in females at 45 mg/kg/day with NOELs of 2 mg/kg/day for effects in males and 10mg/kg/day in females (associated with blood AUC of about 1.2 and 8 times the maximum observed human value, respectively). Reduced serum sex hormone levels and morphological changes in reproductive organs (reduced ovarian activity, atrophy of the uterine and vaginal epithelium, decreased prostate weight with prostate atrophy and/or epithelial atrophy in seminal vesicles) have been observed in mice and rats following repeated administration of pimecrolimus, but these effects usually occurred at systemic exposures significantly higher (8-28 times) than that anticipated in humans.

Use in pregnancy (Category B3)

There are no adequate data from the use of Elidel cream in pregnant women. The effects of pimecrolimus on embryofoetal development have not been adequately assessed in animals following dermal administration. Following oral administration, pimecrolimus and at least some of its metabolites crossed the placenta of rats and rabbits. Oral administration of pimecrolimus to rats and rabbits produced no evidence of teratogenicity at respective doses up to 45 and 20 mg/kg/day (associated with blood AUC of 27 and 3 times the maximum value observed in adult patients during clinical trials, respectively). However, evidence of embryofoetal toxicity (increased post-implantation loss, reduced live litter size, decreased placental weight, decreased foetal body weight and increased foetal retardation) was observed in rats at oral doses of >10 mg/kg/day. No maternal or embryofoetal toxicity was observed in rats dosed at 2 mg/kg/day (corresponding to blood AUC below the maximum value observed in adult patients during clinical trials) or in rabbit doses at 20 mg/kg/day (corresponding to an AUC of 3 times the maximum value observed in adult patients during clinical trials). Elidel cream should not be used in pregnant women.

Use in lactation

Animal studies have not been conducted to investigate the milk excretion of pimecrolimus. However, reduced postnatal growth of offspring was observed in rats treated orally with pimecrolimus at a maternal dose of 40 mg/kg/day, with a NOEL of 10 mg/kg/day. It is not known whether pimecrolimus is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse effects on nursing infants, caution should be

exercised when Elidel cream is to be used in a breastfeeding woman. In particular, breastfeeding women should not apply Elidel cream onto the breast.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No data exist on the effects of pimecrolimus on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse Events Reported in Clinical Trials

The safety profile of Elidel cream has been established in more than 2000 patients, including infants (≥ 3 months), children, adolescents and adults enrolled in phase II and III studies. Over 1500 of these patients were treated with Elidel cream and over 500 were treated with control treatment i.e. either Elidel vehicle and/or topical corticosteroids. The most common adverse events were application site reactions which were reported by approximately 19% of the patients treated with Elidel cream and 16% of patients in the control group. These reactions generally occurred early in treatment, were mild/moderate in severity and were of short duration.

Adverse reactions (Table 1) 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), including isolated reports.

Table 1

Skin and subcutaneous tissue disorders	
Common	skin infections (folliculitis)
Uncommon	furuncle, impetigo, herpes simplex, herpes zoster, herpes simplex dermatitis (eczema herpeticum), molluscum contagiosum, skin papilloma, condition aggravated
General disorders and administration site conditions	
Very common	application site burning
Common	application site reactions (irritation, pruritus and erythema)
Uncommon	application site disorders (rash, paraesthesia, desquamation, dryness, pain, oedema)

Post-marketing data

In addition to the adverse effects in Table 1, the following adverse reactions have also been reported during clinical trials and post-marketing experience. The frequency has been estimated from the reporting rates. Because these reactions are reported voluntarily from a population of uncertain size, the frequency reflects only an estimate.

Table 2

Immune system disorders	
Very rare	anaphylactic reactions
Metabolism and nutrition disorders	
Rare	alcohol intolerance[1)]

Skin and subcutaneous tissue disorders	
Rare	allergic reactions (e.g. rash, urticaria, angioedema), skin discoloration (e.g. hypopigmentation, hyperpigmentation)

[1)] In most cases, flushing, rash, burning, itching or swelling occurred shortly after the intake of alcohol.

Worldwide, there have been rare reports of malignancy, including cutaneous (squamous cell carcinoma, basal cell carcinoma) and other types of lymphoma in paediatric and adult patients treated with Elidel cream. Causality has not been established (see Section 4.4 **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There has been no experience of overdose with Elidel cream. From the company's experience with developing orally administered pimecrolimus, the maximal systemic exposure in humans was achieved when 30 mg was administered twice daily for 4 weeks. At this dosage level, the drug was generally well tolerated. By comparison, each gram of Elidel cream contains 10 mg pimecrolimus. The excipients used in Elidel cream are not known to be toxic via the oral route. Hence, the accidental ingestion of Elidel cream is unlikely to be a clinical concern.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The actual mechanism of action of pimecrolimus in atopic dermatitis is not known. Pimecrolimus is an ascomycin macrolactam derivative. *In vitro* studies showed that pimecrolimus binds with high affinity to macrophilin-12 and inhibits the calcium-dependent phosphatase, calcineurin. As a consequence, it inhibits T-cell proliferation and prevents the transcription and release of both T helper type 1 cell (TH1) and T helper type 2 cell (TH2) inflammatory cytokines such as interleukin-2, interferon-γ, interleukin-4, interleukin-5, interleukin-10, tumour necrosis factor alpha and granulocyte macrophage colony-stimulating factor. Pimecrolimus inhibits recall antigen responses in human T-helper cell clones, isolated from the skin of an atopic dermatitis patient. Pimecrolimus also prevents the release of inflammatory cytokines and mediators from mast cells *in vitro* after stimulation by antigen/IgE. In contrast to corticosteroids, Pimecrolimus does not impair the differentiation, maturation, functions and viability of murine Langerhans cells and human monocyte-derived dendritic cells, thus, underlining its cell-selective mode of action *in vitro*, but it affects

the maturation of human Langerhans cells *in vitro*. The clinical significance of the *in vitro* findings in atopic dermatitis is unclear.

In studies using various topical formulations, including the pimecrolimus cream, pimecrolimus penetrates similarly into, but permeates less through skin *in vitro* than corticosteroids, suggesting a lower systemic exposure to pimecrolimus after topical application as compared to corticosteroids.

Pimecrolimus exhibits high anti-inflammatory activity in animal models of skin inflammation after topical and systemic application. Pimecrolimus is effective in the pig model of allergic contact dermatitis (ACD). Topical pimecrolimus also inhibits the inflammatory response to irritants, as shown in murine models of irritant contact dermatitis. Furthermore, topical and oral pimecrolimus effectively reduces skin inflammation and pruritis and normalises histopathological changes in hypomagnesemic hairless rats, a model that mimics acute aspects of atopic dermatitis.

Topical pimecrolimus does not affect epidermal Langerhans´ cells in mice. In contrast, treatment with standard topical corticosteroids, including hydrocortisone, resulted in a reduction in Langerhans cells by 96-100%. A recent analysis of skin biopsies of atopic dermatitis patients has confirmed that treatment with the corticosteroid betamethasone 0.1%, but not Elidel cream, for 3 weeks results in depletion of Langerhans cells, while both drugs significantly reduce T cells.

From preclinical studies, the potential of pimecrolimus for affecting systemic immune responses appears to be lower than that of ciclosporin, as shown in models of systemic immunosuppression and based on the dose comparison. Subcutaneous injections of ciclosporin suppress the localised graft-versus-host reaction in rats 8-fold more potently than pimecrolimus. In contrast to ciclosporin, oral treatment of mice with pimecrolimus neither impairs the primary immune response nor decreases lymph node weight and cellularity in ACD.

Clinical trials

Short-term (acute) treatment in paediatric patients

Children and Adolescents: Two 6-week, vehicle-controlled trials were conducted in which a total of 403 paediatric patients 2-18 years old were treated twice daily with Elidel (pimecrolimus) cream 1%. The data of both studies were pooled. The physician's global evaluation of atopic dermatitis (i.e. The Investigator's Global Assessment, or IGA score) was used to evaluate the overall disease severity at baseline and throughout the duration of the trial. The IGA scores and descriptions are presented in the following table.

Investigator's Global Assessment (IGA) score and description

Score	Description
0 = Clear	No inflammatory signs of atopic dermatitis
1 = Almost clear	Just perceptible erythema, and just perceptible papulation/infiltration
2 = Mild disease	Mild erythema and mild papulation/infiltration

3 = Moderate disease	Moderate erythema and moderate papulation/infiltration
4 = Severe disease	Severe erythema and severe papulation/infiltration
5 = Very severe disease	Severe erythema and severe papulation/infiltration with oozing/crusting

The primary endpoint in the short-term trials was the achievement of 'clear' or 'almost clear' disease (IGA 0 or 1) at 6 weeks. At study entry, about 31% of patients had mild disease (IGA=2), 59% of patients had moderate disease (IGA=3) and 8% had severe disease (IGA=4). The percentage mean body surface area (BSA) affected was 26% (range 5-96%). About 75% of patients had atopic dermatitis affecting the face and/or neck region. In these studies, patients applied either Elidel 1% cream or vehicle cream twice daily for up to 6 weeks. After 6 weeks of treatment, 34.8% of patients treated with Elidel were clear or almost clear of signs of atopic dermatitis compared to only 18.4% of vehicle-treated patients. More Elidel patients (56.6%) had mild or no pruritus at 6 weeks compared to vehicle patients (33.8%). The improvement in pruritus occurred in conjunction with the improvement of the signs and symptoms of atopic dermatitis.

Infants: A similar 6-week study was conducted in 186 patients aged 3 to 23 months. At baseline, two-thirds of these patients had moderate disease (IGA = 3) and one-third had mild disease (IGA=2). At 6 weeks, the proportion of patients whose atopic dermatitis was assessed as clear or almost clear was significantly greater in the Elidel-treated group (54.5%) compared with the vehicle-treated group (23.8%). In addition, more Elidel patients (72.4%) had no or mild pruritus at 6 weeks compared with vehicle-treated patients (33.3%).

In these three 6-week studies, the efficacy results at the end of the study 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#	34.8%	18.4%	< 0.001[1]	54.5%	23.8%	< 0.001[1]
Pruritus	Absent or mild	56.6%	33.8%	< 0.001	72.4%	33.3%	< 0.001
EASI°:	Overall (mean % change)	- 43.6	- 0.7	< 0.001[2]	- 61.8	+ 7.35	< 0.001[2]
EASI°:	Head/Neck (mean % change)	- 61.1	+ 0.6	< 0.001[2]	- 74.0	+ 31.48	<0.001[2]

* Investigators Global Assessment (IGA)

° Eczema Area Severity Index (EASI) : mean % change in clinical signs (erythema, infiltration, excoriation, lichenification) and body surface area involved

Treatment success was defined as an IGA score of 0 (clear) or 1 (almost clear) at the end of 6 weeks

[1]: p-value based on Cochran Mantel Haenszel (CMH) test stratified by centre

[2]: p-value based on Analysis of Co-variance (ANCOVA) model of EASI at Day 43 endpoint, with centre and treatment as factors and baseline (Day 1) EASI a covariate;

In the three paediatric studies, a significant improvement in pruritus was observed within the first week of treatment with Elidel 1% cream in 44% of children and adolescents, and in 70% of infants.

Long-term treatment

Paediatric patients: Elidel 1% cream was also evaluated in two double-blind studies of long-term management of atopic dermatitis in 713 children and adolescents (2-17 years) and 251 infants (3-23 months).

The Elidel group used Elidel 1% cream twice daily at the first signs of itching and redness to prevent progression to flares of atopic dermatitis. Patients in the control group used the vehicle in place of Elidel cream to maintain the studies blind. In both groups, treatment with medium potency topical corticosteroids was initiated only in case of flare not controlled by trial medication (i.e. IGA score of at least 4). Patients in both groups were advised to use emollients throughout the course of the study.

The primary efficacy endpoint in these studies was the number of flares of atopic dermatitis in the first 6 months, although 12 month data are also presented. Both studies showed a reduction in the incidence of flares ($p < 0.001$) in favour of Elidel 1% cream first-line treatment; Elidel 1% cream first-line treatment showed better efficacy in all secondary assessments (Eczema Area Severity Index, Investigator Global Assessment, subject assessment); pruritus was controlled within a week with Elidel 1% cream. Significantly more patients on Elidel 1% cream completed 6 months and 12 months of treatment with no flares and did not use topical corticosteroids as rescue therapy (see Table below). The efficacy of Elidel 1% cream was maintained over time, with the ability to prevent disease progression to severe flares.

	After 6 months of treatment				**After 12 months of treatment**			
	children		**infants**		**children**		**infants**	
	Elidel	**control**	**Elidel**	**control**	**Elidel**	**control**	**Elidel**	**control**
% patients with no flare*	61%	34%	70%	33%	51%	28%	57%	28%
% patients not using topical corticosteroids	65%	37%	70%	39%	57%	32%	63%	35%

*Between group (Elidel vs. control) comparison p <0.001

In Studies 313 and 315, approximately 20% and 10% of patients, respectively, had used a potent topical corticosteroid at some stage before entry into the studies. However, no studies were conducted to specifically examine the effects of pimecrolimus cream in patients with a history of severe, recalcitrant atopic dermatitis who require management with potent topical corticosteroids and/or systemic therapies such as ciclosporin.

Adult patients: A 6-month, randomised, double-blind, parallel group, vehicle-controlled study of similar design to the paediatric long-term studies was performed in 192 adults with moderate (IGA =3) to severe (IGA=4) atopic dermatitis at baseline. Topical corticosteroid medication was used on an average of 14.2 ± 24.2 % of the days of the 24-week treatment period in the 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 randomised to the control group.

Exposure to study medication in long-term trials

As shown in the following table, the overall exposure to study medication was higher in the Elidel group than in the vehicle group. This was due in part to higher rates of discontinuation and corticosteroid use in the vehicle group.

Similarities in number of treatment days (i.e. the number of days the subject received study medication irrespective of the number of times the medication was applied during the day) and drug days (i.e. days assigned if study medication was applied at least twice daily), within groups indicate good overall compliance with the twice daily regimen. The frequency of use of Elidel 1% cream decreased over the duration of the study.

Overall exposure to study medication by median number of treatment days in long-term clinical trials [1]

	Infants (3-23 months)		**Older children (2-17 years)**		**Adults**	
Study period	**Elidel (N=204)**	**Vehicle (N=46)**	**Elidel (N=473)**	**Vehicle (N=235)**	**Elidel (N=96)**	**Vehicle (N=96)**
Total 6 months[2]	97.5	63.0	146.0	93.0	131.0	81.5
End of study	152.0	116.0	205.0	111.0	-	-

[1]: Treatment days refer to the number of days the subject received study medication, as recorded on diary cards

[2]: "Total 6 months" represents median treatment data up to day 183 for infants and older children and up to day 168 for adults

Other studies

Tolerability studies demonstrated that Elidel 1% cream is devoid of any irritation, contact sensitising, phototoxic or photosensitising potential.

The atrophogenic potential of Elidel 1% cream 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 1% cream and vehicle, which did not induce a reduction of skin thickness.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Absorption in adults: Systemic exposure to pimecrolimus was investigated in 12 adult patients treated with Elidel cream twice daily for 3 weeks. These patients had atopic dermatitis (eczema) lesions affecting 15-59% of their body surface area (BSA). 77.5% of pimecrolimus blood concentrations were below 0.5 ng/mL, the assay limit of quantitation (LoQ), and 99.8% of the total samples were below 1 ng/mL. The highest blood concentration of pimecrolimus measured in one patient was 1.4 ng/mL.

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 consistently low, mostly below the LoQ. 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 13 adult patients with hand dermatitis treated with Elidel twice daily for 3 weeks (palmar and dorsal surfaces of hands treated, overnight occlusion), the maximum blood concentration of pimecrolimus measured was 0.91 ng/mL.

Given the high proportion of pimecrolimus blood levels below the LoQ after topical application, the AUC could only be calculated from a few individuals.

In 8 adult AD patients presenting with at least three quantifiable blood levels per visit day, the AUC (0-12h) values ranged from 2.5 to 11.4 ng x h/mL.

Absorption in children: Systemic exposure to pimecrolimus was investigated in 58 paediatric patients aged 3 months to 14 years, who had atopic dermatitis (eczema) lesions involving 10-92% of the total body surface area. These children were treated with Elidel cream twice daily for 3 weeks and five out of them were treated for up to 1 year on an "as needed" basis.

Pimecrolimus blood concentrations measured in these paediatric patients 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 treated under the same dosing regimen. 60% of pimecrolimus blood concentrations were below 0.5 ng/mL (LoQ) 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 of age were 2.0 ng/mL.

In the youngest patients (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, and the maximum blood concentration measured was 1.94 ng/mL (one patient). In these five patients, 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 presenting at least three measurable blood concentrations per visit day, AUC(0-12h) ranged from 5.4 to 18.8 ng x h/mL. AUC ranges observed in patients with < 40% BSA affected at baseline were comparable to those in patients with ≥ 40% BSA.

Distribution

In vitro plasma protein binding studies have shown that 99.5% of pimecrolimus in plasma is bound to proteins. The major fraction of pimecrolimus in plasma is bound to different lipoproteins.

Metabolism

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 radiolabelled pimecrolimus in healthy subjects, unchanged pimecrolimus was the major drug-related component in blood and there were numerous minor metabolites of moderate polarity that appeared to be products of O-demethylations and oxygenation. No drug metabolism was observed in human skin *in vitro*.

Excretion

Drug-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.

Comparison to oral pharmacokinetic data

In psoriatic patients treated with oral pimecrolimus doses ranging from 5 mg once daily to 30 mg twice daily for 4 weeks, the highest dose was associated

with an AUC(0-12h) of 294.9 ng x h/mL. This exposure is approximately 26 and 16 times higher, respectively, than the highest systemic exposure observed in adult and paediatric atopic dermatitis (eczema) patients treated topically with Elidel twice daily for 3 weeks (AUC (0-12h) of 11.4 ng x h/mL and 18.8 ng x h/mL, respectively).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Pimecrolimus was not genotoxic, as assessed *in vitro* for gene mutations and chromosomal aberrations. An *in vivo* assay of chromosomal damage (micronucleus test in mice) was also negative.

Carcinogenicity

In a 2-year dermal carcinogenicity study in rats using Elidel cream, no cutaneous or systemic carcinogenic effects were observed at doses up to 10 mg/kg/day associated with a mean blood AUC0-24h for pimecrolimus of 3.3 times the maximum value observed in paediatric patients during clinical trials. In a mouse dermal carcinogenicity study using pimecrolimus in ethanolic solutions, no increase in incidence of neoplasms was observed in the skin or other organs at doses up to 4 mg/kg/day corresponding to a mean blood AUC (0-24h) of approximately 30 times the maximum value observed in paediatric patients during clinical trials. In a dermal photocarcinogenicity study in hairless mice using Elidel cream, no photocarcinogenic effect versus vehicle-treated animals was noted at pimecrolimus doses up to 10 mg/kg/day. However, the topical cream base was found to enhance the development of skin tumours induced by UV-radiation. Care should be taken to avoid exposure of Elidel cream treated skin area to the sun (see Section 4.4 **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

In an oral carcinogenicity study in mice, an increased incidence of malignant lymphoma along with signs of systemic immunosuppression was evident in both males and females treated with 45 mg/kg/day pimecrolimus. No carcinogenic effect was apparent at 15 mg/kg/day associated with a blood AUC (0-24h) of 60-135 times the maximum value observed in paediatric patients during clinical trials. In an oral carcinogenicity study in rats, an increased incidence of benign thymoma was observed in males treated with 5 mg/kg/day pimecrolimus and in both males and females treated with 10 mg/kg/day pimecrolimus. No oncogenic effect was apparent in males dosed at 1 mg/kg/day or females dosed at 5 mg/kg/day, associated with a blood AUC (0-24h) of up to 1.1 and 21 times the maximum value observed in paediatric patients during clinical trials, respectively.

In a repeat-dose toxicity study in Cynomolgous monkeys, pimecrolimus given orally for 19-39 weeks was associated at all doses tested with lymphoproliferative disorders, including lymphomas and leukaemias. As a no effect dose was not established, a margin of safety cannot be determined for these disorders. A chronic monkey study using topical dermal administration of pimecrolimus has not been performed.

Lymphoproliferative disorders and other neoplasm have been observed in humans and animals administered oral immunosuppressive therapies. Examples include calcineurin inhibitors such as tacrolimus and ciclosporin; inhibitors of

m-TOR (a critical kinase for cell progression) such as sirolimus and everolimus; and glucocorticoids and azathioprine.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- benzyl alcohol
- cetyl alcohol
- citric acid
- mono- and di-glycerides
- oleyl alcohol
- propylene glycol
- sodium cetostearyl sulfate
- sodium hydroxide
- stearyl alcohol
- medium chain triglycerides
- purified water

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Once opened, the contents of the tube should be used within 12 weeks.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not freeze. Keep out of reach and sight of children.

6.5 NATURE AND CONTENTS OF CONTAINER

Elidel is available in aluminium tubes with an epoxy protective inner lacquer and polypropylene screw cap.

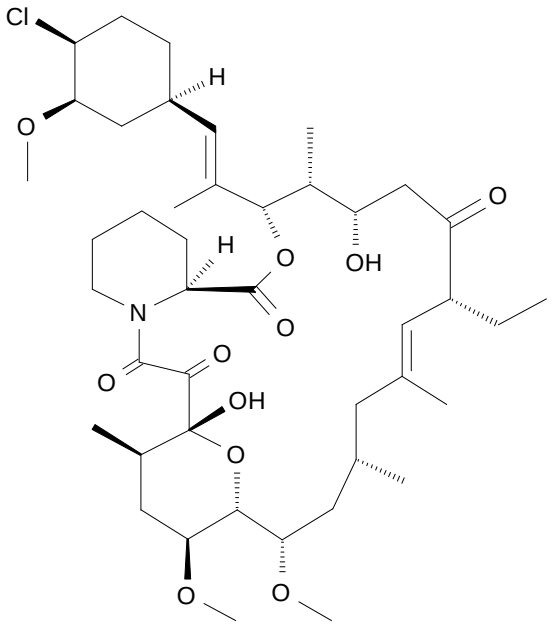
Tubes of 5 g, 15 g and 30 g are available. The 100 g tube is not marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Chemical name: (1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-2-{(1R,3R,4S)-4-chloro-3-methoxycyclohexyl}-1-methylvinyl]-17-ethyl-1,14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.04,9]octacos-18-ene-2,3,10,16-tetraone

Molecular formula: $C_{43}H_{68}ClNO_{11}$

Relative molecular mass: 810.47

CAS number

137071-32-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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Millers Point, NSW 2000

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Phone: 1800 314 527

9 DATE OF FIRST APPROVAL

5 June 2003

10 DATE OF REVISION

11 May 2018

Summary table of changes

Section changed	Summary of new information
All	Minor editorial changes for improved clarity and consistency
4.2 and 4.4	Minor editorial changes to subheadings for consistency
4.5, 4.6 and 5.1	Spelling updates (AAN) and corrections
4.8	Addition of subheading 'Reporting suspected adverse effects'
8	Sponsor details updated
10	Removal of Australian Register of Therapeutic Goods (ARTG) number.

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