ELIDEL® 1% CREAM PACKAGE INSERT

Scheduling status:

Schedule S4

Proprietary name and dosage form:

ELIDEL® 1% CREAM

Composition :

One gram of cream contains 10 mg of pimecrolimus.

Preservative: benzyl alcohol 10 mg per gram of cream.

Pharmacological classification:

A. 34 Other

Pharmacological action:

Pharmacodynamic properties:
Non-clinical pharmacology:

Pimecrolimus is an anti-inflammatory ascomycin macrolactam derivative and a selective inhibitor of the production and release of pro-inflammatory cytokines and mediators in T cells and mast cells. 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, tumor necrosis factor alpha and granulocyte macrophage colony-stimulating factor. Pimecrolimus has inhibitory effects on recall antigen responses in human T-helper cell clones, isolated from the skin of an atopic dermatitis patient. Pimecrolimus also prevents the release of cytokines and pro-inflammatory mediators from mast cells in vitro after stimulation by antigen/IgE. Pimecrolimus does not affect the growth of keratinocyte, fibroblast or endothelial cell lines. Pimecrolimus exhibits high anti-inflammatory activity in animal models of skin inflammation after topical and systemic application. 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 pruritus and normalises histopathological changes in hypomagnesemic hairless rats, a model that mimics acute aspects of atopic dermatitis. In contrast to its efficacy in skin inflammation models, the potential of pimecrolimus for affecting systemic immune responses is low. In the rat, after subcutaneous administration, the potency of pimecrolimus in inhibiting the formation of antibodies is 48-fold lower than with tacrolimus. In animal safety pharmacology studies, single oral doses of pimecrolimus had no effect on basal lung and cardiovascular functions. CNS and endocrine parameters (e.g. GH, prolactin, LH, testosterone, corticosterone) were also unaffected. Based on its mechanism of action as a selective inhibitor of the production and release of pro-inflammatory cytokines and mediators in T cells and mast cells, pimecrolimus is not expected to have any effect on the HPA axis.

Pharmacokinetic properties:

Absorption in adult

Systemic exposure to pimecrolimus in 12 adult patients treated with ELIDEL 1 % CREAM twice daily for 3 weeks. 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 1 % CREAM, having 14 to 62 % of their BSA affected at baseline, 98 % of pimecrolimus blood concentrations of pimecrolimus 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 1 % CREAM twice daily for 3 weeks (palmer 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 Atopic Dermatits (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

The 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 8 paediatric patients aged 2 to 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

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.

Metabolism

After single oral administration of radiolabeled 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.

Elimination

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.

INDICATIONS

ELIDEL 1 % CREAM is indicated in mild to moderate Atopic Dermatitis (AD) in children (2 to 11 years), adolescents (12 to 17 years) and adults for:

• short term (acute) treatment of signs and symptoms

• and intermittent therapy for prevention of progression of flares, in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or intolerant of alternative, conventional therapies.

CONTRA-INDICATIONS

Known hypersensitivity to pimecrolimus or to any of the excipients.

Safety and efficacy in pregnancy and lactation has not been established.

As the long-term effect on the local skin immune response and on the incidence of skin malignancies is unknown, ELIDEL 1% CREAM should not be applied to potentially malignant or pre-malignant skin lesions.

WARNINGS AND SPECIAL PRECAUTIONS

General:

Long-term safety of treatment with ELIDEL 1% CREAM has not been established. Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including ELIDEL 1% CREAM (see section Side-effects).

As the long-term effect on the local skin immune response and on the incidence of skin malignancies is unknown, ELIDEL 1% CREAM should not be applied to potentially malignant or pre-malignant skin lesions (See Contra-indications). ELIDEL 1 % CREAM (pimecrolimus) should not be applied to areas of active cutaneous viral infections. Studies have not evaluated the safety and efficacy of ELIDEL 1 % CREAM in the treatment of clinically infected atopic dermatitis. Before commencing treatment with ELIDEL 1 % CREAM, 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 1 % CREAM may be associated with an increased

risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum. In the presence of these skin infections, the balance of risks and benefits associated with ELIDEL 1 % CREAM use should be evaluated.

In clinical studies, 14 cases of lymphadenopathy (0.9 %) were reported while using ELIDEL 1 % CREAM. These cases of lymphadenopathy were usually related to infections and noted to resolve upon appropriate antibiotic therapy. Of these 14 cases, the majority either had a clear aetiology or was known to resolve. Patients who receive ELIDEL 1 % CREAM and who develop lymphadenopathy should have the aetiology of their lymphadenopathy investigated. In the absence of a clear aetiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, discontinuation of ELIDEL 1 % CREAM should be considered. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves. In clinical studies, 15 cases of skin papilloma or warts (1 %) were observed in patients using ELIDEL 1 % CREAM. The youngest patient was age 2 and the oldest was age 12. In cases where there is worsening of skin papillomas or they do not respond to conventional therapy, discontinuation of ELIDEL 1 % CREAM should be considered until complete resolution of the warts is achieved. The safety of ELIDEL 1% CREAM has not been established in patients with Netherton's syndrome and generalised erythroderma. ELIDEL 1% 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 1% CREAM in immunocompromised patients have not been studied. The use in immunocompromised patients is therefore not recommended. In clinical studies, 14/1,544 (0.9%) cases of lymphadenopathy were reported while using ELIDEL 1% 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 aetiology or was known to resolve. Patients who receive ELIDEL 1% CREAM and who develop lymphadenopathy should have the aetiology of their lymphadenopathy investigated. In the absence of a clear aetiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, ELIDEL 1% CREAM should be discontinued. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves. Throughout the course of treatment, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure. The potential effects of ELIDEL 1% CREAM on skin response to ultra-violet damage is not known.

ELIDEL 1% CREAM shortened the time to skin tumour formation in an animal photo carcinogenicity study (see Carcinogenesis, Mutagenesis, Impairment of Fertility).

Use of ELIDEL 1% CREAM may cause mild and transient reactions at the site of application, such as a feeling of warmth and/or burning sensation. Patients should see a physician if an application site reaction is severe (See Side-effects and special precautions).

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.

DRUG INTERACTIONS

Potential interactions between ELIDEL 1 % CREAM and other drugs, including immunisations, have not been systematically evaluated. Due to the very low blood levels of pimecrolimus detected in some patients after topical application, systemic drug interactions are not expected, but cannot be ruled out. The concomitant administration of known CYP3A family of inhibitors in patients with widespread and/or erythrodermic disease should be done with caution. Some examples of such drugs are erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers and cimetidine.

Interaction with other medicinal products and other forms of interaction

Potential interactions between ELIDEL 1 % CREAM and other medicines have not been systemically evaluated. Based on its minimal extent of absorption, interactions of ELIDEL 1 % CREAM with systemically administered drugs is unlikely to occur (see Pharmacokinetic properties).

A study that included 79 infants treated for up to 2 years showed that treatment with ELIDEL 1% CREAM did not interfere with the protective immune response to childhood vaccinations, i.e. tetanus, diphtheria, measles and rubella. Application of ELIDEL 1 % CREAM to vaccination sites, as long as local reactions persist, was not studied and is therefore not recommended.

PREGNANCY AND LACTATION

Pregnancy:

There are no adequate data from the use of ELIDEL 1 % CREAM in pregnant women. Animal studies using dermal application do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. Caution should be exercised when

prescribing ELIDEL 1 % CREAM to pregnant women. However, based on the minimal extent of pimecrolimus absorption after topical application of ELIDEL 1 % CREAM the potential risk for humans is considered limited.

Lactation:

Animal studies on milk excretion after topical application was not conducted. It is not known whether pimecrolimus is excreted in the milk after topical application. Because many drugs are excreted in human milk, caution should be exercised when ELIDEL 1 % CREAM is administered to a nursing woman. However, based on the minimal extent of pimecrolimus absorption after topical application of ELIDEL 1 % CREAM the potential risk for humans is considered limited.

Nursing mothers should not apply ELIDEL 1 % CREAM to the breast.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year rat dermal carcinogenicity study using ELIDEL 1 % CREAM, a statistically significant increase in the incidence of follicular cell adenoma of the thyroid was noted in low, mid and high dose male animals compared to vehicle and saline control male animals. Follicular cell adenoma of the thyroid was noted in the dermal rat carcinogenicity study at the lowest dose of 2 mg/kg/day [0.2 % pimecrolimus cream; 1.5X the Maximum Recommended Human Dose (MRHD) based on AUC comparisons].

No increase in the incidence of follicular cell adenoma of the thyroid was noted in the oral carcinogenicity study in male rats up to 10 mg/kg/day (66X MRHC based on AUC comparisons). However, oral studies may not reflect continuous exposure or the same metabolite profile as by the dermal route. In a mouse dermal carcinogenicity study using pimecrolimus in an ethanolic solution, no increase in incidence of neoplasms was observed in the skin or other organs up to the highest dose of 4 mg/kg.day (0.32 % pimecrolimus in ethanol) 27X MRHD based on AUC comparisons.

However, lymphoproliferative changes (including lymphoma) were note in a 13 week repeat dose dermal toxicity study conducted in mice using pimecrolimus in an ethanolic solution at a dose of 25 mg/kg/day (47X MRHD based on AUC comparisons). No lymphoproliferative changes were noted in this study at a dose of 10 mg/kg/day (17X MRHD based on AUC comparison). However, the latency time to lymphoma formation was shortened by 8 weeks after dermal administration of pimecrolimus dissolved in ethanol at a dose of 100 mg/kg/day (179 to 217X MRHD based on AUC comparisons).

In a mouse oral (gavage) carcinogenicity study, a statistically significant increase in the incidence of lymphoma was noted in high dose male and female animals compared to vehicle control male and female animals. Lymphomas were noted in the oral mouse carcinogenicity study at a dose of 45 mg/kg/day (258 to 340X MRHD based on AUC comparisons). No drug-related tumors were noted in the mouse oral carcinogenicity study at a dose of 15 mg/kg/day (60 to 133X MRHD based on AUC comparisons)/

In an oral (gavage) rat carcinogenicity study, a statistically significant increase in the incidence of benign thymoma was noted in 10 mg/kg/day pimecrolimus treated male and female animals compared to vehicle control treated male and female animals. In addition, a significant increase in the incidence of benign thymoma was noted in another oral (gavage) rat carcinogenicity study in 5 mg/kg/day pimecrolimus treated male animals compared to vehicle control treated male animals. No drug-related tumors were noted in the rat oral carcinogenicity study at a dose of 1 mg/kg/day male animals (1.1X MRHD based on AUC comparisons) and at a dose of 5 mg/kg/day for female animals (21X MRHD based on AUC comparisons).

In a 52-week dermal photo-carcinogenicity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing with concurrent exposure to UV radiation (40 weeks of treatment followed by 12 weeks of observation) with the ELIDEL 1% CREAM vehicle alone. No additional effect on tumor development beyond the vehicle effect was noted with the addition of the active ingredient, pimecrolimus, to the vehicle cream.

A battery of in vitro genotoxicity tests, including the Ames assay, mouse lymphoma L5178Y assay, and chromosome aberration test in V79 Chinese hamster cells and an in vivo mouse micronucleus test revealed no evidence for a mutagenic or clastogenic potential for the drug.

An oral fertility and ambryofetal developmental study in rats revealed estrus cycle disturbances, post-implantation loss and reduction in litter size at the 45 mg/kg/day dose (38X MRHD based on AUC comparisons). No effect on fertility in female rats was noted at 10 mg/kg/day (12X MRHC based on AUC comparisons). No effect on fertility in male rats was noted at 45 mg/kg/day (23X MRHD based on AUC comparisions), which was the highest dose tested in this study.

A second oral fertility and embryofetal developmental study in rats revealed reduced testicular and epididymal weights, reduced testicular sperm counts and motile sperm for males and estrus cycle

disturbances, decreased corpora lutea, decreased implantations and viable foetuses for females at 45 mg/kg/day dose.

In a 39 week monkey oral toxicity study, a dose-related (immunosuppressive-related lymphoproliferative disorder) IRLD associated with lymphocryptovirus (LCV) and other opportunistic infections were observed, beginning at 15 mg/kg/day, corresponding to a mean $AUC_{(0-24)}$ value of 1193 ng x h/mL (31 times the maximum exposure observed in pediatric patients in clinical trials). At 45 mg/kg/day, corresponding to a mean $AUC_{(0-24)}$ value of 3945 ng x h/mL (104 times the maximum exposure observed in pediatric patients in clinical trials) IRLD was accompanied by mortality/morbidity, food consumption and body weight reductions, and pathological changes secondary to compound-related immunosuppression. Recovery and/or at least partial reversibility of the effects were noted upon cessation of dosage.

The most common local adverse event in the short-term studies of ELIDEL 1% CREAM in paediatric patients ages 2 to 17 was application site burning (10 % vs. 13 % vehicle); the incidence in the long-term study was 9 % ELIDEL 1% CREAM vs. 7% vehicle (See *Side effects and Special precautions).* Adverse events that were more frequent (>5%) in patients treated with ELIDEL 1% CREAM compared to vehicle were headache (14% vs. 9%) in the short-term trial. Nasopharyngitis (26% vs. 21%), influenza (13% vs. 4%), pharyngitis (8% vs. 3%), viral infection (7% vs. 1%), pyrexia (13% vs. 5%), cough (16% vs. 11%), and headache (25% vs. 16%) were increased over vehicle in the 1-year safety study (See *Side-effects and Special precautions)*.

In 843 patients ages 2 to 17 years treated with ELIDEL 1% CREAM 9(0.8%) developed eczema herpeticum (5 on ELIDEL 1% CREAM alone and 4 on ELIDEL 1% CREAM used in sequence with corticosteroids). In 211 patients on vehicle alone, there were no cases of eczema herpeticum. The majority of adverse events were mild to moderate in severity.

ELIDEL 1% CREAM is not recommended for use in paediatric patients below the age of 2 years. Two Phase 3 studies were conducted involving 436 infants age 3 months – 23 months. One 6-week randomised vehicle-controlled study with a 20 week open-label phase and one long term safety study were conducted. In the 6-week study, 11% of ELIDEL 1% CREAM and 48 % of vehicle patients did not complete this study; no patient in either group discontinued due to adverse events. Infants on

ELIDEL 1% CREAM had an increased incidence of some adverse events compared to vehicle. In the 6 week vehicle-controlled study these adverse events included pyrexia (32 % vs. 13 % vehicle), URI (24 % vs. 14 %), nasopharyngitis (15 % vs. 8 %), gastro-enteritis (7 % vs. 3 %), otitis media (4 % vs. 0 %), and diarrhoea (8 % vs. 0 %). In the open-label phase of the study, for infants who switched to ELIDEL 1 % CREAM from vehicle, the incidence of the above-cited adverse events approached or equalled the incidence of those patients who remainded on ELIDEL 1% CREAM. In the 6 month safety data, 16 % of ELIDEL 1 % CREAM and 35 % of vehicle patients discontinued early and 1.5 % ELIDEL 1 % CREAM and 0 % vehicle patients discontinued due to adverse events.
Infants on ELIDEL 1 % CREAM had a greater incidence of some adverse events as compared to vehicle. These included pyrexia (30 % vs. 20 %), URI (21 % vs. 17 %), cough (15 % vs. 9 %), hypersensitivity (8 % vs. 2 %), teething (27 % vs. 22 %), vomiting (9 % vs. 4 %), rhinitis (13 % vs. 9 %), viral rash (4 % vs. 0 %), rhinorrhea (4 % vs. 0 %), and wheezing (4 % vs. 0 %).

The effects of ELIDEL 1 5 CREAM on the developing immune system in infants is unknown.

Fertility

There are no clinical data on the effects of pimecrolimus on male or female fertility.

DOSAGE AND DIRECTIONS FOR USE

Apply a thin layer of ELIDEL 1 % CREAM to the affected skin twice daily and rub in gently and completely.
ELIDEL 1 % CREAM may be used on all skin areas, including the head and face, neck and intertriginous areas.
In the long-term management of atopic dermatitis (eczema), ELIDEL 1% CREAM treatment should begin at first appearance of signs and symptoms of atopic dermatitis to prevent flares of the disease.
ELIDEL 1 % CREAM should be used twice daily until signs and symptoms resolve.
If signs and symptoms persist beyond 6 weeks, patients should be re-examined to confirm the diagnosis of atopic dermatitis. If discontinued, treatment should be resumed upon first recurrence of signs and symptoms to prevent flares of the disease.

Emolients can be applied immediately after using ELIDEL 1 % CREAM. However, after a bath/shower, emollients should be applied before using ELIDEL 1 % CREAM. Due to the low level of systemic absorption, there is no restriction either in the total daily dose applied or in the extent of the body surface area treated or in the duration of treatment.

Use in paediatric patients:

For children (2 to 11 years), and adolscents (12 to 17 years) the dosing recommendation is the same as for adults.

Insufficient data are available on safety and efficacy in children less than 2 years of age.

Use in elderly:

Atopic dermatitis (eczema) is rarely observed in patients aged 65 and over. Clinical studies with ELIDEL 1 % CREAM did not include a sufficient number of patients in this age range to determine whether they respond differently from younger patients.

Incompatibilities:

In the absence of compatibility studies, this medicinal product must not be mixed with other topical medicinal products.

Emollients can be applied together with ELIDEL 1 % CREAM (see Dosage and directions for use).

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

The adverse events are listed by system organ class and frequency: very common (≥ 1/100, < 1/10), uncommon (≥ 1/1 000, < 1/100), rare (≥ 1/10 000, < 1/1 000) and very rare (< 1/10 000).

Table 1

Skin and subcutaneous tissue disorders	
Very common:	Application site burning
Common:	Application site reactions (irritation, pruritic and erythema), skin infections (Folliculitis)
Uncommon:	Impetigo, condition aggravated, herpes simplex, herpes simplex dermatitis

	(eczema herpeticum), mollusucm contagiosum, application site disorders such as rash, pain, paraesthesia, desquamation, dryness, oedema, skin papilloma, furuncle
The following adverse reactions have been reported during post-marketing experience. The frequence is unknown. Because these reactions are reported voluntarily from a population uncertain size, the frequencies are unknown.	
Immune system disorders	Anaphylactic reactions
Metabolism and nutrition disorders	Alcohol intolerance[1] [1] In most cases, flushing, rash, burning, itching or swelling occurred shortly after the intake of alcohol
Skin and subcutaneous tissue disorders	Allergic reactions (e.g. rash, urticaria, angioedema), skin discoloration (e.g. hypopigmentation, hyperpigmentation)

Rare cases of malignancy, including cutaneous and other types of lymphoma, and skin cancers, have been reported in patients using ELIDEL 1 % CREAM, although no causal relationship has been established (Wee Warnings and Special precautions).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ELIDEL 1 % CREAM has no known effect on the ability to drive and use machines.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

There has been no experience of overdose with ELIDEL 1 % CREAM.

IDENTIFICATION

Whitish, homogenous cream.

PRESENTATION

White aluminium tube with an epoxy protective inner lacquer and a white polypropylene screw cap.

15 g, 30 g or 60 g.

STORAGE INSTRUCTIONS:

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

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

REGISTRATION NUMBER:

South Africa: 36/34/0522

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Viatris South Africa (Pty) Ltd.

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