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Elidel®

(pimecrolimus) Cream 1%

FOR DERMATOLOGIC USE ONLY
NOT FOR OPHTHALMIC USE

Rx only

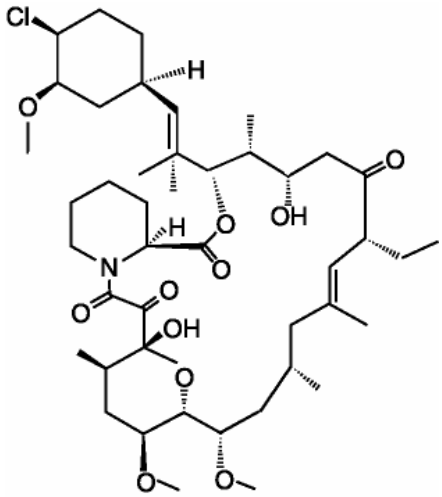
Prescribing Information

DESCRIPTION

Elidel® (pimecrolimus) Cream 1% contains the compound pimecrolimus, the 33-epi-chloro-derivative of the macrolactam ascomycin.

Chemically, pimecrolimus is (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.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone.

The compound has the empirical formula $C_{43}H_{68}ClNO_{11}$ and the molecular weight of 810.47. The structural formula is



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

Each gram of Elidel Cream 1% contains 10 mg of pimecrolimus in a whitish cream base of benzyl alcohol, cetyl alcohol, citric acid, mono- and di-glycerides, oleyl alcohol, propylene glycol, sodium cetostearyl sulphate, sodium hydroxide, stearyl alcohol, triglycerides, and water.

CLINICAL PHARMACOLOGY

Mechanism of Action/Pharmacodynamics

The mechanism of action of pimecrolimus in atopic dermatitis is not known. While the following have been observed, the clinical significance of these observations in atopic dermatitis is not known. It has been demonstrated that pimecrolimus binds with high affinity to macrophilin-12 (FKBP-12) and inhibits the calcium-dependent phosphatase, calcineurin. As a consequence, it inhibits T cell activation by blocking the transcription of early cytokines. In particular, pimecrolimus inhibits at nanomolar concentrations Interleukin-2 and interferon gamma (Th1-type) and Interleukin-4 and Interleukin-10 (Th2-type) cytokine synthesis in human T cells. In addition, pimecrolimus prevents the release of inflammatory cytokines and mediators from mast cells in vitro after stimulation by antigen/IgE.

Pharmacokinetics

Absorption

In adult patients being treated for atopic dermatitis [13%-62% Body Surface Area (BSA) involvement] for periods up to a year, blood concentrations of pimecrolimus are routinely either at or below the limit of quantification of the assay (< 0.5 ng/mL). In those subjects with detectable blood levels they are routinely < 2 ng/mL and show no sign of drug accumulation with time. Because of the low systemic absorption of pimecrolimus following topical application the calculation of standard pharmacokinetic measures such as AUC, C_{max}, $T_{1/2}$, et cetera cannot be reliably done.

Distribution

In vitro studies of the protein binding of pimecrolimus indicate that it is 74%-87% bound to plasma proteins.

Metabolism

Following the administration of a single oral radiolabeled dose of pimecrolimus numerous circulating O-demethylation metabolites were seen. Studies with human liver microsomes indicate that pimecrolimus is metabolized in vitro by the CYP3A sub-family of metabolizing enzymes. No evidence of skin mediated drug metabolism was identified in vivo using the minipig or in vitro using stripped human skin.

Elimination

Based on the results of the aforementioned radiolabeled study, following a single oral dose of pimecrolimus ~81% of the administered radioactivity was recovered, primarily in the feces (78.4%) as metabolites. Less than 1% of the radioactivity found in the feces was due to unchanged pimecrolimus.

Special Populations

Pediatrics

The systemic exposure to pimecrolimus from Elidel® (pimecrolimus) Cream 1% was investigated in 26 pediatric patients with atopic dermatitis (20%-69% BSA involvement) between the ages of 2-14 yrs. Following twice daily application for three weeks, blood concentrations of pimecrolimus were consistently low (< 3 ng/mL), with the majority of the blood samples being below the limit of quantification (0.5 ng/mL). However, the children (20 children out of the total 23 children investigated) had at least one detectable blood level as compared to the adults (13 adults out of the total 25 adults investigated) over a 3-week treatment period. Due to the low and erratic nature of the blood levels observed, no correlation could be made between amount of cream, degree of BSA involvement, and blood concentrations. In general, the blood concentrations measured in adult atopic dermatitis patients were comparable to those seen in the pediatric population.

In a second group of 22 pediatric patients aged 3- 23 months with 10%-92% BSA involvement, a higher proportion of detectable blood levels was seen ranging from 0.1 ng/mL to 2.6 ng/mL (limit of quantification 0.1 ng/mL). This increase in the absolute number of positive blood levels may be due to the larger surface area to body mass ratio seen in these younger subjects. In addition, a higher incidence of upper respiratory symptoms/infections was also seen relative to the older age group in the PK studies. At this time a causal relationship between these findings and Elidel use cannot be ruled out. Use of Elidel in this population is not recommended (see **Pediatric Use**).

Renal Insufficiency

The effect of renal insufficiency on the pharmacokinetics of topically administered pimecrolimus has not been evaluated. Given the very low systemic exposure of pimecrolimus via the topical route, no change in dosing is required.

Hepatic Insufficiency

The effect of hepatic insufficiency on the pharmacokinetics of topically administered pimecrolimus has not been evaluated. Given the very low systemic exposure of pimecrolimus via the topical route, no change in dosing is required.

CLINICAL STUDIES

Three randomized, double-blind, vehicle-controlled, multi-center, Phase 3 studies were conducted in 1335 pediatric patients ages 3 months -17 years old to evaluate Elidel® (pimecrolimus) Cream 1% for the treatment of mild to moderate atopic dermatitis. Two of the three trials support the use of Elidel Cream in patients 2 years and older with mild to moderate atopic dermatitis (see **Pediatric Use**). Three other trials provided additional data regarding the safety of Elidel Cream in the treatment of atopic dermatitis. Two of these other trials were vehicle-controlled with optional sequential use of a medium potency topical corticosteroid in pediatric patients and one trial was an active comparator trial in adult patients with atopic dermatitis (see **Pediatric Use** and **ADVERSE REACTIONS**).

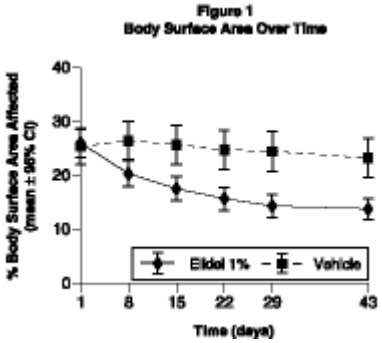
Two identical 6-week, randomized, vehicle-controlled, multi-center, Phase 3 trials were conducted to evaluate Elidel Cream for the treatment of mild to moderate atopic dermatitis. A total of 403 pediatric patients 2-17 years old were included in the studies. The male/female ratio was approximately 50% and 29% of the patients were African American. At study entry, 59% of patients had moderate disease and the mean body surface area (BSA) affected was 26%. About 75% of patients had atopic dermatitis affecting the face and/or neck region. In these studies, patients applied either Elidel Cream or vehicle cream twice daily to 5% to 96% of their BSA for up to 6 weeks. At endpoint, based on the physician's global evaluation of clinical response, 35% of patients treated with Elidel Cream were clear or almost clear of signs of atopic dermatitis compared to only 18% of vehicle-treated patients. More Elidel patients (57%) had mild or no pruritus at 6 weeks compared to vehicle patients (34%). The improvement in pruritus occurred in conjunction with the improvement of the patients' atopic dermatitis.

In these two 6-week studies of Elidel, the combined efficacy results at endpoint are as follows:

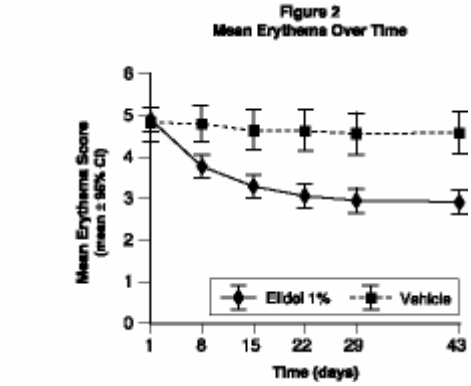
	% Patients	
	Elidel® (N= 267)	Vehicle (N= 136)
Global Assessment		
Clear	28 (10%)	5 (4%)
Clear or Almost Clear	93 (35%)	25 (18%)
Clear to Mild Disease	180 (67%)	55 (40%)

In the two pediatric studies that independently support the use of Elidel Cream in mild to moderate atopic dermatitis, a significant treatment effect was seen by day 15. Of the key signs of atopic dermatitis, erythema, infiltration/papulation, lichenification, and excoriations, erythema and infiltration/papulation were reduced at day 8 when compared to vehicle.

The following graph depicts the time course of improvement in the percent body surface area affected as a result of treatment with Elidel Cream in 2-17 year olds.



The following graph shows the time course of improvement in erythema as a result of treatment with Elidel Cream in 2-17 year olds.



INDICATIONS AND USAGE

Elidel® (pimecrolimus) Cream 1% is indicated for short-term and intermittent long-term therapy in the treatment of *mild to moderate* atopic dermatitis in non-immunocompromised patients 2 years of age and older, 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 (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Elidel® (pimecrolimus) Cream 1% is contraindicated in individuals with a history of hypersensitivity to pimecrolimus or any of the components of the cream.

PRECAUTIONS

General

Elidel® (pimecrolimus) Cream 1% should not be applied to areas of active cutaneous viral infections.

Studies have not evaluated the safety and efficacy of Elidel Cream in the treatment of clinically infected atopic dermatitis. Before commencing treatment with Elidel 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 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 Cream use should be evaluated.

In clinical studies, 14 cases of lymphadenopathy (0.9%) were reported while using Elidel 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 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, discontinuation of Elidel 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 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 Cream should be considered until complete resolution of the warts is achieved.

The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Despite the absence of observed phototoxicity in humans (see **ADVERSE REACTIONS**), Elidel Cream shortened the time to skin tumor formation in an animal photo-carcinogenicity study (see **Carcinogenesis, Mutagenesis, Impairment of Fertility**). Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure.

The use of Elidel Cream in patients with Netherton's Syndrome is not recommended due to the potential for increased systemic absorption of pimecrolimus.

There are no data to support use of Elidel in immunocompromised patients.

The use of Elidel Cream may cause local symptoms such as skin burning. Localized symptoms are most common during the first few days of Elidel Cream application and typically improve as the lesions of atopic dermatitis resolve. Most application site reactions lasted no more than 5 days, were mild to moderate in severity, and started within 1-5 days of treatment. (See **ADVERSE REACTIONS**.)

Information for Patients

Patients using Elidel should receive the following information and instructions:

- Patients should use Elidel Cream as directed by the physician. Elidel Cream is for external use on the skin only. As with any topical medication, patients or caregivers should wash hands after application if hands are not an area for treatment.
- Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using Elidel Cream.
- Patients should not use this medication for any disorder other than that for which it was prescribed.
- Patients should report any signs or symptoms of adverse reactions to their physician.
- Therapy should be discontinued after signs and symptoms of atopic dermatitis have resolved. Treatment with Elidel should be resumed at the first signs or symptoms of recurrence.
- Use of Elidel may cause reactions at the site of application such as a mild to moderate feeling of warmth and/or sensation of burning. Patients should see a physician if an application site reaction is severe or persists for more than 1 week.
- The patient should contact the physician if no improvement in the atopic dermatitis is seen following 6 weeks of treatment, or if at any time the condition worsens.

Drug Interactions

Potential interactions between Elidel and other drugs, including immunizations, 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year rat dermal carcinogenicity study using Elidel 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 MRHD based on AUC comparisons). However, oral studies may not reflect continuous exposure or the same metabolic 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 noted 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 to 8 weeks after dermal administration of pimecrolimus dissolved in ethanol at a dose of 100 mg/kg/day (179-217X 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 (258-340X 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 (60-133X 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 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 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 embryofetal 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 MRHD based on AUC comparisons). No effect on fertility in male rats was noted at 45 mg/kg/day (23X MRHD based on AUC comparisons), 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 fetuses for females at 45 mg/kg/day dose (123X MRHD for males and 192X MRHD for females based on AUC comparisons). No effect on fertility in female rats was noted at 10 mg/kg/day (5X MRHD based on AUC comparisons). No effect on fertility in male rats was noted at 2 mg/kg/day (0.7X MRHD based on AUC comparisons).

Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies of topically administered pimecrolimus in pregnant women. The experience with Elidel Cream when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy.

In dermal embryofetal developmental studies, no maternal or fetal toxicity was observed up to the highest practicable doses tested, 10 mg/kg/day (1% pimecrolimus cream) in rats (0.14X MRHD based on body surface area) and 10 mg/kg/day (1% pimecrolimus cream) in rabbits (0.65X MRHD based on AUC comparisons). The 1% pimecrolimus cream was administered topically for 6 hours/day during the period of organogenesis in rats and rabbits (gestational days 6-21 in rats and gestational days 6-20 in rabbits).

A second dermal embryofetal development study was conducted in rats using pimecrolimus cream applied dermally to pregnant rats (1g cream/kg body weight of 0.2%, 0.6% and 1.0% pimecrolimus cream) from gestation day 6 to 17 at doses of 2, 6, and 10 mg/kg/day with daily exposure of approximately 22 hours. No maternal, reproductive, or embryo-fetal toxicity attributable to pimecrolimus was noted at 10 mg/kg/day (0.66X MRHD based on AUC comparisons), the highest dose evaluated in this study. No teratogenicity was noted in this study at any dose.

A combined oral fertility and embryofetal developmental study was conducted in rats and an oral embryofetal developmental study was conducted in rabbits. Pimecrolimus was administered during the period of organogenesis (2 weeks prior to mating until gestational day 16 in rats, gestational days 6-18 in rabbits) up to dose levels of 45 mg/kg/day in rats and 20 mg/kg/day in rabbits. In the absence of maternal toxicity, indicators of embryofetal toxicity (post-implantation loss and reduction in litter size) were noted at 45 mg/kg/day (38X MRHD based on AUC comparisons) in the oral fertility and embryofetal developmental study conducted in rats. No malformations in the fetuses were noted at 45 mg/kg/day (38X MRHD based on AUC comparisons) in this study. No maternal toxicity, embryotoxicity or teratogenicity were noted in the oral rabbit embryofetal developmental toxicity study at 20 mg/kg/day (3.9X MRHD based on AUC comparisons), which was the highest dose tested in this study.

A second oral embryofetal development study was conducted in rats. Pimecrolimus was administered during the period of organogenesis (gestational days 6 – 17) at doses of 2, 10 and 45 mg/kg/day. Maternal toxicity, embryolethality and fetotoxicity were noted at 45 mg/kg/day (271X MRHD based on AUC comparisons). A slight increase in skeletal variations that were indicative of delayed skeletal ossification was also noted at this dose. No maternal toxicity, embryolethality or fetotoxicity were noted at 10 mg/kg/day (16X MRHD based on AUC comparisons). No teratogenicity was noted in this study at any dose.

A second oral embryofetal development study was conducted in rabbits. Pimecrolimus was administered during the period of organogenesis (gestational days 7 – 20) at doses of 2, 6 and 20 mg/kg/day. Maternal toxicity, embryotoxicity and fetotoxicity were noted at 20 mg/kg/day (12X MRHD based on AUC comparisons). A slight increase in skeletal variations that were indicative of delayed skeletal ossification was also noted at this dose. No maternal toxicity, embryotoxicity or fetotoxicity were noted at 6 mg/kg/day (5X MRHD based on AUC comparisons). No teratogenicity was noted in this study at any dose.

An oral peri- and post-natal developmental study was conducted in rats. Pimecrolimus was administered from gestational day 6 through lactational day 21 up to a dose level of 40 mg/kg/day. Only 2 of 22 females delivered live pups at the highest dose of 40 mg/kg/day. Postnatal survival, development of the F1 generation, their subsequent maturation and fertility were not affected at 10 mg/kg/day (12X MRHD based on AUC comparisons), the highest dose evaluated in this study.

Pimecrolimus was transferred across the placenta in oral rat and rabbit embryofetal developmental studies.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed during pregnancy.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from pimecrolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Elidel Cream may be used in pediatric patients 2 years of age and older. Three Phase 3 pediatric studies were conducted involving 1114 patients 2-17 years of age. Two studies were 6-week randomized vehicle-controlled studies with a 20-week open-label phase and one was a vehicle-controlled long-term (up to 1 year) safety study with the option for sequential topical corticosteroid use. Of these patients 542 (49%) were 2-6 years of age. In the short-term studies, 11% of Elidel patients did not complete these studies and 1.5% of Elidel patients discontinued due to adverse events. In the one-year study, 32% of Elidel patients did not complete this study and 3% of Elidel patients discontinued due to adverse events. Most discontinuations were due to unsatisfactory therapeutic effect.

The most common local adverse event in the short-term studies of Elidel Cream in pediatric patients ages 2-17 was application site burning (10% vs. 13% vehicle); the incidence in the long-term study was 9% Elidel vs. 7% vehicle (see **ADVERSE REACTIONS**). Adverse events that were more frequent (>5%) in patients treated with Elidel 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 **ADVERSE REACTIONS**). In 843 patients ages 2-17 years treated with Elidel Cream, 9 (0.8%) developed eczema herpeticum (5 on Elidel Cream alone and 4 on Elidel Cream used in sequence with cortico-steroids). 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 Cream is not recommended for use in pediatric patients below the age of 2 years. Two Phase 3 studies were conducted involving 436 infants age 3 months - 23 months. One 6-week randomized 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 and 48% of vehicle patients did not complete this study; no patient in either group discontinued due to adverse events. Infants on Elidel 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%), gastroenteritis (7% vs. 3%), otitis media (4% vs. 0%), and diarrhea (8% vs. 0%). In the open-label phase of the study, for infants who switched to Elidel Cream from vehicle, the incidence of the above-cited adverse events approached or equaled the incidence of those patients who remained on Elidel Cream. In the 6 month safety data, 16% of Elidel and 35% of vehicle patients discontinued early and 1.5% of Elidel and 0% of vehicle patients discontinued due to adverse events. Infants on Elidel 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 Cream on the developing immune system in infants are unknown.

Geriatric Use

Nine (9) patients ≥ 65 years old received Elidel Cream in Phase 3 studies. Clinical studies of Elidel did not include sufficient numbers of patients aged 65 and over to assess efficacy and safety.

ADVERSE REACTIONS

In human dermal safety studies, Elidel® (pimecrolimus) Cream 1% did not induce contact sensitization, phototoxicity, or photoallergy, nor did it show any cumulative irritation.

In a one-year safety study in pediatric patients age 2-17 years old involving sequential use of Elidel Cream and a topical corticosteroid, 43% of Elidel patients and 68% of vehicle patients used corticosteroids during the study. Corticosteroids were used for more than 7 days by 34% of Elidel patients and 54% of vehicle patients. An increased incidence of impetigo, skin infection, superinfection (infected atopic dermatitis), rhinitis, and urticaria were found in the patients that had used Elidel Cream and topical corticosteroid sequentially as compared to Elidel Cream alone.

In 3 randomized, double-blind vehicle-controlled pediatric studies and one active-controlled adult study, 843 and 328 patients respectively, were treated with Elidel Cream. In these clinical trials, 48 (4%) of the 1171 Elidel patients and 13 (3%) of 408 vehicle-treated patients discontinued therapy due to adverse events. Discontinuations for AEs were primarily due to application site reactions, and cutaneous infections. The most common application site reaction was application site burning, which occurred in 8%-26% of patients treated with Elidel Cream.

The following table depicts the incidence of adverse events pooled across the 2 identically designed 6-week studies with their open label extensions and the 1-year safety study for pediatric patients ages 2-17. Data from the adult active-controlled study is also included in this table. Adverse events are listed regardless of relationship to study drug.

Treatment Emergent Adverse Events (≥ 1%) in Elidel® Treatment Groups

	Pediatric Patients* Vehicle-Controlled (6 weeks)		Pediatric Patients* Open-Label (20 weeks)	Pediatric Patients* Vehicle-Controlled (1 year)		Adult Active Comparator (1 year)
	Elidel® Cream (N=267) N (%)	Vehicle (N=136) N (%)	Elidel® Cream (N=335) N (%)	Elidel® Cream (N=272) N (%)	Vehicle (N=75) N (%)	Elidel® Cream (N=328) N (%)
At least 1 AE	182 (68.2%)	97 (71.3%)	240 (72.0%)	230 (84.6%)	56 (74.7%)	256 (78.0%)
Infections and Infestations						
Upper Respiratory Tract Infection NOS	38 (14.2%)	18 (13.2%)	65 (19.4%)	13 (4.8%)	6 (8.0%)	14 (4.3%)
Nasopharyngitis	27 (10.1%)	10 (7.4%)	32 (19.6%)	72 (26.5%)	16 (21.3%)	25 (7.6%)
Skin Infection NOS	8 (3.0%)	9 (5.1%)	18 (5.4%)	6 (2.2%)	3 (4.0%)	21 (6.4%)
Influenza	8 (3.0%)	1 (0.7%)	22 (6.6%)	36 (13.2%)	3 (4.0%)	32 (9.8%)
Ear Infection NOS	6 (2.2%)	2 (1.5%)	19 (5.7%)	9 (3.3%)	1 (1.3%)	2 (0.6%)
Otitis Media	6 (2.2%)	1 (0.7%)	10 (3.0%)	8 (2.9%)	4 (5.3%)	2 (0.6%)
Impetigo	5 (1.9%)	3 (2.2%)	12 (3.6%)	11 (4.0%)	4 (5.3%)	8 (2.4%)
Bacterial Infection	4 (1.5%)	3 (2.2%)	4 (1.2%)	3 (1.1%)	0	6 (1.8%)
Folliculitis	3 (1.1%)	1 (0.7%)	3 (0.9%)	6 (2.2%)	3 (4.0%)	20 (6.1%)
Sinusitis	3 (1.1%)	1 (0.7%)	11 (3.3%)	6 (2.2%)	1 (1.3%)	2 (0.6%)
Pneumonia NOS	3 (1.1%)	1 (0.7%)	5 (1.5%)	0	1 (1.3%)	1 (0.3%)
Pharyngitis NOS	2 (0.7%)	2 (1.5%)	3 (0.9%)	22 (8.1%)	2 (2.7%)	3 (0.9%)
Pharyngitis Streptococcal	2 (0.7%)	2 (1.5%)	10 (3.0%)	0	<1%	0
Molluscum Contagiosum	2 (0.7%)	0	4 (1.2%)	5 (1.8%)	0	0
Staphylococcal Infection	1 (0.4%)	5 (3.7%)	7 (2.1%)	0	<1%	3 (0.9%)
Bronchitis NOS	1 (0.4%)	3 (2.2%)	4 (1.2%)	29 (10.7%)	6 (8.0%)	8 (2.4%)
Herpes Simplex	1 (0.4%)	0	4 (1.2%)	9 (3.3%)	2 (2.7%)	13 (4.0%)
Tonsillitis NOS	1 (0.4%)	0	3 (0.9%)	17 (6.3%)	0	2 (0.6%)
Viral Infection NOS	2 (0.7%)	1 (0.7%)	1 (0.3%)	18 (6.6%)	1 (1.3%)	0
Gastroenteritis NOS	0	3 (2.2%)	2 (0.6%)	20 (7.4%)	2 (2.7%)	6 (1.8%)
Chickenpox	2 (0.7%)	0	3 (0.9%)	8 (2.9%)	3 (4.0%)	1 (0.3%)
Skin Papilloma	1 (0.4%)	0	2 (0.6%)	9 (3.3%)	<1%	0
Tonsillitis Acute NOS	0	0	0	7 (2.6%)	0	0
Upper Respiratory Tract Infection Viral NOS	1 (0.4%)	0	3 (0.9%)	4 (1.5%)	0	1 (0.3%)
Herpes Simplex Dermatitis	0	0	1 (0.3%)	4 (1.5%)	0	2 (0.6%)
Bronchitis Acute NOS	0	0	0	4 (1.5%)	0	0
Eye Infection NOS	0	0	0	3 (1.1%)	<1%	1 (0.3%)
General Disorders and Administration Site Conditions						
Application Site Burning	28 (10.4%)	17 (12.5%)	5 (1.5%)	23 (8.5%)	5 (6.7%)	85 (25.9%)
Pyrexia	20 (7.5%)	12 (8.8%)	41 (12.2%)	34 (12.5%)	4 (5.3%)	4 (1.2%)
Application Site Reaction NOS	8 (3.0%)	7 (5.1%)	7 (2.1%)	9 (3.3%)	2 (2.7%)	48 (14.6%)
Application Site Irritation	8 (3.0%)	8 (5.9%)	3 (0.9%)	1 (0.4%)	3 (4.0%)	21 (6.4%)
Influenza Like Illness	1 (0.4%)	0	2 (0.6%)	5 (1.8%)	2 (2.7%)	6 (1.8%)
Application Site Erythema	1 (0.4%)	0	0	6 (2.2%)	0	7 (2.1%)
Application Site Pruritus	3 (1.1%)	2 (1.5%)	2 (0.6%)	5 (1.8%)	0	18 (5.5%)

Respiratory, Thoracic and Mediastinal Disorders						
Cough	31 (11.6%)	11 (8.1%)	31 (9.3%)	43 (15.8%)	8 (10.7%)	8 (2.4%)
Nasal Congestion	7 (2.6%)	2 (1.5%)	6 (1.8%)	4 (1.5%)	1 (1.3%)	2 (0.6%)
Rhinorrhea	5 (1.9%)	1 (0.7%)	3 (0.9%)	1 (0.4%)	1 (1.3%)	0
Asthma Aggravated	4 (1.5%)	3 (2.2%)	13 (3.9%)	3 (1.1%)	1 (1.3%)	0
Sinus Congestion	3 (1.1%)	1 (0.7%)	2 (0.6%)	<1%	<1%	3 (0.9%)
Rhinitis	1 (0.4%)	0	5 (1.5%)	12 (4.4%)	5 (6.7%)	7 (2.1%)
Wheezing	1 (0.4%)	1 (0.7%)	4 (1.2%)	2 (0.7%)	<1%	0
Asthma NOS	2 (0.7%)	1 (0.7%)	11 (3.3%)	10 (3.7%)	2 (2.7%)	8 (2.4%)
Epistaxis	0	1 (0.7%)	0	9 (3.3%)	1 (1.3%)	1 (0.3%)
Dyspnea NOS	0	0	0	5 (1.8%)	1 (1.3%)	2 (0.6%)
Gastrointestinal Disorders						
Abdominal Pain Upper	11 (4.1%)	6 (4.4%)	10 (3.0%)	15 (5.5%)	5 (6.7%)	1 (0.3%)
Sore Throat	9 (3.4%)	5 (3.7%)	15 (5.4%)	22 (8.1%)	4 (5.3%)	12 (3.7%)
Vomiting NOS	8 (3.0%)	6 (4.4%)	14 (4.2%)	18 (6.6%)	6 (8.0%)	2 (0.6%)
Diarrhea NOS	3 (1.1%)	1 (0.7%)	2 (0.6%)	21 (7.7%)	4 (5.3%)	7 (2.1%)
Nausea	1 (0.4%)	3 (2.2%)	4 (1.2%)	11 (4.0%)	5 (6.7%)	6 (1.8%)
Abdominal Pain NOS	1 (0.4%)	1 (0.7%)	5 (1.5%)	12 (4.4%)	3 (4.0%)	1 (0.3%)
Toothache	1 (0.4%)	1 (0.7%)	2 (0.6%)	7 (2.6%)	1 (1.3%)	2 (0.6%)
Constipation	1 (0.4%)	0	2 (0.6%)	10 (3.7%)	<1%	0
Loose Stools	0	1 (0.7%)	4 (1.2%)	<1%	<1%	0
Reproductive System and Breast Disorders						
Dysmenorrhea	3 (1.1%)	0	5 (1.5%)	3 (1.1%)	1 (1.3%)	4 (1.2%)
Eye Disorders						
Conjunctivitis NEC	2 (0.7%)	1 (0.7%)	7 (2.1%)	6 (2.2%)	3 (4.0%)	10 (3.0%)
Skin & Subcutaneous Tissue Disorders						
Urticaria	3 (1.1%)	0	1 (0.3%)	1 (0.4%)	<1%	3 (0.9%)
Acne NOS	0	1 (0.7%)	1 (0.3%)	4 (1.5%)	<1%	6 (1.8%)
Immune System Disorders						
Hypersensitivity NOS	11 (4.1%)	6 (4.4%)	16 (4.8%)	14 (5.1%)	1 (1.3%)	11 (3.4%)
Injury and Poisoning						
Accident NOS	3 (1.1%)	1 (0.7%)	1 (0.3%)	<1%	1 (1.3%)	0
Laceration	2 (0.7%)	1 (0.7%)	5 (1.5%)	<1%	<1%	0
Musculoskeletal, Connective Tissue and Bone Disorders						
Back Pain	1 (0.4%)	2 (1.5%)	1 (0.3%)	<1%	0	6 (1.8%)
Arthralgias	0	0	1 (0.3%)	3 (1.1%)	1 (1.3%)	5 (1.5%)
Ear and Labyrinth Disorders						
Earache	2 (0.7%)	1 (0.7%)	0	8 (2.9%)	2 (2.7%)	0
Nervous System Disorders						
Headache	37 (13.9%)	12 (8.8%)	38 (11.3%)	69 (25.4%)	12 (16.0%)	23 (7.0%)

*Ages 2-17 years

OVERDOSAGE

There has been no experience of overdose with Elidel® (pimecrolimus) Cream 1%. No incidents of accidental ingestion have been reported. If oral ingestion occurs, medical advice should be sought.

DOSAGE AND ADMINISTRATION

Apply a thin layer of Elidel® (pimecrolimus) Cream 1% to the affected skin twice daily and rub in gently and completely. Elidel may be used on all skin surfaces, including the head, neck, and intertriginous areas.

Elidel should be used twice daily for as long as signs and symptoms persist. Treatment should be discontinued if resolution of disease occurs. If symptoms persist beyond 6 weeks, the patient should be re-evaluated.

The safety of Elidel Cream under occlusion, which may promote systemic exposure, has not been evaluated. **Elidel Cream should not be used with occlusive dressings.**

HOW SUPPLIED

Elidel® (pimecrolimus) Cream 1% is available in tubes of 30 grams, 60 grams, and 100 grams.

30 gram tube .....NDC 0078-0375-46

60 gram tube NDC 0078-0375-49

100 gram tube .....NDC 0078-0375-63

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). Do not freeze.

NOVARTIS

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Wehr, Germany

Distributed by:
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East Hanover, NJ 07936

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