6.1 Clinical Trials Experience

Topical pimecrolimus emulsion (1%) has been evaluated in a 12-week, double-blind, vehicle-controlled, parallel-group, 3-arm study in 1010 subjects with moderate to severe atopic dermatitis. In this study, 54% of subjects treated with topical calcineurin inhibitors had a 75% or greater improvement in their signs and symptoms as compared to 54% of vehicle-treated subjects. In a second clinical trial, 843 subjects with moderate to severe atopic dermatitis were treated for 24 weeks with 1% topical pimecrolimus or vehicle. In this study, 45% of subjects treated with topical calcineurin inhibitors demonstrated a 75% or greater improvement in their signs and symptoms as compared to 32% of vehicle-treated subjects.

Two identically designed 6-week trials with their open label extensions were conducted, respectively, in 843 and 328 subjects, 68% of whom were children and young adolescents. The open label extensions followed treatment periods of 6-12 weeks. In these clinical studies, 54% and 45% of the 1% pimecrolimus cream treated subjects respectively, and 56% and 45% of the vehicle-treated subjects respectively, demonstrated a 75% or greater improvement in their signs and symptoms. In the large 12-week vehicle-controlled clinical trial, 68% of vehicle-treated subjects used corticosteroids during the trial.

In a 24-week vehicle-controlled, parallel group study in 1171 subjects with moderate to severe atopic dermatitis, 48 (4%) of the 1171 ELIDEL Cream, 1% treated subjects and 54% of vehicle-treated subjects demonstrated a ≥ 75% improvement of signs and symptoms.

68% of vehicle-treated subjects used corticosteroids during the trial. In addition, a higher incidence of upper respiratory symptoms were reported in the pimecrolimus treated group than in the vehicle-treated group.

6.1.1 Adverse Reactions

Discontinuations for AEs were primarily due to adverse dermatologic events which were predominantly dry skin, pruritus, and eczematous skin disorders. In the large 12-week vehicle-controlled clinical trial, 23% of the 1% pimecrolimus cream treated subjects, and 39% of vehicle-treated subjects discontinued due to adverse events. In infants of less than one year of age, the incidence of upper respiratory symptoms, conjunctivitis, and epistaxis was greater in the topical pimecrolimus cream group than in the vehicle group. No differences in the incidence of serious adverse events were noted between the topical pimecrolimus cream and vehicle groups. Two cases of septic arthritis have been reported in infants less than one year of age in clinical trials conducted with ELIDEL Cream, 1% (n = 2443).

Topical pimecrolimus emulsion (1%) is not indicated for use in children less than 2 years of age

6.2 Cytotoxicity

The potential effects of pimecrolimus on the skin were investigated in 28 pediatric subjects with atopic dermatitis (20%-80% body surface area involvement). Cytotoxicity was evaluated after brief applications of topical pimecrolimus emulsion (1%) and pimecrolimus was found to be non-cytotoxic in pediatric subjects.

6.3 Rebound Efficacy

ECG monitoring during double-blind treatment periods of 12 weeks with ELIDEL Cream, 1% in pediatric subjects ages 2-17 was application limited to areas of involvement with atopic dermatitis. Rebound efficacy was assessed at 20 weeks after treatment discontinuation with ELIDEL Cream, 1% or vehicle.

8.1 Pregnancy

Pimecrolimus is not known to be excreted in human milk. In rat studies, pimecrolimus was not detected in milk. Because many drugs are excreted in human milk, and 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.

8.2 Carcinogenesis, Mutagenesis, Impairment of Fertility

An oral carcinogenicity study was conducted in rats with a daily exposure of approximately 22 hours (271X MRHD based on AUC comparisons). No statistically significant increases in adverse endpoints were observed. In a dermal developmental study, significant increases in skeletal defects, including ribos, were observed in rats at a dose of 10 mg/kg/day with daily exposure of approximately 22 hours (12X MRHD based on AUC comparisons).

6.1.2 Pimecrolimus Pharmacokinetics

Pimecrolimus (pimecrolimus) is metabolized by CYP2C19. The mean steady-state AUC was 178% greater in the presence of clarithromycin than in the absence of clarithromycin.

6.4.2 Drug Interactions

In vitro and in vivo data indicate that pimecrolimus (pimecrolimus) is not a substrate or an inhibitor of CYP enzymes and does not inhibit P-gp. Pimecrolimus is not known to influence the blood levels of other drugs. Pimecrolimus is not known to influence the blood levels of other drugs in the same way as those that inhibit CYP enzymes or P-gp. However, pimecrolimus may affect systemic drug concentrations in patients who are taking drugs that are metabolized by CYP enzymes or P-gp. The effect of pimecrolimus on plasma concentrations of other drugs has not been studied. Pimecrolimus is not known to influence the blood levels of other drugs. The safety of pimecrolimus in the presence of drugs that affect serum blood levels is not known. The safety of pimecrolimus in the presence of drugs that affect serum blood levels is not known.

6.1.4 Pimecrolimus Metabolism

Pimecrolimus is metabolized by CYP2C19. The mean steady-state AUC was 178% greater in the presence of clarithromycin than in the absence of clarithromycin.
Metabolism bound to proteins over the pimecrolimus concentration range of Body Surface Area (BSA) involvement] for periods up to a year, a
Absorption (Th2-type) cytokine synthesis in human T-cells. In addition, pimecrolimus inhibits at nanomolar concentrations Interleukin-2 and to macrophilin-12 (FKBP-12) and inhibits the calcium-dependent
sodium cetostearyl sulphate, sodium hydroxide, stearyl alcohol, [22.3.1.04,9]octacos-18-ene-2,3,10,16-tetraone.
pimecrolimus, the immunosuppressant 33-epi-chloro-derivative of ELIDEL Cream, 1%, for topical use, contains the compound
Phase 3 trials. Clinical trials of ELIDEL Cream, 1% did not include
8.5 Geriatric Use
At this time, a causal relationship between these findings and ELIDEL.
No drug-related tumors were noted in the rat oral carcinogenicity oral (gavage) rat carcinogenicity study in 5 mg/kg/day pimecrolimus control treated male and female animals. In addition, a significant incidence of neoplasms was observed in the skin or other organs up to metabolic profile as by the dermal route. In a mouse dermal carcinogenicity comparison). However, the latency time to lymphoma formation was ethanolic solution at a dose of 25 mg/kg/day (47X MRHD based on 27X MRHD based on AUC comparisons. However, lymphoproliferative response was not observed. No effect on fertility in male rats was noted at 2 mg/kg/day (179-217X MRHD based on AUC comparisons). A no observed adverse effect level (NOAEL) for pimecrolimus was determined in this study. The NOAEL for pimecrolimus was 15 mg/kg/day (60-133X MRHD based on AUC comparisons). No effect on fertility in male rats was noted at 2 mg/kg/day (179-217X MRHD based on AUC comparisons).

ELIDEL Cream, 1% is for external use only. If you get any of these areas, burning or irritation can result of treatment with ELIDEL Cream, 1%. See the end of this Medication Guide for a complete list of side effects.

No drug-related tumors were noted in the rat oral carcinogenicity study in 5 mg/kg/day pimecrolimus control treated male and female animals. In addition, a significant incidence of neoplasms was observed in the skin or other organs up to 1 year. A no observed adverse effect level (NOAEL) for pimecrolimus was determined in this study. The NOAEL for pimecrolimus was 15 mg/kg/day (60-133X MRHD based on AUC comparisons). No effect on fertility in male rats was noted at 2 mg/kg/day (179-217X MRHD based on AUC comparisons). A no observed adverse effect level (NOAEL) for pimecrolimus was determined in this study. The NOAEL for pimecrolimus was 15 mg/kg/day (60-133X MRHD based on AUC comparisons).

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