

ELIDEL[®] (pimecrolimus) Cream 1%

FDA Pediatric Advisory Committee Meeting

May 16, 2011

Presentation Overview

- ◆ US Indication (2006-present)
- ◆ Usage since 2005
- ◆ Medical need
- ◆ Reviews and study update
- ◆ Global DSMB Conclusions
- ◆ Registry update
- ◆ Conclusions

US Indication (2006 – present)

ELIDEL[®] (pimecrolimus) Cream 1% is indicated as *second-line* therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis (AD) in non-immunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable.

Elidel Cream 1% is not indicated for use in children less than 2 years of age (See *WARNINGS, boxed WARNING, and PRECAUTIONS, Pediatric Use*).

US-Label: Boxed Warning

Long-term Safety of Topical Calcineurin Inhibitors Has Not Been Established

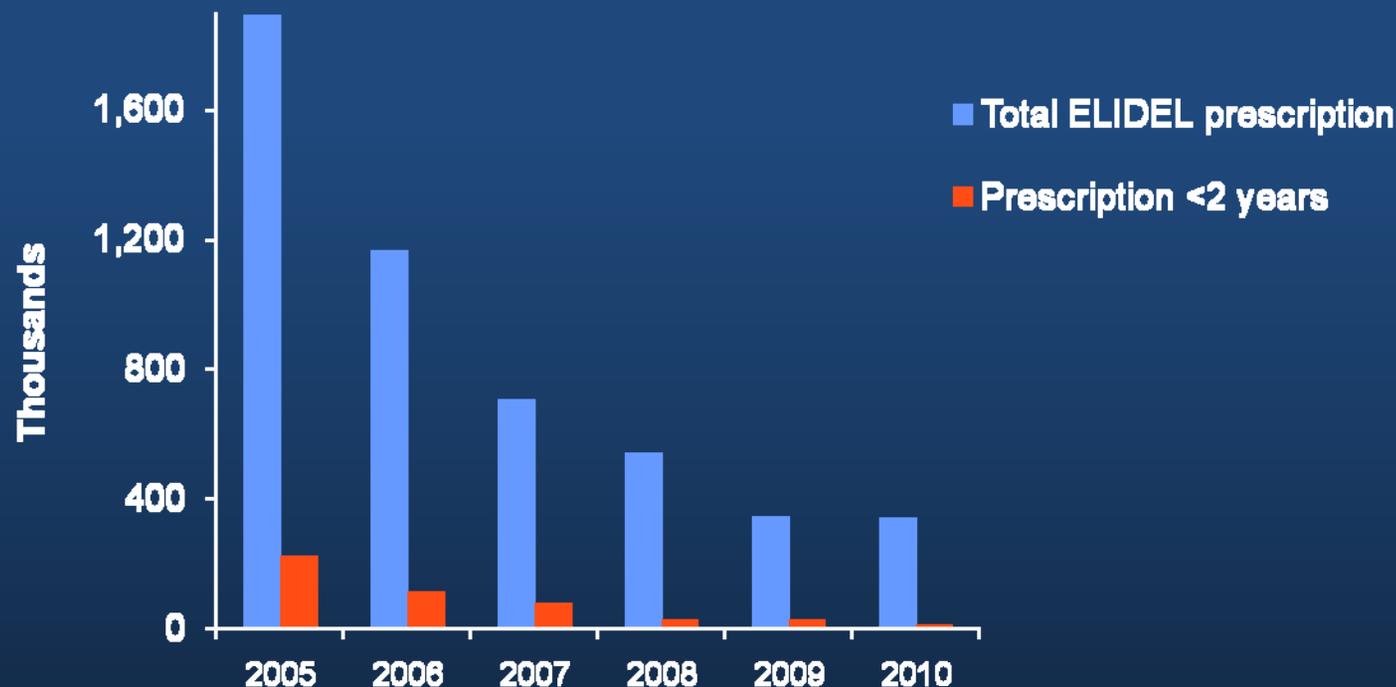
Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including ELIDEL Cream.

Therefore:

- Continuous long-term use of topical calcineurin inhibitors, including ELIDEL Cream, in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis.
- ELIDEL Cream is not indicated for use in children less than 2 years of age.

Significant reduction in Elidel Cream 1% use in the US from 2005 to 2010

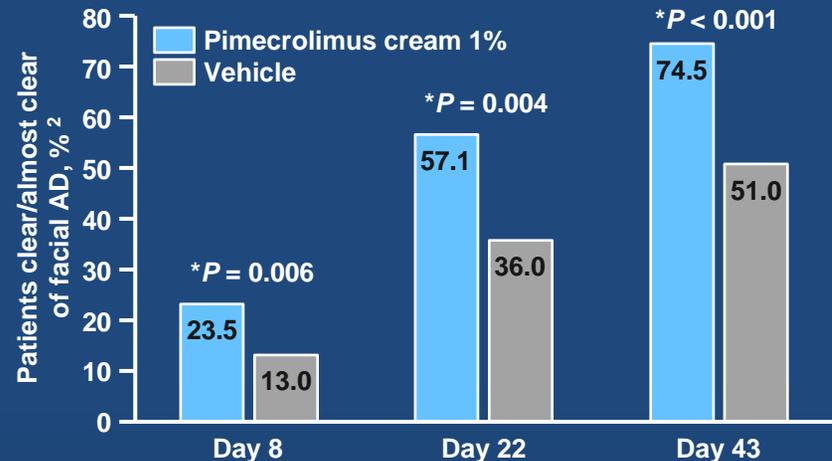
- ◆ Significant decline in prescription
- ◆ Overall prescription decline by 81.8%
- ◆ 98% decrease in Elidel prescription in children <2 years



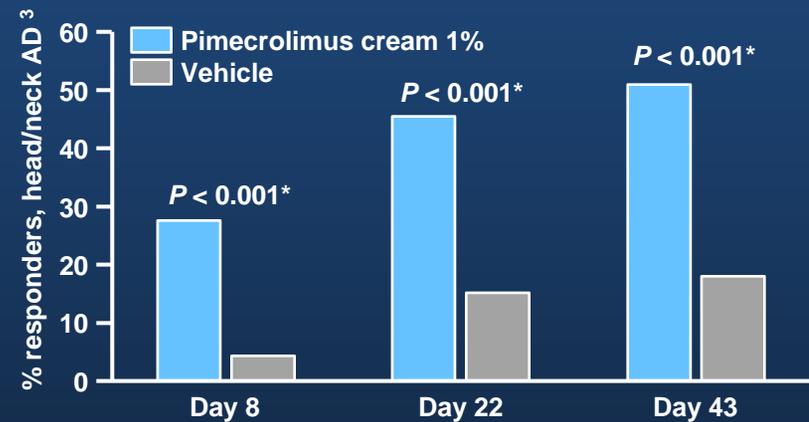
Data supplied by IMS Health in March 2011 covering the period 2005 – 2010. 2% of prescriptions were for patients of unspecified age.

Elidel fulfills a medical need in the treatment of AD patients for whom it is indicated

- ◆ AD is associated with symptoms that can result in skin damage, secondary infection, sleep loss and significant impairment of quality of life¹
- ◆ Elidel 1% Cream is an important therapeutic alternative to TCS for mild to moderate AD
- ◆ Clinical studies show that Elidel Cream 1% effectively controls:
 - Eczema and pruritus in children with facial dermatitis intolerant to TCS²
 - Head and neck dermatitis in adolescents and adults intolerant to TCS³
 - Improvement of skin atrophy may occur during TCS-free intervals³



*Fisher's exact test of difference in proportions between groups.



[†]Treatment responder was defined as at least a 60% change from baseline in head and neck EASI score

*Fisher's exact test of difference in proportions between groups.

¹ Zuberbier T, et al (2006) J Allergy Clin Immunol.; 118(1):226-32.

² Hoeger PH, et al (2009) Br.J.Dermatol.; 160 (2):415-422.

³ Murrell DF, et al (2007) Br.J.Dermatol.; 157 (5):954-959.

No increased risk of malignancies in association with Elidel Cream 1%

Study	Design	Outcome of interest	Key results (related to Elidel)
<i>Hui et al 2009</i> (not Novartis-sponsored)	Cohort study in Kaiser Permanente California databases in 953,064 AD/eczema patients of all ages	Cancer overall, specific cancer subtypes (including lymphoma)	No increased risk of cancer/cancer subtypes in association with Elidel Cream
<i>Arellano et al 2007</i>	Case-control (c-c) study nested in a cohort of >293,000 AD patients of all ages from large U.S. health claims database (PharMetrics)	Lymphoma	<ul style="list-style-type: none"> ◆ No increased lymphoma risk in association with Elidel Cream compared to non-use ◆ AD independently associated with increased lymphoma risk
<i>Arellano et al 2009</i>	Nested c-c study in a cohort of patients < 80 yrs from U.K.-based electronic medical record database (THIN)	Lymphoma	<ul style="list-style-type: none"> ◆ Exposure prevalence to Elidel Cream too low for meaningful analyses; no lymphoma cases identified among Elidel Cream users ◆ AD independently associated with increased lymphoma risk
<i>Schneeweiss et al 2009</i>	Cohort study in large U.S. health claims database (United Health Care) in cohorts including initiators of topical ELIDEL, topical tacrolimus, and medium-/high-potency TCS, along with untreated dermatitis cohort and cohort without dermatitis and without TCIs/TCS including a nested c-c analysis (all ages)	Lymphoma	No increased lymphoma risk among initiators of Elidel Cream compared with tacrolimus or medium-/high-potency TCS (in propensity score matched cohort analysis)
<i>Margolis et al 2007</i>	C-c study nested in a cohort of dermatology outpatients with dermatitis including 875 NMSC cases and 1,946 controls (>30 years)	Non-melanoma skin cancer (NMSC)	No increased risk of NMSC in association with Elidel Cream

Additional analyses also suggest no increased risk of malignancies in association with Elidel Cream 1%

- ◆ Systematic Review of Epidemiological Studies by Tennis et al. (BrJDerm, April 2011)
 - Epidemiological studies up to April 2010, conducted in a variety of populations
 - No evidence suggesting an increased risk of lymphomas overall or specific sub-types of lymphoma in association with exposure to topical pimecrolimus
 - No evidence indicating that melanoma or non-melanoma skin cancer is associated with topical pimecrolimus use
- ◆ Case-Control Study on Lymphoma in PharMetrics - C2457T (ICPE congress 2010)
 - No evidence of increased risk of lymphoma overall or specific sub-types of lymphoma in association with exposure to topical pimecrolimus
- ◆ Clinical study C2306 completed in November 2010, enrolled 2,439 patients
 - “A 5-year, multicenter, open-label, parallel group, randomized study to demonstrate the short and long-term safety of Elidel Cream 1% in mild to moderate AD in infants (3 to <12 months of age)”
- ◆ Safety update review completed in July 2010 by the FDA
 - Data from all non-clinical and clinical studies of Elidel was assessed as per FDA request

Global Data and Safety Monitoring Board identified no safety signals associated with Elidel Cream 1%

- ◆ Independent Global DSMB established in 2006
- ◆ Meets twice per year to review:
 - Study-specific DSMB summary reports for ongoing studies
 - Medwatch forms of malignancies and other clinically relevant SAEs
 - Pooled analysis of all AE/SAEs from completed clinical studies
 - Post-marketing data
- ◆ “The DSMB concludes on the basis of the information provided between 2007 and 2010 (inclusive) that there are no indications of an increased risk of development of cancers following the use of pimecrolimus. There is no specific pattern of certain type of cancers developing, especially lymphomas including cutaneous T-cell lymphoma and no pattern of lymphoproliferation short of malignancy has been reported.”
 - Last Global DSMB meeting, held on January 19-20, 2011

Ongoing PEER registry study reveals no safety findings to date

- ◆ Pediatric Eczema Elective Registry (PEER, C2311):
 - “A prospective 10 year observational registry of pediatric patients (age ≥ 2 to ≤ 17 years) with AD who have used Elidel Cream 1%”
 - SEER database to provide comparator data for the incidence of systemic malignancies observed in the general population
- ◆ 8,000 patients to be enrolled with an expected follow up period of 10 years
- ◆ Study initiated in Nov 2004; 5,791 patients enrolled as of March 23, 2011
 - 16,986 patient-years of follow-up have been accumulated to date
- ◆ Both C2311 DSMB and Global DSMB reported “No safety findings” to date

Conclusion

- ◆ ELIDEL[®] (pimecrolimus) Cream 1% fulfills a medical need in those patients for whom it is indicated
- ◆ Studies suggest no increased risk of malignancies overall, lymphoma, or non-melanoma skin cancer in association with Elidel Cream 1%
- ◆ Benefit/ risk profile of Elidel Cream 1% is favorable in the approved population
- ◆ Current prescribing information, including medication guide, adequately reflect the known safety profile of Elidel Cream 1%