



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration  
Rockville, MD 20857

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TO: Jonathan K. Wilkin, M.D., Director  
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SUBJECT: ODS Postmarketing Safety Review (PID 040609)  
Update - All Adverse Events in Children Less Than 2 years, and Update on Malignancy Related  
Events in all Age Groups  
Drug: Pimecrolimus (Elidel®, NDA 21-302)

**\*\*\* Confidential: Contains IMS Health Data\*\*\***

**Data Cleared by IMS January 26, 2005 to share with Audience/Intent: Pediatric Advisory Subcommittee members, Public, Media, Web**

**EXECUTIVE SUMMARY**

This document summarizes all reports of adverse events associated with topical pimecrolimus use in children less than two years of age; IMS drug usage data in children less than two years of age; and malignancy-related adverse event reports in all age groups. The information in this review is provided in preparation of an upcoming label revision meeting with OCTAP/DPDD/HFD-960, scheduled for October 4, 2004. We conducted hands-on review of reports with serious outcomes, and reports describing malignancy related adverse events.

We searched the AERS database on September 22, 2004 for all adverse event reports associated with pimecrolimus use in children less than two years old, as well as malignancy-related reports in all age groups. Since approval on December 13, 2001 we identified 54 reports in children less than two years old, and eight malignancy-related reports in all age groups. The majority of cases were domestic, and were reported for male patients. The median age in the non-malignancy-related cases was six months, with an age range from seven weeks to 23 months. Pimecrolimus was used primarily to treat atopic dermatitis. The majority of the 54 cases reported skin-related adverse events (27), followed by systemic effects (13), many of which are labeled. The most serious outcomes reported included hospitalization in 15 children, and one case of congenital anomaly.

The subset of hospitalized cases reported primarily systemic adverse events, followed by skin-related reactions, of which many are labeled events. One foreign case reporting liver enzyme elevations, and a positive dechallenge-

rechallenge response concomitantly used an anti-histamine product which was started and discontinued the same time as pimecrolimus. Although, liver enzyme elevation is listed as an adverse event for topical tacrolimus<sup>1</sup>, another calcineurin inhibitor, we are unsure of the role of pimecrolimus in this single report of liver enzyme elevation.

The congenital anomaly case occurred in a mother treated with pimecrolimus who delivered a pre-term child with multiple congenital anomalies, including Noonan syndrome, a genetic disorder. The role of topical pimecrolimus in the development of the genetic disorder is unknown.

We found eight cases reporting malignancy-related adverse events. There were no cases reported in children less than two years old. The patients ranged in age from two to 61 years, with at least one-half of the reports occurring in children less than 16 years old. All of the malignancy cases reported non-serious outcomes. The majority of the cases were domestic, and pimecrolimus was used primarily to treat atopic dermatitis. The cases reported a variety of malignancy-related events, although no specific pattern could be identified at this time. Two new pediatric cases since the September 2003 ODS analysis reported non-Hodgkin's lymphoma and "tumor" – papilloma. The role of pimecrolimus in these cases is unknown.

We also looked at drug use information and found that the overall number of prescriptions for pimecrolimus more than doubled from 2002 to 2003, from 1,532,000 to 3,445,000. It is possible that drug indication data for pimecrolimus, as well as drug use data for the topical corticosteroids may help to explain the increased in use of pimecrolimus. It is possible that the increased use of pimecrolimus may in part reflect a shift from using topical corticosteroids in the treatment of mild to moderate atopic dermatitis. We also note that nearly 13% of all pimecrolimus is used in children less than two years old, an age for which pimecrolimus is not indicated. Similar to the September 2003 analysis, we did not obtain information concerning the duration of pimecrolimus use<sup>2</sup>.

The majority of the adverse events found in children less than two years old are expected and reflected in the product label. We have received eight cases of malignancy-related adverse events occurring in children and adults, but none in children less than two years old. The reports of adverse events with serious outcomes, although many of them labeled, as well as the malignancy related events, warrants further monitoring.

### **Background/Relevant Product Labeling**

Elidel® (pimecrolimus) Cream 1% was approved December 13, 2001 for short-term and intermittent long-term therapy in the treatment of *mild to moderate* atopic dermatitis. Elidel® was approved for use in non-immunocompromised patients at least 2 years old, in whom the use of alternative, conventional therapies is deemed

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<sup>1</sup> Electronic PDR – Protopicl®, extracted September 2004

<sup>2</sup> Pitts MR. ODS Safety Review – Pimecrolimus NDA 21-302, All Adverse Events, PID # 0303434, September 24, 2003

inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or intolerant of alternative, conventional therapies<sup>3</sup>.

On September 23, 2003 ODS completed a review of all adverse events reported for topical pimecrolimus<sup>4</sup>. The September 2003 review analyzed 32 pediatric cases, 14 of whom were less than two years old. The skin was the single most affected organ system in the pediatric group, as well as in the subgroup of children less than two years old. The September 2003 analysis reviewed two cases of tumor growth in the pediatric group, although neither case occurred in children less than two years old. The reader is referred to the September 2003 review if more details are required. Information from that review was presented at the October 29-30, 2003 Pediatric Advisory Subcommittee of the Anti-Infectives Drugs Advisory Committee.<sup>5</sup>

This document is organized into two parts:

- Part I provides AERS demographic information, and IMS drug use data for children less than 2 years old
- Part II analyzes all cases describing tumor growth.

## **LABELING<sup>6</sup>**

The *Clinical Pharmacology* section of the pimecrolimus label indicates systemic absorption of pimecrolimus occurs in both adult and pediatric patients with atopic dermatitis. Pimecrolimus blood concentrations measured in a pediatric population aged 2 to 14 years was comparable to the adult population.<sup>7</sup> However, in a second pediatric group aged 3 to 23 months with 10 – 92% body surface area involvement, a higher proportion of detectable blood levels was seen, ranging from 0.1 ng/ml to 2.6 ng/ml.<sup>8</sup> 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 patients.

The *Precautions Section* of the pimecrolimus label includes, but is not limited to the following systemic and local adverse events:

- Lymphadenopathy
- Papilloma or warts
- Local symptoms such as skin burning

The *Adverse Reaction Section* includes, but is not limited to gastroenteritis, sinus congestion, conjunctivitis and breathing difficulties.

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<sup>3</sup> Electronic PDR - Elidel®, extracted September 2004

<sup>4</sup> Pitts MR. ODS Safety Review – Pimecrolimus NDA 21-302, All Adverse Events, PID # 0303434, September 24, 2003

<sup>5</sup> Pediatric Subcommittee of the Anti-Infectives Drugs Advisory Committee, October 29 – 30, 2003

<sup>6</sup> Electronic PDR – Elidel®, extracted September 2004

<sup>7</sup> Electronic PDR– Elidel®, extracted September 2004

<sup>8</sup> Limit of quantification 0.1 ng/ml

## LITERATURE SEARCH

A MEDLINE search of the English-language literature published from 1966 to 2004 did not produce case reports describing pimecrolimus associated adverse events.

### **Part I: AERS Demographic Information, and IMS Drug Use Data For Children Less Than 2 Years Old**

On September 22, 2004 we searched the AERS database for all reports of adverse events associated with pimecrolimus use in children less than two years old. We found 54 reports that listed pimecrolimus as a suspect drug. Forty-one reports were US, and 13 were foreign. There were 27 males, 23 females and four reports with an unreported gender. The patients were aged seven weeks to 23 months old, with a median age of six months (n = 52). The most serious outcome was hospitalization in 15 reports. There was one report of a congenital anomaly, and the remaining 38 reported non-serious outcomes. There were no reports of death. Pimecrolimus was primarily used to treat atopic dermatitis (43), followed by dry skin (2), dermatitis (1) and neurodermatitis (1). Seven reports did not report the indication for use. The majority of adverse events reported were skin-related (27), followed by systemic reactions (13). There were five reports describing both skin-related and systemic reactions; three reporting accidental exposure; and one report each describing crying, papilloma and congenital anomaly. The report types included expedited (26), periodic (25) and direct (3). Reports were submitted in 2002 (5), 2003 (21) and 2004 (28). Please keep in mind that these are reports and not patients, and duplicate<sup>9</sup> reports may have been submitted for the same patient. An analysis of the serious reports, including the one reporting congenital anomaly follows.

#### **Hospitalization (15) and Congenital Anomaly Reports (1)**

There were 15 reports of hospitalization, and one report of congenital anomaly associated with pimecrolimus use in children less than two years old. Four<sup>10</sup> of the hospitalization cases were previously analyzed in the September 2003 Elidel Safety Review. Six hospitalizations and the congenital anomaly report were US. The remaining nine hospitalization reports were of foreign origin. Hospitalization was reported for children aged four months to 22 months, with a median age of six months (n = 14). Thirteen reported using pimecrolimus for atopic dermatitis, and three did not report the indications for use. One case was coded for a positive dechallenge response. The congenital anomaly case was a domestic case where the mother used pimecrolimus for approximately two years, including during the time of her pregnancy. A preterm baby was delivered at 33 weeks diagnosed with ventriculoseptal defects, Noonan syndrome, broad thumbs, low set ears, gastroesophageal reflux, postnatal growth failure, cardiomyopathy and pneumonic stenosis. The mother had used pimecrolimus on her eyelids and elbows (< 1% BSA) once a day.

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<sup>9</sup> Duplicate reports may have included follow-up information from the manufacturer, or multiple reporters (e.g., family member, physician, pharmacist, nurse, etc.).

<sup>10</sup> FDA Case #: 3888675, 3810623, 3918360 and 3963635

The majority of cases reported systemic reactions, including labeled and unlabeled events. Labeled systemic reactions included gastroenteritis, sinus congestion, conjunctivitis, breathing difficulties, and hypersensitivity reactions. Unlabeled systemic reactions included convulsions and spasms, liver enzyme elevation and type 1 diabetes. Stomatitis was reported for two children. Local dermatologic reactions were also reported, including localized swelling, redness, urticaria and itching. There were no reports of malignancy-related adverse events reported in this subgroup. Four hospitalization cases were previously reviewed in the September 2003 analysis and will not be re-presented here, however, we do provide a brief narrative of the eleven new hospitalization cases in Appendix 1 of this document.

### Drug Use

The following table summarizes projected U.S. prescriptions dispensed by retail pharmacies (chain, independent, food stores, and mail order) by calendar years from 2002, through August 2004. *This information is from IMS Health Prescription Audit Plus™ (on-line) and is not authorized for use outside the FDA without IMS Health clearance.*

#### Prescriptions of Pimecrolimus Dispensed – By Year

	2004 YTD <sup>11</sup>	2003	2002	Total
<b>Pimecrolimus</b>	2,751,000	3,445,000	1,532,000	7,728,000

IMS Health National Prescription Audit Plus™, 2002 – 2004, data extracted September 2004

The number of prescriptions for Elidel® has increased from 1,532,000 in 2002 to more than double in 2003. The trend of increasing prescriptions continued from January to August, 2004.

**Age: Appearances** (already in thousands, do not add three zero's to each figure)

<b>Pimecrolimus</b>	<b>Jan – Jul 2004</b>	<b>2003</b>	<b>2002</b>	<b>Total</b>	<b>Percentage</b>
Less Than 2 years old	197,000	317,000	143,000	657,000	13%
2 to 11 years	523,000	829,000	508,000	1,860,000	38%
12 to 16 years	557,000	129,000	97,000	783,000	16%
017 years and older	65,000	923,000	631,000	1,619,000	33%
<b>Total</b>	1,342,000	2,198,000	1,379,000	4,919,000	100%

IMS Health National Disease & Therapeutic Index™, 2001 to 2004, data extracted September, 2004

We obtained drug usage information stratified by age from IMS Health National Disease and Therapeutic Index™ (NDTI)<sup>12</sup>. Drug use age data is based on “appearances” as determined by patient visits to office-based practitioners in the continental US. Appearance data is different from the number of prescriptions dispensed. Based on appearance data, IMS Health NDTI™ shows 67% of all pimecrolimus is used in children aged 16 years and younger, and 13% of use occurred in children less than two years old. When use is analyzed on an annual basis, the

<sup>11</sup> January to August 2004

largest increase in use occurred in children aged 12 to 16 years old, from 7% in 2002 to slightly more than 41% from January to July 2004. The amount of use for children less than two years old was approximately the same, 10.4% in 2002 compared to 14.7% during the first seven months of 2004. Similar to the September 2003 analysis, we did not obtain information concerning the duration of pimecrolimus use, or the indication for use.

## **Part II: Malignancy Related Reports**

On September 22, 2004 we searched the AERS database for all reports of pimecrolimus-associated malignancies in all patient age groups using the following search terms and levels:

- Granuloma – PT
- Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps) - SOC

We found eight cases reporting malignancy related adverse events. The patients were aged two years (2), five years (1), 53 (1), 58 (1) and 61 (1). Two cases did not provide the age of the patients, although one was described as a child. There were four males and three females, and one case of unreported gender. Six of the cases were US, and two were foreign. Pimecrolimus was used to treat atopic dermatitis (5), vitiligo (1) rosacea (1) and was unreported in one patient. A variety of malignancy-related events were reported including non-Hodgkin's lymphoma (1), "tumor" papilloma (1), granulomatous lymphadenitis (1), facial tumor (1), lymphoma (2), intraductal papilloma of the nipple (1), and basal cell carcinoma. The role of pimecrolimus in the development of these malignancies is unknown, since some of the cases reported diagnosis that occurred as soon as one to two weeks of starting pimecrolimus. A non-serious outcome was reported for all eight of the pimecrolimus-associated malignancy cases. A brief narrative of the cases is provided in Appendix 2 of this document.

## **Discussion/Conclusion**

ODS analyzed adverse event and malignancy-related reports for pimecrolimus in September 2003. This review is an update to the previous review. We found 54 reports submitted since approval for patients less than two-years old. The majority of the 54 cases were domestic and the patients were male. The patients were aged from seven weeks to 23 months, with a median age of six months. Pimecrolimus was used primarily to treat atopic dermatitis. The majority of the adverse events were skin related (27), followed by systemic effects (13), many of which were labeled. The most serious outcomes reported included hospitalization which was coded for fifteen patients and one case of congenital anomaly. In the congenital anomaly case a mother delivered a premature child with a variety of abnormalities after using a small amount (< 1% BSA) of pimecrolimus daily for two years, including the time she was pregnant. The patient was diagnosed with Noonan syndrome, a genetic disorder, as well as other abnormalities. The role of pimecrolimus in the development of this genetic disorder is unlikely.

Additionally, we reviewed fifteen cases of hospitalization in children less than two years old. Four of the cases had been previously reviewed. The majority of the hospitalization cases were foreign. The patients hospitalized were similarly aged (median = 6 months) to all the children under the age of two years. Many of the hospitalized cases reported primarily systemic reactions, followed by skin-related reactions, although the role of pimecrolimus in the development of the reactions was not clear in some cases. Many of the systemic reactions and skin-related reactions are labeled events. One foreign case reporting liver enzyme elevations, and a positive dechallenge-rechallenge response concomitantly used an anti-histamine product which was started and discontinued the same time as pimecrolimus. Although, liver enzyme elevation is listed as an adverse event for topical tacrolimus<sup>13</sup>, another calcineurin inhibitor, we are unsure of the role of pimecrolimus in this single report of liver enzyme elevation.

We also looked at drug use information and found that the overall number of prescriptions for pimecrolimus more than doubled from 2002 to 2003, from 1,532,000 to 3,445,000. It is possible that drug indication data for pimecrolimus, as well as drug use data for the topical corticosteroids may help to explain the increased in use of pimecrolimus from 2002 to 2003. It is possible that the increased use of pimecrolimus may in part reflect a shift from using topical corticosteroids in the treatment of mild to moderate atopic dermatitis. We also note that nearly 13% of all pimecrolimus is used in children less than two years old, an age for which pimecrolimus is not indicated.

We found eight cases reporting malignancy-related adverse events. The patients' ages ranged from two to 61 years, with at least half of the cases occurring in children. There were no reports of malignancy-related adverse events in children less than two years old. The majority of the cases were domestic, and pimecrolimus was used primarily to treat atopic dermatitis. All of the cases reported non-serious outcomes. The cases reported a variety of malignancy-related events, although no specific pattern could be identified at this time. Two new pediatric cases since the September 2003 ODS review reported non-Hodgkin's lymphoma and "tumor" – papilloma. The role of pimecrolimus in these cases is unknown.

Most of the adverse events found in these pediatric cases are expected and reflected in the product label. We have received eight cases of malignancy-related adverse event occurring in children and adults, but none in children less than two years old. The reports of adverse events with serious outcomes, although many of them labeled, as well as the malignancy-related events warrants further monitoring.

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cc:

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<sup>13</sup> Electronic PDR – Protopic®, extracted September 2004

NDA: 21-302

Electronic only cc:

HFD-400/Seligman

HFD-430/Avigan/Karwoski/Nguyen/Pimecrolimus (Drug File)

HFD-540/Nikhar/Wright/Kozma-Fornaro

## Appendix 1: Hospitalization Narratives

**2004 Foreign, FDA 4180292, MCN PHBS2004GR10034.** A 13-month-old male received pimecrolimus for an unknown indication. Approximately two months after starting pimecrolimus the baby was admitted to the hospital to treat gastroenteritis, convulsions and spasms. No further information was provided.

*Reviewers comment: Gastroenteritis is a labeled adverse event in a pediatric and adult open label trial, as well as in a pediatric vehicle controlled trial. Convulsions and spasms are not labeled events, and the role of pimecrolimus is unclear.*

**2004 Foreign, FDA 4173229, MCN PHBS2004IL09320.** A 10-month-old male with a history of atopic dermatitis over his entire body since the age of six months was admitted to the hospital due to aggravation of his atopic dermatitis while receiving treatment with pimecrolimus and mebhydrolin, and for better diagnosis. While in the hospital the patient was noticed to have increased liver enzymes, four months after the starting pimecrolimus, and three months after starting mebhydrolin. The patient's liver enzymes continued to increase with continued use of pimecrolimus, and mebhydrolin. Pimecrolimus and mebhydrolin were discontinued. One week after the discontinuation of both drugs the patient's liver enzymes decreased. One month after discontinuation of both drugs, the child's elevated enzymes were reported as resolving. The patient also had several periods of upper viral respiratory infections while using pimecrolimus and mebhydrolin.

*Reviewers comment: Although a positive dechallenge-rechallenge response is described, it is unclear if the liver enzyme elevations were due to pimecrolimus alone or in combination with the concomitant use of mebhydrolin, an ethylenediamine sedating antihistamine.*

**2004 Foreign, FDA 4131068, MCN PHBS2004CZ05437.** A 5-month-old male received pimecrolimus to treat atopic dermatitis. Seven days later the patient experienced aphthous stomatitis and candida of the oral cavity and the tongue. Pimecrolimus was applied repeatedly during February and March. On each of these occasions, the stomatitis and candida occurred within two days. Pimecrolimus was discontinued and the stomatitis spontaneously disappeared. The oral candida also disappeared. Pimecrolimus was re-started without recurrence of the events. Hospitalization was coded, although not described in the narrative of the report.

*Reviewers comment: Although a positive dechallenge-rechallenge response is described, it is unclear the role of pimecrolimus in the stomatitis and candida.*

**2004 Foreign, FDA 4131055, MCN PHBS2004CA05378.** A one-year-old female received pimecrolimus for an unknown indication. An unknown time later the patient experienced aphthous stomatitis. Although pimecrolimus was discontinued, the stomatitis continued. Hospitalization was coded, although not described in the narrative of the report.

*Reviewers comment: The role of pimecrolimus is uncertain in this report. The report lack sufficient detail to determine temporal relationship, confounders and other information necessary to provide a complete assessment of pimecrolimus' role.*

**2004 Foreign, FDA 4131052, MCN PHBS2004CH05475.** A one-year-old female received pimecrolimus to treat atopic dermatitis located on the thigh and buttocks. After two tubes of pimecrolimus, the patient developed an abscess on the right thigh. The patient was hospitalized for drainage and antibiotic treatment. The reaction abated rapidly with treatment. Pimecrolimus therapy continued

*Reviewers comment: Pimecrolimus is labeled for local reactions, and infections. However, the role of pimecrolimus in the development of the abscess is unclear.*

**2004 US, FDA 4129962, MCN PHEH2004US04324.** A four-month-old female started pimecrolimus for severe atopic dermatitis. Approximately 30 to 45 days after starting the patient stopped breathing, and was hospitalized for a lot of mucous. This was considered a hypersensitivity reaction. The patient had a history of multiple food allergies, but no history of respiratory difficulties. No further information was provided.

*Reviewers comment: Pimecrolimus is labeled for hypersensitivity reactions and respiratory reactions, including rhinorrhea, rhinitis and sinus congestion; however, the role of pimecrolimus is unclear in this patient with a history of multiple food allergies.*

**2004 US, FDA 4099524, MCN PHEH2004US02237.** A six-month-old female started pimecrolimus to treat atopic dermatitis on the “oral area”. Approximately three months later the patient was hospitalized with ketoacidosis and an elevated blood sugar. The patient was diagnosed with type I diabetes. Pimecrolimus was discontinued. The patient was also placed under the care of an endocrinologist. The patient was responding well. The patient has a family history of diabetes.

*Reviewers comment: Pimecrolimus is not labeled for glucose intolerance, and the role of pimecrolimus in this case is unclear. The patient has a positive family history for diabetes.*

**2003 Foreign, FDA 4028293, MCN PHBS2003BR12688.** A six-month-old female was treated with pimecrolimus for atopic dermatitis. Immediately after application the baby experienced swelling, redness and urticaria all over her body. Patient was admitted to the hospital for less than 24 hours. Pimecrolimus was discontinued. The patient was further treated with an oral corticosteroid and antihistamine. The patient slowly recovered. Pimecrolimus was not restarted.

*Reviewers comment: Pimecrolimus is labeled for local skin reactions and hypersensitivity reactions. The temporal relationship of this reaction supports a role for pimecrolimus in the development of these reactions.*

**2003 US, FDA 3989686, MCN PHEH2003US07238.** A 22-month-old male was treated with pimecrolimus for eczema. The patient experienced flare ups at the site of application whenever he went outside. The patient was hospitalized four months later for a cellulitis skin infection on his thigh. Prior to hospitalization the patient was started on cephalexin for cellulitis. The patient used cephalexin on three more occasions, for 10 days per occasion over a three-month time period when his skin was broken and he developed an infection. The patient concomitantly used triamcinolone. Patient continued to use pimecrolimus, although less often.

*Reviewers comment: The role of pimecrolimus in the development of the cellulitis is unclear since the product was continued throughout the outbreaks of cellulitis; however, pimecrolimus is labeled for local skin reactions, as well as localized skin infections.*

**2003 Foreign, FDA 4021069, MCN PHBS2003PH11857.** A five-month-old baby developed inflamed eyes and a clogged nose 20 minutes after an application of pimecrolimus for atopic dermatitis. The patient was hospitalized. Pimecrolimus was discontinued, the patient recovered and was discharged. No further information was provided.

*Reviewers comment: Pimecrolimus is labeled for sinus congestion and conjunctivitis.*

**2003 Foreign, FDA 4000001, MCN PHBS2003RU09333.** A 7-month-old baby was treated with pimecrolimus for atopic dermatitis. For one week, the patient responded well to the treatment. However, one to two weeks later new skin eruptions appeared and pimecrolimus was restarted. Within two hours the patient experienced redness and itching at the site of application. Pimecrolimus was continued, and the redness and itching persisted. The patient was diagnosed with Quincke’s edema at an outpatient clinic, and was hospitalized. During hospitalization pimecrolimus was discontinued, and the reactions resolved. Pimecrolimus was restarted and the patient again experienced Quincke’s edema. Pimecrolimus was permanently discontinued, corticosteroids and other treatment modalities instituted. All symptoms of Quincke’s edema resolved. The patient had a history of Quincke’s edema to polyvalent vaccinations when he was four-months old. The reporting physician was different from the treating physician, and did not see Quincke’s edema diagnosed in the hospital.

*Reviewers comment: Pimecrolimus is labeled for local skin reactions, as well as hypersensitivity reactions. Pimecrolimus is not labeled for angioedema, however, it is unclear in this case if the patient experienced a positive rechallenge Quinck’s edema reaction.*

**Appendix 2: Malignancy Related Adverse Events Reported with Topical Pimecrolimus (Elidel®)**

	AERS #	MCN	Report Year	Age (years)/ Gender	Loc	Outcome	Type of Malignancy- Related AE	Narrative
1	4434206-2	PHEH2004US07674	2004	2 M	US	Other	Non-Hodgkins Lymphoma	A 2-year-old male with a 1&1/2 history of atopic dermatitis (affecting ~ 20% bsa) was diagnosed with lymphoblastic lymphoma approximately 10 months after starting Elidel. The patient had used ~ 100 grams of Elidel over the 10 month period. Prior to Elidel the patient had only been treated with a moisturizer, and no other medications. The patient has been treated, is currently in the maintenance phase, and reportedly is doing well at the time of the last update.
2	4374915-7	PHEH2004US04627	2004	2 M	US	Other	"Tumor" papilloma	A 2-year-old male with a history of atopic dermatitis and topical and systemic corticosteroid use developed a "tumor" on his chin after using 4 to 5 sample tubes of Elidel over nearly a three-month period. The patient has had three warts on his chin since four months before this report, but after the use of the Elidel cream. The patient has a history of reactive airway disease.
3	4095555-3	PHEH2003US01826	2003	5 M	US	Other	Granulomatous lymphadenitis with reactive hyperplasia	A 5-year-old male was applied Elidel for eczema on his face and arms. On day 49 the patient developed a large lymphadenopathy on his scalp. Three lymph nodes were surgically resected. The patient was diagnosed by biopsy with a granulomatous lymphadenitis with reactive hyperplasia. The granulomas were non-caseating. Toxoplasmosis, as well sarcoidosis was ruled out. An infectious etiology was possible.
4	4249574-4	PHEH2003US04920	2003	Child Female	US	Other	Facial tumor	A female child of unreported age was treated with Elidel for an unknown indication. The patient developed a facial tumor while using pimecrolimus. No further information was provided.
5	4319844-X	PHEH2003US01380	2004	61 F	US	Other	Lymphoma	A 61-year-old woman with a history of eczema used pimecrolimus on the arm a few weeks before the diagnosis of lymphoma. Diagnosis of histiocytic lymphoma was confirmed by biopsy. The physician stated that the patient has a "long hx of using hair dyes and colorations" that may have contributed to the development of the lymphoma. The patient was reported in good health with no other medical problems prior to the diagnosis. The reporter requested no further contact.
6	4294166-4	PHEH2003US11219	2003	58 F	US	Other	Intraductal papilloma of the nipple	A 58-year-old woman used a few samples of Elidel for eczema on the palms of her hands. Approximately 2 months later she noticed a slight discharge from her breast, and was diagnosed with intraductal papilloma. The patient had a normal mammogram one month before starting Elidel, and a normal physical exam three months before starting Elidel. The patient was surgically treated. On follow-up the pathology report showed that the papilloma was benign. The patient did not have a history of breast/nipple discharge, abnormal mammogram or family history of breast cancer.
7	4454775-6	PHBS2004CA12158	2004	NR	Canada	Other	Lymphoma	A poorly documented report of a person of unreported age with vitiligo

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	AERS #	MCN	Report Year	Age (years)/ Gender	Loc	Outcome	Type of Malignancy- Related AE	Narrative
								who developed "lymphoma" five months after using pimecrolimus to treat vitiligo.
8	4385807-1	PHBS2004CA06077	2004	53 M	Canada	Other	Basal cell carcinoma	A 53-year-old male with a history of nodules on the nose was diagnosed with a basal cell carcinoma on the nose approximately one to two weeks after starting pimecrolimus for rosacea. Pimecrolimus was discontinued. The patient reportedly recovered.