

## **Report of the Topical Calcineurin Inhibitor Task Force of the ACAAI and AAAAI**

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**Atopic dermatitis (AD) is a common chronic inflammatory skin disease that causes significant suffering and has limited treatment options<sup>1,2</sup>. It is often the first step in the atopic march and may contribute to the severity/persistence of asthma<sup>2-4</sup>. On February 15, 2005, the Pediatric Advisory Committee of the Food & Drug Administration (FDA) recommended "black box" warnings for pimecrolimus (Elidel, Novartis) and tacrolimus (Protopic, Fujisawa) because of a potential risk of cancer. The ACAAI and the AAAAI formed a Joint Task Force to review the data and present it to their membership with the following objectives:**

- 1. To review current FDA concerns regarding safety of the use of topical pimecrolimus (Elidel®, Novartis) and tacrolimus (Protopic®, Fujisawa) in atopic dermatitis (AD).**
- 2. To assist the allergist in providing their patients with appropriate information and to assist them in proper use of these products**
- 3. To address the Black Box Warning and its impact on the treatment of AD at this time**

### **I. FDA Concerns:**

**A. Because of a perception by physicians and patients that topical pimecrolimus and tacrolimus are safer than steroid preparations, they have increasingly been used as first-line therapy and off label. There were almost 2 million prescriptions written of these topical medications for children between June 2003 and May 2004 and approximately half a million were for those under 2 years of age. There is also heavy direct-to-consumer advertising, which may be related to its increasing use.**

**B. The FDA is investigating post-marketing reports of malignancy in children and adults who have used these medications (Table 1 & 2). A post marketing non-human primate study with an oral formulation of pimecrolimus demonstrated an occurrence of lymphoma in monkeys**

exposed to the lowest dose, which represented 30x the maximum recommended human dose (MRHD)<sup>5</sup>.

C. A definitive answer regarding risk of carcinogenicity from topical pimecrolimus and tacrolimus will not be known for years, and if such a risk was real, the Advisory Panel was concerned that people may think they were not provided adequate information to assist them in proper use of these products.

## **II. Current Data:**

A. After topical application of tacrolimus and pimecrolimus, serum concentrations are usually low or undetectable<sup>5-8</sup>, and absorption decreases as dermatitis improves. Additional absorption studies are needed in infants and young children.

B. Although there are animal data showing dose dependent carcinogenicity, it should be noted that the lymphoma formation was only reported in mice with the application of tacrolimus and pimecrolimus dissolved in ethanol at 26X and 47X the maximum recommended human dose (MRHD)<sup>5</sup>.

C. Based on the malignancy rates in the general population of the United States for tacrolimus (Table 3) and the incidence of Non Hodgkin's Lymphoma based on the person-years of exposure for pimecrolimus (Table 4), there is no evidence of increased incidence of lymphoma with the short-term or intermittent long-term application of topical tacrolimus and pimecrolimus at this time, despite the use of these drugs in nearly 7 million people.

D. There are features that characterize lymphomas occurring in the setting of immunomodulatory or immunosuppressive therapy. These are: 1) frequent occurrence in unusual sites including soft tissue, joint spaces, lungs; 2) polymorphous, pleomorphic large cell or Hodgkin's-like morphology; 3. presence of Epstein Barr genome in lymphoma cells; 4) B-cell lymphomas develop weeks, months or less commonly up to several years of receiving immunomodulatory therapy; 5) In a significant percentage of cases (30-50%), the lymphomas spontaneously regress following withdrawal of immunomodulatory therapy without the need for chemotherapy or radiation therapy.

**None of the information provided for the cases of lymphoma associated with the use of topical pimecrolimus or tacrolimus in AD indicate or suggest a causal relationship.** The histology reported and the clinical presentations are not those usually associated with post transplant lymphoproliferative disorder or of lymphoma occurring in the

immunocompromised setting. Five independent external experts in the areas of dermatology, epidemiology, Posttransplantation Lymphoproliferative Disorders (PTLD)/oncology, and pediatric oncology concluded that there was no clear-cut link between pimecrolimus or tacrolimus<sup>5</sup> and increased risk of lymphoma.

E. There is no evidence of systemic immunosuppression from topical pimecrolimus or tacrolimus as measured by response to childhood immunizations (B cell)<sup>9,10</sup> and delayed hypersensitivity (T cell)<sup>11,12</sup>.

F. In clinical trials, infants and children younger than 2 years of age treated with topical pimecrolimus were reported to have higher rates of upper respiratory infections than those treated with placebo cream. However, when data was adjusted for time on medication, pimecrolimus was not associated with increased prevalence of systemic infection. There was also no difference in systemic infections in children 2-17 years of age or adults<sup>5, 9, 12-16</sup>.

G. AD itself has been associated with malignancy, such as cutaneous T cell lymphoma<sup>17</sup>.

H. There is an increased risk of adverse effects and malignancies among users of oral corticosteroids<sup>18,19</sup> and other systemic therapies such as cyclosporin and psoralen plus ultraviolet A (PUVA) for AD that are occasionally required for treatment of severe AD.<sup>18-32</sup> (Table 5)

### **III. Conclusions and Recommendations**

A. Guidelines for the use of pimecrolimus cream 1% and tacrolimus ointment 0.03 and 0.1%.

1. Current FDA guidelines recommend that topical pimecrolimus and tacrolimus are indicated for the short term or intermittent long term treatment of AD in patients  $\geq$  2 years who are unresponsive to or intolerant of other conventional therapies or in whom these therapies are inadvisable due to potential risks.
2. The long-term effect of pimecrolimus and tacrolimus on the developing immune system in infants and children is not known. Children and adults with a compromised immune system should not use pimecrolimus or tacrolimus.
3. Based on information available, it would be prudent to use these medications as has been previously recommended and approved and at the amount needed to control the patient's symptoms. Animal data suggest that the risk of cancer increases with increased exposure to pimecrolimus

- or tacrolimus. However the doses in which cancers occur were substantially higher than the levels used in humans.
4. It is important to reinforce the need for adjunctive treatment for AD including liberal moisturization, evaluation for food and inhalant allergies, treatment of infections and referral to an allergist/immunologist or a dermatologist for identification of triggers and optimal skin care.
  5. There is no evidence to date of systemic immunosuppression after short-term or intermittent long-term topical application of FDA approved formulations of pimecrolimus and tacrolimus in patients with AD.

**B. Patient information should be adequate and must include the risk and benefits of the drug and the proper use of these products. This includes:**

1. Addressing the chronic, relapsing nature of AD and its complications such as infection, associated allergies, skin barrier dysfunction, risk of asthma etc.
2. Acknowledging that topical calcineurin inhibitors have significantly improved the clinical management of patients with AD.
3. Discussing current product label in the use of these drugs on patients
  - a. younger than 2 years of age
  - b. with compromised immune system
  - c. treated with concurrent phototherapy
  - d. pregnant or breast feeding
  - e. with severely impaired skin barrier function (e.g. Netherton's syndrome) that may result in immunosuppressive blood levels of the drug
4. Discussing treatment options for AD, including topical corticosteroids that may have adverse effects relating to potency, occlusiveness of the preparation, site of application, percentage of body surface covered, and duration of treatment including skin atrophy.
5. Discussing alternative treatments for moderate to severe AD, which include oral corticosteroids, cyclosporin A and phototherapy, all of which have significant potential for causing serious adverse events including malignancy.

**C. The Topical Calcineurin Inhibitor Task Force of ACAAI and the AAAAI concludes that based on current data, the risk-benefit ratio of topical pimecrolimus and tacrolimus are similar to most conventional therapies for the treatment of chronic relapsing eczema.**

In children < 2 years of age with poorly controlled persistent AD who require more than hydration and use of emollients to keep their skin disease under control, use of off label therapy may be necessary as most topical steroids or other immunomodulators have not been studied or approved in this age group.

#### **IV. Black Box Warning**

Current data does not support the use of the black box warning on topical pimecrolimus and tacrolimus based on the following facts:

1. Lymphoma formation is generally associated with high dose and sustained systemic exposure to pimecrolimus and tacrolimus.
2. The reported cases of lymphoma from topical pimecrolimus and tacrolimus are not consistent with lymphomas observed with systemic immunomodulator therapy.
3. The actual rate of lymphoma formation reported to date for topical calcineurin inhibitors is lower than predicted in the general population.

Current labeling and product package inserts for both topical pimecrolimus and tacrolimus clearly state the potential of malignancy in animal studies. There is no new data except for a few cases of post marketing adverse events that are anecdotal at this time and a non-human primate study with an oral formulation of pimecrolimus demonstrating an occurrence of lymphoma in the lowest dose representing 30x MRHD.

#### **V. Recommendation:**

1. More controlled studies are needed on the use of topical calcineurin inhibitors, especially under the age of 2 years old
2. Controlled long term safety studies are also needed for topical corticosteroids in patients with AD, especially those under 2 years of age.
3. Likewise, warnings regarding the use of unproven treatments perceived to be safer than conventional therapies are warranted.
4. Vigilance and education on the prudent use of all products for management of AD are needed.

**Tables of Post marketing Data: (after 12/08/00 for Topical Tacrolimus & 12/13/01 for Topical Pimecrolimus)**

**Table 1: Post Marketing Total Tumor Adverse Events as of December 31, 2004.**

		Total Tumor <sup>5</sup>	Total US cases of Lymphoma <sup>5</sup>	**Median time from initial treatment until diagnosis <sup>5</sup>
<b>Pimecrolimus</b>	<b>Children &lt; 16 yrs</b>	<b>1</b>	<b>1</b>	<b>90 (7 to 300 days)</b>
	<b>Adult</b>	<b>5†</b>	<b>3†</b>	
<b>Tacrolimus</b>	<b>Children &lt; 16 yrs</b>	<b>3</b>	<b>0</b>	<b>240 (21 to 940 days)</b>
	<b>Adult</b>	<b>18</b>	<b>4</b>	

† There is one non-US case of lymphoma that is poorly documented.

**Table 2: US FDA cases of Spontaneous Reports of Lymphoma†<sup>5</sup>**

<b>Drug</b>	<b>Age</b>	<b>Lymphoma Histology</b>	<b>Independent Expert Assessment of Causality</b>
<b>Pimecrolimus</b>	<b>61</b>	<b>Histiocytic Lymphoma</b>	<b>Unlikely</b>
<b>Pimecrolimus</b>	<b>53</b>	<b>Subcutaneous panniculitis like T-cell lymphoma</b>	<b>Unlikely</b>
<b>Pimecrolimus</b>	<b>2.5</b>	<b>Lymphoblastic lymphoma (T cell)</b>	<b>Unlikely</b>
<b>Tacrolimus</b>	<b>52</b>	<b>Non-Hodgkin's Lymphoma</b>	<b>Insufficient evidence</b>
<b>Tacrolimus</b>	<b>50</b>	<b>Anaplastic large cell lymphoma-T-cell "type"</b>	<b>Insufficient evidence</b>
<b>Tacrolimus</b>	<b>40</b>	<b>Lymphoma "possible"</b>	<b>Insufficient evidence</b>
<b>Tacrolimus</b>	<b>54</b>	<b>Non-Hodgkin's Lymphoma</b>	<b>Insufficient evidence</b>

**Table 3: Tacrolimus Analysis of Malignancy Rates**

	<b>Malignancy Rates in the General US Population</b>	<b>Malignancies Reported in Tacrolimus Treated patients<sup>†</sup></b>
<b>Lymphoma</b>	<b>22/100,000<sup>34*</sup></b>	<b>0.65/100,000<sup>5</sup></b>
<b>Non Melanoma Skin Cancer</b>	<b>533/100,000<sup>35**</sup></b>	<b>0.94/100,000<sup>5</sup></b>

**\*Surveillance Epidemiology & End Result (SEER)    \*\* PHS**

<sup>†</sup> For the time period upto Dec 2004, 1,700,000 patients have been treated with tacrolimus. 11 lymphomas including 6 cutaneous T-cell lymphoma [CTCL] and 16 non-melanoma skin cancer have been reported in US<sup>5</sup>

**Table 4: Pimecrolimus Analysis of Malignancy Rates<sup>5</sup>:**

**Based on the person-years of exposure, there is no evidence of increased incidence of Non Hodgkin’s Lymphoma in any age group in patients receiving pimecrolimus**

	<b>&lt; 5</b>	<b>5-9</b>	<b>10-14</b>	<b>15-19</b>	<b>Total Children</b>	<b>Total adults</b>	<b>Total (US)</b>
<b>Person yrs of exposure</b>	<b>278,842</b>	<b>118,196</b>	<b>65,224</b>	<b>33,431</b>	<b>495,694</b>	<b>237,030</b>	<b>732,724</b>
<b>Expected no of cases (SEER)<sup>35*</sup></b>	<b>1.8</b>	<b>1.0</b>	<b>0.7</b>	<b>0.5</b>	<b>4.0</b>	<b>42.1</b>	<b>46.1</b>
<b>Reported Cases<sup>5</sup></b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>

**\* Surveillance Epidemiology & End Result**

**Table 5: Malignancy Risks of Anti-Inflammatory Therapy used in Atopic Dermatitis**

Therapy	Malignancy Risk	Adverse Event
Topical Corticosteroids*	<b>Evidence-based:</b> No evidence of immunosuppressive malignancy	HPA axis suppression; skin atrophy; telangiectasia; percutaneous absorption; ↓ bone mineral density <sup>31, 37-44</sup>
Oral Corticosteroids**	Increase risk of squamous cell/basal cell carcinoma; increase risk of non-Hodgkin's lymphoma <sup>18,19</sup>	↑ infection, hypertension, myopathy, glaucoma, aseptic necrosis of the hip, cataracts, Cushing Syndrome, cataracts, weight gain, osteopenia <sup>45,46</sup>
Topical Calcineurin Inhibitors	<b>Theoretical:</b> topical dosing can induce cancer in mice at >40x maximum human recommended dose <sup>6,7</sup> <b>Evidenced-based:</b> No evidence of immunosuppressive malignancy	Skin irritation at application site <sup>6,7,11,45-49</sup>
Oral Immunosuppressives (cyclosporin A)**	Increases B cell Lymphoproliferative Disease and skin cancer. No significant risk if therapy less than 2 year <sup>21,26,29,30</sup>	Nephrotoxicity; hepatotoxicity <sup>24,46,52,53</sup>
Phototherapy (UVA, UVB) Photochemotherapy (PUVA)	Increased risk of squamous cell and basal cell carcinoma, & malignant melanoma <sup>20,23,27,28,33</sup> (UVB less than PUVA) <sup>22</sup>	Erythema, pruritis, nausea, headache, chronic actinic skin damage, dyskeratotic and precancerous skin conditions <sup>20,23,25,32</sup>

\* adverse effects relate to corticosteroid potency, occlusiveness of the preparations, site of application, percentage of the body surface covered, and duration of treatment

\*\* occasionally required for severe atopic dermatitis treatment

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#### **Declared Conflicts of Interest**

Vincent Beltrani: Advisory Board: Pfizer; Speaker: Pfizer, Aventis, Fujisawa and AstraZeneca

Mark Boguniewicz: Research grants and Speaker's Bureau: Fujisawa and Novartis Pharmaceuticals

Jan Broadbent: Speaker's Bureau: Novartis

Ernie Charlesworth: Clinical Investigator: Novartis; Lecturer: Novartis and Fujisawa

Luz Fonacier: Speakers' Bureau: Novartis, Genetech, Aventis, Pfizer, GlaxoSKB; Research/Clinical trials: Genentech, Dyaxx, GlaxoSKB

Donald Leung: Speaker's Bureau, Consultant: Fujisawa, Novartis Pharmaceuticals, GlaxoSKB, Leo Pharmaceuticals, sanofi-aventis

Jonathan Spergel: Speaker's Bureau: GlaxoSKB, Fujisawa  
Research/Clinical trials: Novartis

David Weldon: Speaker's Bureau: Primary Care Network, Aventis and GlaxoSmithKline; Consultant: AstraZeneca