

# **Update on post-marketing AERS cases of pediatric malignancies reported with topical pimecrolimus and tacrolimus use**

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# Outline

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## **Abbreviations**

AERS- Adverse Event Reporting System

PAC- Pediatric Advisory Committee

PIM- pimecrolimus (Elidel)

TCI- Topical calcineurin inhibitors

tTAC- topical tacrolimus (Protopic)

# Background

- Previous post-marketing AERS reviews relevant to pediatric malignancies associated with TCI use

OSE Review Date	Pediatric malignancy cases (Drug)*	
24-Sep-03	2 cases (PIM-2)	
24-Sep-03	No cases identified	PAC: Oct-03
28-Sep-04	2 cases (PIM-2)	
5-Oct-04	3 cases (tTAC-3)	
15-Dec-04	No new cases identified	PAC: Feb-05
8-Jan-10	46 cases (PIM-27, tTAC-15, Both-4)	
15-Mar-10	10 cases (PIM-6, tTAC-3, Both-1)	PAC: Mar-10

\*Numbers reflect pediatric malignancy cases discussed in completed post-marketing AERS reviews. Case counts presented today reflect information we have to-date, accounting for both new cases and follow-up information received for previously captured cases; therefore current case counts do not match the previous case counts.

# Objective

- To provide an update of pediatric malignancy cases in AERS reported with TCI use
  - Summary of new cases
  - Updated total case counts
    - Reflects both new malignancy cases and follow-up information for previously identified cases

# Adverse Event Reporting System

- Voluntary, spontaneous adverse event reporting system
- Useful for detecting adverse events not seen in clinical trials
  - Unlabeled use
  - Chronic use
  - Diverse patient population
  - Rare background rate, etc.
- Limitations
  - Under-reporting
  - Variable quality and quantity of information
  - Not the optimal tool for adverse events with a long latency

# Inclusion Criteria

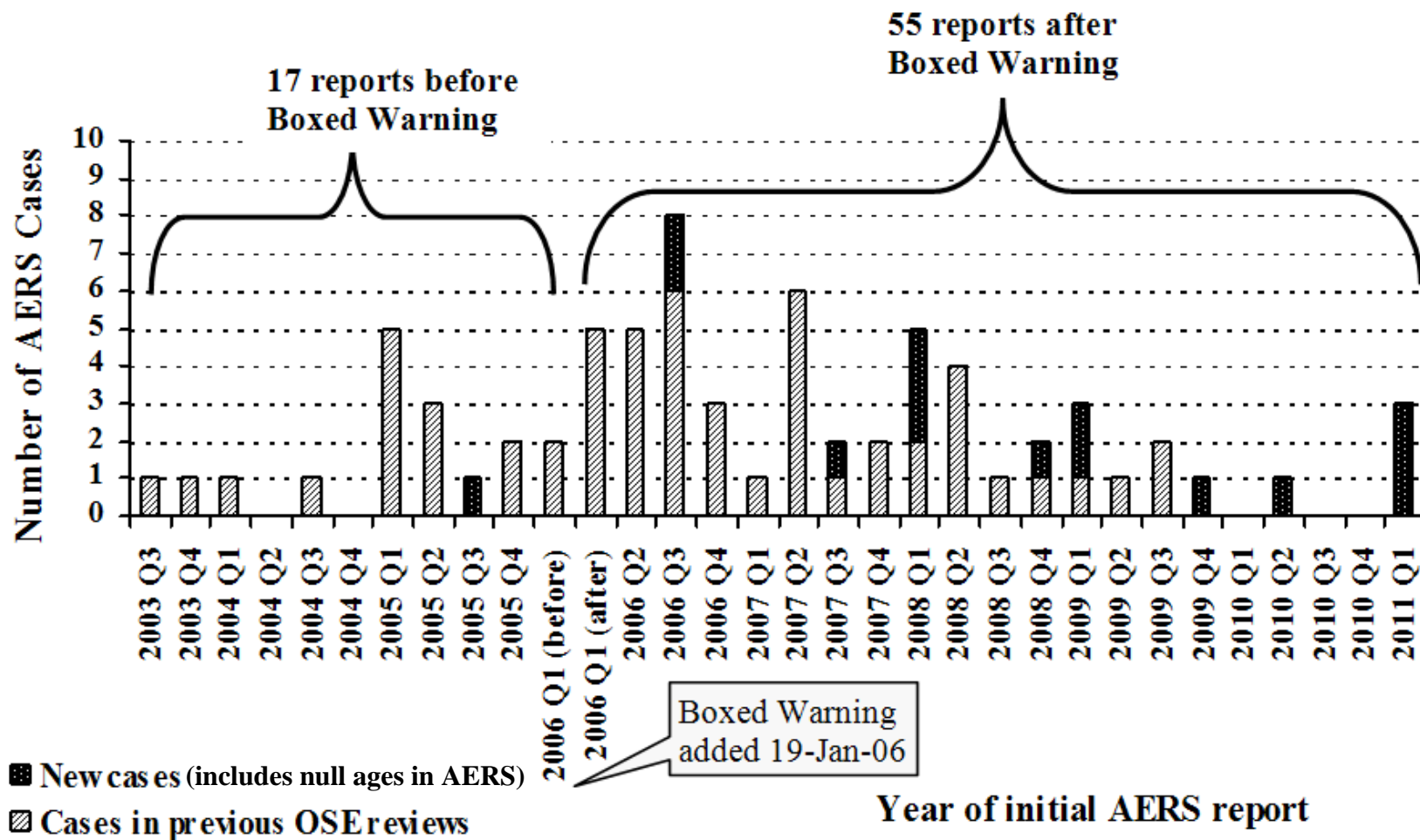
- AERS cases of pediatric malignancies reported with TCI use
- Initially received by the FDA from market approval to March 4, 2011

<b><u>Inclusion criteria</u></b>	<ul style="list-style-type: none"> <li>• Age of 0-16 years or “child,” “infant,” “pediatric patient,” etc.</li> <li>• Cases that reported a malignancy or cancer</li> <li>• Cases that reported an uncontrolled growth of cells that results in lack of differentiation, local tissue invasion, or metastasis</li> <li>• Cases that reported “brain tumors” and other tumors affecting the central nervous system</li> </ul>
<b><u>Exclusion criteria</u></b>	<ul style="list-style-type: none"> <li>• Adults or cases that did not indicate the adverse event occurred in a “child,” “infant,” “pediatric patient,” etc.</li> <li>• Benign, non-malignant, or unspecified “tumors” or “neoplasms” that did not have the potential to affect surrounding normal tissue and function</li> <li>• Pre-malignant conditions</li> <li>• No definitive diagnosis of malignancy</li> </ul>

# AERS Results

- 72 unduplicated AERS cases of pediatric malignancies reported with TCI use met the inclusion criteria (PIM-43, tTAC-22, Both-7)
  - **15 new cases**
    - 4 cases reported after the March 2010 PAC
    - 11 cases reported prior to the March 2010 PAC
  - 57 cases captured in previous reviews

# Total Cases Over Time (n=72)





# Reported Diagnoses: Total Cases (n=72)

	Total cases	Previously captured cases	New cases
<b>Total pediatric malignancies</b>	<b>72</b>	<b>57</b>	<b>15</b>
Lymphomas	25	21	4
Leukemias	25	19	6
Skin Malignancies	8	6	2
Other	14	11	3

# Total Lymphoma Cases

	Total cases	Previously captured cases	New cases
<b>Total lymphoma cases</b>	<b>25</b>	<b>21</b>	<b>4</b>
B-cell lymphoma	5	4	1
Hodgkin's disease	4	3	1
Lymphoblastic lymphoma	4	4	---
Cutaneous T-cell lymphoma	4	3	1
Non-Hodgkin's lymphoma	3	2	1
Anaplastic large cell lymphoma	3	3	---
Malignant lymphoma	1	1	---
Cutaneous T-cell and B-cell lymphoma	1	1	---

# Total Leukemia Cases

	Total cases	Previously captured cases	New cases
<b>Total leukemia cases</b>	<b>25</b>	<b>19</b>	<b>6</b>
Acute lymphocytic leukemia	19	14	<b>5</b>
Acute myeloid leukemia	2	2	---
Leukemia	2	1	<b>1</b>
Chronic myeloid leukemia	1	1	---
T-cell leukemia	1	1	---

# Total Skin Malignancy Cases

	Total cases	Previously captured cases	New cases
<b>Total skin malignancy cases</b>	<b>8</b>	<b>6</b>	<b>2*</b>
Melanoma	5	4	1
Basal cell carcinoma	1	1	---
Cutaneous myoepithelial neoplasm	1	1	---
Skin cancer	1	---	1

\* Melanoma (1; may be duplicate of a previously captured case)  
Unspecified skin cancer (1; follow-up information pending)

# Other Cases

	Total cases	Previously captured cases	New cases
<b>Total other cases</b>	<b>14</b>	<b>11</b>	<b>3</b>
Brain tumor	2	2	---
Hepatoblastoma	2	2	---
Rhabdomyosarcoma	2	1	1
Wilm's tumor	2	2	---
Glioneuronal tumor	1	1	---
Lung cancer	1	1	---
Neuroblastoma	1	1	---
Angiosarcoma	1	1	---
Nephroblastoma	1	---	1
Pituitary microadenoma	1	---	1

# Conclusions: AERS Update

- Spectrum of new pediatric malignancy cases consistent with previously identified cases
- No new trends identified
- Cases support previously identified potential safety signal for malignancies reported with TCI use
- Precise role of TCIs in malignancies unknown

# Conclusions: AERS Update

- For malignancies, information provided in spontaneous post-marketing case reports is generally not sufficient to determine causality
  - Information regarding clinical course
  - Details regarding drug exposure
  - Role of underlying diseases
  - Other contributing factors may be unknown
  - Malignancies may be associated with a long latency period

# Conclusions: FDA Reviews

- The review of observational literature suggests a possible association between TCI use, particularly tTAC, and an increased risk of T-cell lymphoma in all ages combined
  - Potential study biases remain a possible explanation for this observed association
  - Results were not specific to the pediatric population
- The post-marketing safety review did not identify new signals for pediatric malignancies reported with TCI
- Current TCI labeling and medication guide reflects the safety risk as we understand it



# Does the committee agree with the following recommendations by FDA?

1. FDA will continue surveillance of spontaneous reports and continue to monitor for registry cases
2. Protopic and Elidel labels and Medication Guides adequately reflect the risk for malignancies



# Additional Slides

# AERS Results: New Cases (n=15)

<b>Lymphomas</b>	<b>N=4</b>
B-cell lymphoma	1 ( <i>PIM-1</i> )
Hodgkin's Disease	1 ( <i>PIM-1</i> )
Cutaneous T-cell lymphoma	1 ( <i>tTAC-1</i> )
Non-Hodgkin's lymphoma	1 ( <i>PIM-1</i> )
<b>Leukemias</b>	<b>N=6</b>
Acute lymphocytic leukemia (ALL)	5 ( <i>PIM- 4, tTAC-1</i> )
Leukemia	1 ( <i>PIM-1</i> )
<b>Skin Malignancies*</b>	<b>N=2</b>
Melanoma	1 ( <i>Both-1</i> )
Skin cancer	1 ( <i>PIM-1</i> )
<b>Other</b>	<b>N=3</b>
Rhabdomyosarcoma	1 ( <i>PIM-1</i> )
Nephroblastoma	1 ( <i>tTAC-1</i> )
Pituitary microadenoma	1 ( <i>PIM-1</i> )

\*Two new cases were identified and captured in the total counts; however, these cases may be reclassified pending additional information (melanoma-1, unspecified skin cancer-1)

# AERS Results: New Cases (n=15)

Origin	US (11)	Foreign (4)		
Initial report year	2005 (1)	2006 (2)	2007 (1)	2008 (4)
	2009 (3)	2010 (1)	2011 (3)	
Drug	PIM (11)	tTAC (3)	PIM and tTAC (1)	
Indications**	Atopic dermatitis (5)		Eczema (2)	
	Dermatitis (1)		Rash + infantile acne (1)	
	Unknown (6)			
Gender	Male (9)		Female (5)	
	Unknown (1)			
Age at time of event (n=10)	Mean: 5.6 years		Median: 3.5 years	
	Range: 11 months - 15 years			
Age at start of therapy	< 2 years (4)		≥ 2 years (3)	Unknown (8) 20

# AERS Results: New Cases (n=15)

<b>Duration of therapy</b>	8 days (1) “Several years” (1)	38 days (1) Unknown (11)	3 months (1)
<b>Time to event from start of therapy (n=6)</b>	Mean: 1.6 years      Median: 1.3 years Range: 3 months – 3.9 yrs		
<b>Primary Outcome</b>	Life-threatening (3)      Hospitalization (1) “Other” Serious / Medically Significant (10) No serious outcome reported (1)		
<b>TCI: action taken</b>	Discontinued (2)	Continued (1)	Unknown (12)
<b>Intervention</b> <i>(more than one is possible per case)</i>	Chemotherapy (7) Unspecified (1)	Radiation (1) Unknown (7)	Transfusion (1)
<b>Event resolution</b>	Improved (3) Eventual outcome unknown (11)	Did not improve (1)	