

# **One Year Post-Exclusivity Adverse Event Review: Imiquimod**

**Pediatric Advisory Committee Meeting  
November 18, 2008**

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## **Background Drug Information**

- **Drug:** Aldara™ (Imiquimod) Topical Cream
- **Therapeutic Category:** immune response modifier
- **Sponsor:** Graceway Pharmaceuticals, LLC
- **Original Market Approval:** February 27, 1997
- **Pediatric Exclusivity Granted:** December 13, 2006

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## Background Drug Information

- **Indications:**

- Treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent **adults**
- Treatment of biopsy confirmed primary superficial basal cell carcinoma in immunocompetent **adults**;
- Treatment of external genital and perianal warts/condyloma acuminata in patients **12 years or older**
- Limitations of Use: Studies in children ages 2 to 12 years with molluscum contagiosum (MC) failed to demonstrate efficacy

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## Background Drug Information

- **Dosage:**

- Actinic keratosis: 2 times per week x 16 weeks
- Superficial basal cell carcinoma: 5 times per week x 6 weeks
- External genital warts: 3 times per week until cleared (maximum 16 weeks)

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## **Background Drug Use Information**

### Pediatric use

- Aldara™ prescriptions in the pediatric population (ages 0-16 years) accounted for approximately 21% of total dispensed Aldara™ prescriptions\*
- Of the prescriptions dispensed to pediatric patients, 40% were dispensed to patients aged 6-10 years and 38% dispensed to patients aged 11-16 years
- Top diagnoses\*\* – viral warts and MC

\*Source: SDI Vector One® National, Years 2005 – 2007. Data Extracted 6-2008.

\*\*Source: SDI Physician Drug and Diagnosis Audit, Years 2005 – 2007. Data Extracted 6-2008

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## **Exclusivity Studies**

### Pharmacokinetic study result:

- Absorption of imiquimod following topical application in pediatric patients was comparable to adults

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## Exclusivity Studies

### Efficacy

- Two double-blind, vehicle-controlled safety and efficacy studies in 702 pediatric patients age 2 to 12 years with MC
  - 470 patients exposed to Aldara™
  - Treatment was up to 16 weeks

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## Exclusivity Studies

### Efficacy results:

- Since the vehicle clearance rates were higher than Aldara™, these studies failed to demonstrate efficacy
- No indication for molluscum contagiosum granted
- Clearance rates
  - Study 1 – Aldara™ (24%); vehicle (26%)
  - Study 2 – Aldara™ (24%); vehicle (28%)

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## Exclusivity Studies

Safety results:

- In general, adverse events in the Aldara™ group resembled those seen in studies with adults
- The most frequently reported possibly or probably related adverse event was application site reaction (31% in Aldara™ group and 20% in vehicle group)
- A decrease in WBC and absolute neutrophil count was observed

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## Exclusivity Studies

Safety results (continued):

- Severe local reactions reported in Aldara™ group
  - Erythema (28%)
  - Edema
  - Scabbing/crusting
  - Flaking/scaling
  - Erosion
  - Weeping/exudate

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## Exclusivity Studies Labeling Changes

### Labeling Sections Changed

#### Highlights Section

- Indications and Usage
  - Limitations of Use

#### Section 1 Indications and Usage

- 1.4 Limitation of Use

#### Section 8 Use in Specific Populations

- 8.4 Pediatric Use

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## Exclusivity Studies Labeling Changes

### Details of Specific Labeling Changes

#### **Section 1 Indications and Usage**

- **1.4 Limitations of Use:** Studies in children 2 to 12 years with MC failed to demonstrate efficacy

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## Exclusivity Studies Labeling Changes

Details of Specific Labeling Changes continued

### Section 8 Use in Specific Populations

#### 8.4 Pediatric Use

- A description of the two efficacy studies and results
- Adverse events observed during the clinical studies, including incidence of severe local reactions
- A description of the pharmacokinetic study and results including extent of systemic absorption and decrease in median WBC/Absolute Neutrophil Count

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## Pediatric Adverse Events in 1 Year Post Exclusivity Period

Crude Counts <sup>1</sup> of AERS Reports for All Sources from Date Pediatric Exclusivity Was Granted (12/13/2006 to 1/13/2008) (US counts in parentheses)			
	All reports (US)	Serious <sup>2</sup> (US)	Death (US)
Adults (≥ 17 yrs.)	32 (27)	13 (11)	0
Pediatrics (0-16 yrs.)	2 (2)	0	0
Age unknown (Null Values)	6 (5)	1 (1)	0
<b>Total</b>	<b>40 (34)</b>	<b>14 (12)</b>	<b>0</b>

<sup>1</sup>May include duplicates  
<sup>2</sup>Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, and congenital anomaly

## Pediatric Adverse Events Since Marketing Approval

Crude Counts <sup>1</sup> of AERS Reports for All Sources from Marketing Approval Date to January 13, 2008 (US counts in parentheses)			
	All reports (US)	Serious <sup>2</sup> (US)	Death (US)
Adults (≥ 17 yrs)	1,289 (1,222)	166 (84)	14 (5)
Pediatrics (0-16 yrs.)	<u>84 (79)</u>	12 (11)	1 (1)
Age unknown (Null values)	193 (159)	20 (8)	1 (0)
<b>Total</b>	<b>1,566 (1,360)</b>	<b>198 (102)</b>	<b>16 (5)</b>

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## Pediatric Uses Reported with Adverse Events Since Marketing Approval

- Viral Warts (49%)
- Molluscum Contagiosum (24%)
- Warts and Common Warts (7%)
- Genital Warts (6%)
- Plantar Warts (3%)
- Alopecia (3%)
- Venereal Warts (1%)
- Herpes (1%)
- Actinic Keratosis (1%)
- Not Reported (5%)

\*Approved uses are underlined

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### Pediatric Deaths Since Market Approval (N=1)

16 year old female committed suicide by gunshot while on 3<sup>rd</sup> month of second course of imiquimod (12.5 mg) three times weekly for viral warts. Total treatment duration 31 weeks. No known history of depression. This is a labeled event.

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### Serious Pediatric Adverse Events Since Market Approval (N=12)

Neurologic (n=3)

- Seizures (n=2); labeled
- Temporary paralysis (n=1); labeled

Congenital Anomaly (n=2)

- Undescended testicles, GU reflux, ASD, VSD; unlabeled
- Hirschsprung's disease; unlabeled

Hematologic (n=1)

- Thrombocytopenia purpura; labeled

## **Serious Pediatric Adverse Events Since Market Approval**

### Localized reactions (n=6) labeled

- 7 year old female with a history of cerebral palsy after two applications for genital warts developed extreme swelling and inability to void necessitating catheterization in the emergency room. Patient also diagnosed with viral infection after developing a sore throat and low grade fever.
- 15 year old female with burning blisters, swelling and inability to void after one application for genital warts. Treated with topical lidocaine.
- 4 year old female with burning pain and inability to void, fever, and flu-like symptoms after 3 days of treatment (daily application) for herpes. Patient was hospitalized 2 days later.

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## **Serious Pediatric Adverse Events Since Market Approval**

### Localized reactions (n=6) labeled

- 15 year old female with skin burns, blisters, pain upon urination, fever and fatigue after 5 days of treatment (1/2 packet 3 times/week) for genital warts. Patient was hospitalized and treated with antibiotics for the skin burns and blisters
- 16 year old female with burning, erosions, and ulcerations after 3 days of treatment (1 packet daily) for genital warts. Patient was hospitalized after developing fever, increase WBC (14,000), and flu-like symptoms.
- 10 year old male with an application site abscess requiring incision and drainage and antibiotics after 1 month of treatment (unknown dosage every other day for 2 weeks and daily for 2 weeks) for MC.

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## Current Labeling

### 17. Patient Counseling Information

#### 17.6 Patients Being Treated for External Genital Warts

- Female patients should take special care if applying the cream at the opening of the vagina because local skin reactions on the delicate moist surfaces can result in pain or swelling and may cause difficulty in passing urine.

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## Summary: Imiquimod

- Pediatrics accounts for 21% of Aldara™ use\*
- Despite studies showing lack of efficacy, off-label use is common including treatment of MC
- Pediatric female patients have reported inability to void secondary to severe local reactions during use in the genital area
  - The Review Division is planning to update this adverse reaction in the labeling.

\*Source: SDI Vector One® National, Years 2005 – 2007. Data Extracted 6-2008.

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## Question for the Committee

- In addition to planning to update the labeling related to severe local reactions in females with use in the genital area, FDA will continue its standard, ongoing safety monitoring for imiquimod.
- Does the Advisory Committee concur?

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## Acknowledgements

### OSE

- Kendra Worthy, Pharm.D
- Vicky Borders-Hemphill, Pharm.D.
- Laura Governale, Pharm.D., M.B.A
- Marilyn Pitts, Pharm.D
- Mark Avigan, M.D., C.M.

### DDDP

- Brenda Carr, M.D.
- Jill Lindstrom, M.D.
- Margo Owens

### PMHS

- Denise Pica-Branco, Ph.D
- Susan Cummins, M.D., M.P.H.
- Hari Cheryl Sachs, M.D.
- Lisa Mathis, M.D.

### OPT

- Debbie Avant, R.Ph.
- Suzanne Malli, B.A., B.S.N.
- Judith Cope, M.D., M.P.H.
- Dianne Murphy, M.D.

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