



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: September 3, 2008

To: CDR Lisa L. Mathis MD, USPHS, Associate Director
Pediatric and Maternal Health Staff (PMHS)
Office of New Drugs (OND), CDER

M. Dianne Murphy, MD, Director
Office of Pediatric Therapeutics (OPT), OC

Thru: Mark Avigan, MD, CM, Director
Division of Pharmacovigilance I (DPV I)
Office of Surveillance and Epidemiology (OSE), CDER

From: Marilyn R. Pitts, Pharm.D.,
Team Leader, Safety Evaluator
Division of Pharmacovigilance I (DPV I)
Office of Surveillance and Epidemiology (OSE), CDER

Subject: 1-year Pediatric Exclusivity Postmarketing Adverse Event Review

Drug Name(s): Imiquimod (Aldara®)

Pediatric Exclusivity Approval Date: December 13, 2006

Application Type/Number: NDA 20-723

Applicant/sponsor: Graceway Pharmaceuticals

OSE RCM #: 2008-714

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

CONTENTS

EXECUTIVE SUMMARY	2
1 BACKGROUND	2
1.1 Introduction (Product Formulations and Indications)	3
1.2 Pediatric Labeling	4
1.3 Product Label – Adverse Events (Excerpted Listing, Not All Inclusive)	4
1.4 Previous OSE Imiquimod Reviews	4
2 METHODS AND MATERIALS	5
2.1 AERS Selection of Cases	5
3 AERS RESULTS for Imiquimod 5%	6
3.1 Count of Reports: All sources- US and Foreign from marketing approval (Table 1)....	6
3.2 Reporting Trend for Pediatric AERS reports	6
3.3 Crude Count of Reports: All Sources- US and Foreign from Pediatric Exclusivity, December 13, 2006 to January 13, 2008 (Table 2)	7
4 Discussion/Summary of the Cases	7
4.1 Summary of Cases received during the Post-Pediatric Exclusivity Period (N = 2)	7
4.2 Summary of Pediatric Adverse Event Reports Submitted for Imiquimod from Marketing to January 13, 2008 (n = 82)	8
4.2.1 Pediatric Case Coded with Death as an Outcome (n = 1)	9
4.2.2 Non-Fatal Serious Pediatric Adverse Event Reports (n = 12)	9
4.2.2.1 Neurologic Events (n = 3)	9
4.2.2.2 Congenital Anomaly (2)	10
4.2.2.3 Hematologic (1)	10
4.2.2.4 Other Serious Pediatric Reports (6)	11
5 CONCLUSION	12
6 RECOMMENDATIONS	12
7 REFERENCES	12

EXECUTIVE SUMMARY

DPV searched the AERS database for all serious and non-serious adverse event reports submitted for imiquimod (Aldara®) in pediatric patients. Up to the “data lock” date of January 13, 2008, AERS contained 1,566 reports associated with imiquimod use (crude count, all ages, foreign and domestic, as well as reports with no information on age and country of origin). Of the 1,566 reports, pediatric reports represented approximately 5.4% (84) of the total. In contrast, during the three 12-month periods from January 1, 2005 to December 13, 2007 patients aged 0 to 16 years old accounted for ~ 21% of the total dispensed prescriptions for Aldara; and for ~ 22% of the total number of patients prescribed Aldara.¹

DPV was asked to focus on the 1-year period following the approval of pediatric exclusivity, December 13, 2006 to December 13, 2007. To allow time for reports received to December 13, 2007 to be entered into the AERS database, DPV used an AERS “data lock” date of January 13, 2008. For the remainder of this review, the 13-month period from December 13, 2006 to the data lock date of January 13, 2008 is defined as the period of pediatric exclusivity. During the 13-month period of pediatric exclusivity, DPV identified 40 adverse event reports for imiquimod in the AERS database, of which 5% (2) were for pediatric patients.

Overall, the two reports submitted during the period of exclusivity did not identify any new safety signals, but did continue to describe already known serious localized reactions. When the review was expanded to include the additional 82 pediatric reports submitted for imiquimod, DPV reviewed two congenital anomaly reports that did not provide compelling evidence to associate the mother’s use of imiquimod during gestational development with the development of the children’s congenital anomalies. Additionally, for the remainder of the pediatric post-marketing reports, the majority of the serious reports described already known flu-like and severe localized reactions. Among the severe localized reactions, a number of female children described painful urination or the inability to void as a consequence of the localized reactions. In particular one female child’s inability to void was treated by catheterization.

Therefore DPV recommends:

- Enhancing the product label to inform the health care community of the potential of difficulty/inability to void as a potentially bothersome consequence of severe localized reactions in female patients using imiquimod.
- Continued monitoring of adverse events with the use of imiquimod pediatric patients.

1 BACKGROUND

Imiquimod cream is a heterocyclic amine immune response modifier originally approved by the FDA on February 27, 1997. Pediatric exclusivity was granted on December 12, 2006 after the sponsor conducted three studies investigating the treatment of molluscum contagiosum (MC)² in

¹ Borders-Hemphill V. Aldara™ (Imiquimod) Cream BPCA Drug Use Review, OSE RCM# 2008-714, July 17, 2008.

² Molluscum contagiosum is a contagious disease caused by a pox virus that largely affects children. It is characterized by skin lesions that are waxy in appearance, with central umbilication usually numbering from 2 to 20. Mechanical removal of the central core usually results in resolution. Alternatively, topical application of peeling agents such as salicylic and lactic acid preparations, or liquid nitrogen may be successful.

children aged 2 to 12 years old.³ The studies included two randomized, double-blind, vehicle-controlled safety and efficacy studies, and one pharmacokinetic study. The two phase 3⁴ randomized studies involved 702 pediatric patients with MC, of which 470 (median age 5 years, range 2 to 12 years) were exposed to Aldara® (imiquimod). According to the sponsor and the clinical reviewer in the Division of Dermatology Drug Products (DDDP) neither of the phase 3 clinical studies demonstrated efficacy, since the response rate was slightly higher in the vehicle treated arms of both studies. Based on this evidence approval to treat MC was not granted to the sponsor.

The safety data from the above two studies reported the most frequently occurring adverse events associated with imiquimod as application site reactions. Additionally, erythema was the most frequently occurring localized skin reaction and occurred more frequently in the imiquimod arm compared to the vehicle arm. In the phase 3 studies, a subgroup of patients demonstrated decreases in white blood cell, neutrophil, and lymphocyte counts from baseline after the end of treatment. Other safety findings included a higher rate of lymphadenopathy in the imiquimod arm. There were no deaths, serious adverse events, or other significant adverse events reported.

The sponsor also submitted a pharmacokinetic study which evaluated the systemic exposure of imiquimod in children under maximal use conditions.⁵ Subjects who weighed ≤ 25 kg were applied 1 to 2 packets per dose and subjects who weighed > 25 kg were applied 1 to 3 packets per dose. The reviewer found that the sponsor adequately characterized the pharmacokinetics of imiquimod following single and multiple topical applications in pediatric patients with MC. The systemic exposure data demonstrated that the extent of absorption of imiquimod following topical application to the MC lesions in pediatric patients was low and comparable to that observed in healthy adults with actinic keratosis and superficial basal cell carcinoma.⁶ No safety concern relative to systemic exposure of imiquimod and/or its metabolites was noted.

1.1 INTRODUCTION (PRODUCT FORMULATIONS AND INDICATIONS)

Imiquimod 5% is a cream for topical use (not for oral, ophthalmic or intravaginal use) supplied as single-use packets, each containing 250mg of cream with an equivalent of 12.5mg of imiquimod per packet. Imiquimod 5% is indicated to treat:

- Clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratosis (AK) on the face or scalp in immunocompetent adults; two times weekly for 16 weeks.
- Biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults with a maximum tumor diameter of 2.0 cm on the trunk, neck or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and the patient follow-up can be reasonably assured; five times weekly for six weeks.

³ Papadopoulos EJ, DDDP, Clinical Executive Summary – Imiquimod 5% Cream, Three Times Weekly for Molluscum Contagiosum in Children 2 to 12; NDA 20-723, Submission SE8-020, March 15, 2007

⁴ Imiquimod was applied three times per week for up to 16 weeks.

⁵ Ahn HY, Clinical Pharmacology Executive Summary of Aldara for Molluscum Contagiosum, March 13, 2007.

⁶ Systemic absorption of imiquimod was observed across the affected skin of 12 subjects with genital/perianal warts, with an average dose of 4.6mg. Mean drug concentration of approximately 0.4ng/ml was seen. Mean urinary recoveries of imiquimod and metabolites combined over the whole course of treatment, expressed as percent of the estimated applied dose, were 0.11 and 2.41% respectively in males and females. Aldara™ product label, April, 2007. <http://dailymed.nlm.nih.gov/dailymed/about.cfm>

- External genital and perianal warts/condyloma acuminata in patients 12 years old or older (original approved indication); three times weekly until clearance or a maximum of 16 weeks.

1.2 PEDIATRIC LABELING

The imiquimod label (Graceway Pharmaceuticals, November 2007) contains the following pediatric targeted information:

Indications and Usage (Section 1.4):

Limitations to use: Aldara Cream has been evaluated in children ages 2 to 12 years with molluscum contagiosum and these studies failed to demonstrate efficacy.

Pediatric Use (Section 8.4)

- The safety and efficacy of Aldara Cream for AK and sBCC in patients less than 18 years of age have not been established.
- Safety and efficacy in patients with external genital/perianal warts below the age of 12 years have not been established.
- Similar to studies conducted in adults, the most frequently reported adverse reactions from 2 studies in children with molluscum contagiosum was application site reaction.

Patient Information (Section 17.7)

- Aldara cream has not been studied in children under 12 years old for external genital and perianal warts.
- Aldara cream has not been studied in children under 18 years old for actinic keratosis or superficial basal cell carcinoma. Children usually do not get actinic keratosis or basal cell carcinoma.

1.3 PRODUCT LABEL – ADVERSE EVENTS (EXCERPTED LISTING, NOT ALL INCLUSIVE)

Imiquimod is labeled for the following adverse events:

Warnings and Precautions

Intense local inflammatory reactions; flu-like systemic signs and symptoms including malaise, fever, nausea, myalgias and rigors.

Adverse Reactions Section

The most common adverse reactions (incidence > 28%) are application site reactions or local skin reactions: itching, burning, erythema, flaking/scaling/dryness, scabbing/crusting, edema, induration, excoriation, erosion, ulceration. Other reported reactions include fatigue, fever, headache (sections 6.1, 6.2, 6.3)

Post-Marketing Experience

...Decreases in red, white cell and platelet counts, suicide, erythema multiforme, convulsions (febrile convulsions)...

1.4 PREVIOUS OSE IMIQUIMOD REVIEWS

OSE conducted the following post-marketing adverse event analyses for imiquimod 5% cream:

- **March 9, 2007:** OSE analyzed post-marketing AERS cases of imiquimod reporting erythema multiforme, Stevens Johnson syndrome or Toxic Epidermal Necrolysis. The post-marketing cases of SJS and TEN were not compelling in supporting a potential association between the use of imiquimod and the development of SJS or TEN. However, the nine unduplicated cases of erythema multiforme were suggestive of a potential association between the use of imiquimod and the development of erythema multiforme. OSE recommended adding erythema multiforme to the product label.⁷
- **December 1, 2004:** An overview of all post-marketing AERS cases, and specifically cardiac events reported with imiquimod. The reviewer discovered that the most commonly reported adverse events were application site reactions (labeled). There were 12 cases with a reported outcome of death, however, no specific pattern could be elucidated, and although the AERS data was not compelling, a potential associated between the use of imiquimod 5% and the outcome of death could not be excluded. Additionally, there were 12 cases reporting cardiac events, of which two cases of tachycardia with a positive rechallenge were described. The potential role of imiquimod in these two cases could not be excluded.⁸
- **August 31, 2001:** OSE analyzed post-marketing AERS cases of imiquimod reporting skin color changes. OSE concurred with the sponsor's labeling to add hyperpigmentation to the product labeling, as well as to add information concerning the persistence of skin color changes after discontinuation of the product.⁹

2 METHODS AND MATERIALS

2.1 AERS SELECTION OF CASES

OSE conducted separate searches of the AERS database on April 23, 2008 for reports of adverse events submitted for imiquimod 5% cream. The searches were conducted as follows:

1. From Marketing to January 13, 2008 for adults aged 17 years old and older (Section 3.1, Results, Table 1)
 - a. All adult cases
 - b. All adult cases coded serious
 - c. All adult cases coded with an outcome of 'death'
2. From Marketing to January 13, 2008 for children aged 0 to 16 years, (Section 3.1, Results, Table 1)
 - a. All pediatric cases
 - b. All pediatric cases coded serious
 - c. All pediatric cases coded with an outcome of 'death'
3. From the Pediatric Exclusivity Period of December 13, 2006 to January 13, 2008 – Adults (Section 3.2, Results, Table 2)
 - a. All adult cases
 - b. All adult cases coded serious

⁷ Wahab N, OSE Post-Marketing Analysis; Imiquimod 5% - Erythema Multiforme, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis; RCM 2007-1, March 9, 2007

⁸ Weaver J; ODS Post-Marketing Analysis; Imiquimod Overview All Adverse Events, Cardiac Events, PID D040786, December 1, 2004

⁹ Pitts M; OPDRA Post-Marketing Analysis; Sponsor's Proposed Label Change Submission for Skin Color Changes, PID D010382, August 29, 2001

- c. All adult cases coded with an outcome of ‘death’
- 4. From the Pediatric Exclusivity Period of December 13, 2006 to January 13, 2008 – Pediatrics (Section 3.2, Results, Table 2)
 - a. All pediatric cases
 - b. All pediatric cases coded serious
 - c. All pediatric cases coded with an outcome of ‘death’

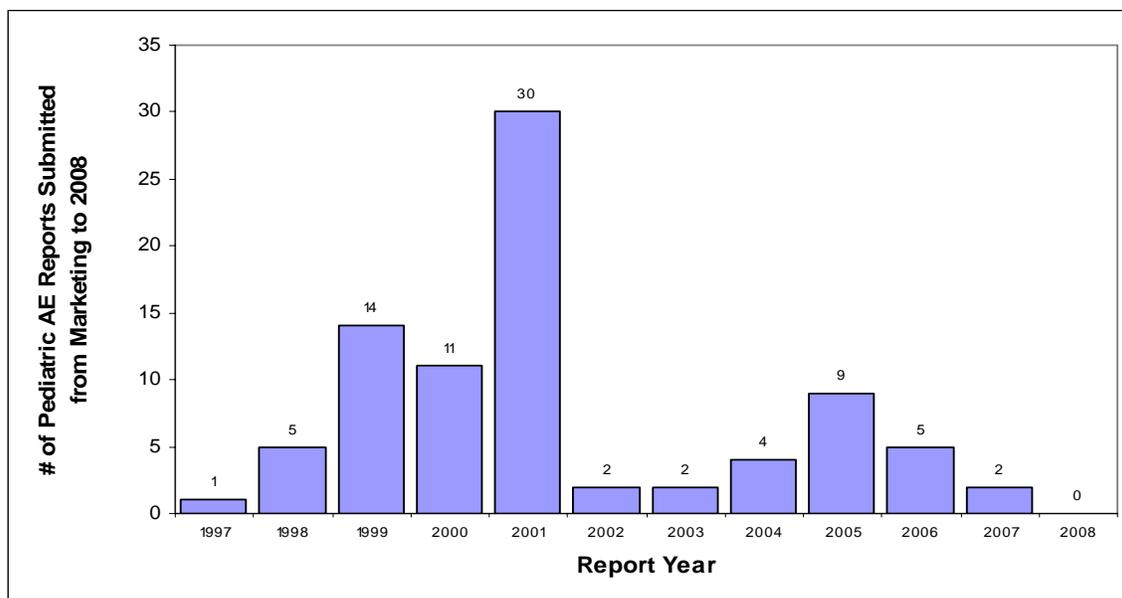
3 AERS RESULTS FOR IMIQUIMOD 5%

3.1 COUNT OF REPORTS: ALL SOURCES- US AND FOREIGN FROM MARKETING APPROVAL (TABLE 1)

Table 1: Crude counts¹ of AERS Reports for All Sources from Marketing Approval Date to January 13, 2008			
(US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	1,289 (1,122)	166 (84)	14 (5)
Pediatrics (0-16 yrs.)	84 (79)	12 (11)	1 (1)
Age unknown (Null values)	193 (159)	20 (8)	1 (0)
Total	1,566 (1,360)	198 (102)	16 (5)
¹ May include duplicates ² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, and congenital anomaly.			

3.2 REPORTING TREND FOR PEDIATRIC AERS REPORTS

The following graph depicts the number of pediatric post-marketing reports submitted to the FDA and the years the reports were submitted (from manufacturing until January 13, 2008). The year 2008 on the graph represents a partial year.



3.3 CRUDE COUNT OF REPORTS: ALL SOURCES- US AND FOREIGN FROM PEDIATRIC EXCLUSIVITY, DECEMBER 13, 2006 TO JANUARY 13, 2008 (TABLE 2)

Table 2: Crude counts ¹ of AERS Reports for All Sources from date Pediatric Exclusivity was Granted (December 13, 2006 to January 13, 2008)			
(US counts in parentheses)			
	All reports (US)	Serious ² (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
Total	40 (34)	14 (12)	0

¹ May include duplicates

² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, and congenital anomaly.

4 DISCUSSION/SUMMARY OF THE CASES

4.1 SUMMARY OF CASES RECEIVED DURING THE POST-PEDIATRIC EXCLUSIVITY PERIOD (N = 2)

The overall characteristics of the two pediatric cases identified between December 13, 2006 and January 13, 2008 are provided in Table 3 below. Additionally, a brief narrative (with reviewer comments) of each case is also provided.

Table 3: Characteristics of pediatric cases reported during the pediatric exclusivity period (December 13, 2006 to January 13, 2008), n = 2	
Gender [n=2]	Female (2)

Table 3: Characteristics of pediatric cases reported during the pediatric exclusivity period (December 13, 2006 to January 13, 2008), n = 2	
Age [n=2]	2 years old, 10 years old
Origin [n=2]	US (2)
Event date (n=2)	2007 (2)
Daily dose [n=2]	1 packet daily (2)
Duration of therapy [n=2]	1 dose, 12 days
Indications [n= 2]	Molluscum contagiosum (1), Plantar wart (1)
Outcomes [n=2]	Required Intervention (1), Other serious (1)

- AERS ISR# 5470542, US, 2007, Required Intervention, 2-year old, Female.** This 2-year old female received one dose of imiquimod (1 packet) to treat molluscum contagiosum. After one application the patient experienced skin blistering, bloody skin, and her skin reportedly “fell off in strips.” The child was taken to the Emergency Department where she was diagnosed with “chemical burns” from the use of the imiquimod product. No further information concerning the ultimate outcome of this case was provided.

Comment: Aldara is not approved for children under 12 years old and clinical studies have not demonstrated efficacy in molluscum contagiosum (labeled information). Aldara is labeled in the Warnings and Precautions section for local inflammatory reactions which can be intense, and can include skin weeping or erosions, potentially requiring an interruption of dosing.

- AERS ISR# 5531545, US, 2007, Other Serious, 10-year old, Female.** This 10-year old insulin dependent Type I diabetic applied imiquimod daily (for 12 days) to outside heel to treat plantar wart. The mother reports that the patient’s insulin requirements increased from 30 to 41 units daily while on imiquimod. After discontinuation of imiquimod the patient’s daily insulin decreased “minimally”, but remained greater than the 30 units that the patient used prior to the start of imiquimod. The mother postulated that the immune activity of imiquimod activated the child’s immune system to attack the patient’s pancreatic islet cells, thus reducing/eliminating the minimal insulin that the patient may have been producing on her own.

Comment: The product label describes systemic absorption of Aldara cream after topical administration. However, it is possible that other co-existing factors may have influenced the insulin requirements in this growing child. Although the case provided the patient’s diabetic diary, some areas were redacted and did not allow for optimal review. Of the areas available for review it appears that the magnitude of the patient’s insulin requirements after discontinuation was slightly more than before imiquimod, but less than the reported peak of 10 additional daily units.

4.2 SUMMARY OF PEDIATRIC ADVERSE EVENT REPORTS SUBMITTED FOR IMIQUIMOD FROM MARKETING TO JANUARY 13, 2008 (N = 82)

Table 4 details the overall characteristics of the 82 pediatric reports submitted from marketing to January 13, 2008, the period of exclusivity. The two reports submitted during the period of exclusivity and detailed in section 4.1 above are excluded from this overall characteristic table.

Table 4: Characteristics of All Pediatric AERS cases reported from Marketing to January 13, 2008 (n = 82)^δ	
Gender [n=82]	Female (55), Males (23)
Age [n=82]	1 day to 16 years old, median = 8 years old
Origin [n= 82]	US (78), Foreign (4)
Event date (n=79)	1997 (7), 1998 (2), 1999 (14), 2000 (34), 2001 (3), 2002 (3), 2003 (1), 2004 (5), 2005 (4), 2006 (5)
Indications [n= 82]	NR (4), Actinic Keratosis (1), Alopecia (2), Warts & Common Warts (6), Genital Warts (5), Herpes (1), Molluscum Contagiosum (20), Plantar Warts (2), Venereal Warts (1), Viral Warts (40)
Outcomes [n=82]	Death (1), Hosp (6), Required Intervention (4), Congenital Anomaly (2), Other (68)

^δ One adult case incorrectly coded as 6 months old, although captured in the search, was excluded from the characteristic table¹⁰

4.2.1 PEDIATRIC CASE CODED WITH DEATH AS AN OUTCOME (N = 1)

There was one report in the AERS database with a coded outcome of death submitted for imiquimod. This case is described as:

- **AERS ISR# 3026194, US, 1998, Death, 16 year old, Female.** This 16 year old female in a clinical study (12233-IMIQ) committed suicide (gunshot) while receiving imiquimod three times weekly. The patient had received ~ 93 doses of topical imiquimod over 31 weeks. The patient did not have a known history of depression.

Comment: The study investigators did not relate the patient's suicide to the use of the study medication. Suicide is included in the product label under Postmarketing Experience (6.5).

4.2.2 NON-FATAL SERIOUS PEDIATRIC ADVERSE EVENT REPORTS (N = 12)

There were 12 reports submitted for imiquimod in the pediatric population with coded serious outcomes, excluding the death report in section 4.2.1. We excluded from final review one adult case coded with hospitalization incorrectly identified as a six-month old child. The reported outcomes in the 12 serious pediatric cases included hospitalization (6), required intervention (4) and congenital anomaly (2). In this subset of pediatric patients treated with imiquimod, excluding the two cases that were potentially exposed via maternal use, imiquimod was used to treat venereal/genital warts (5), molluscum contagiosum (4) and herpes (1). A brief description of the serious cases, categorized by system organ class, is presented below.

4.2.2.1 NEUROLOGIC EVENTS (N = 3)

- 3 year old male hospitalized for febrile seizure ~ 40 days after starting Aldara 3 times weekly to treat *molluscum contagiosum*.¹¹ The patient was concomitantly using Tazorac 1% cream and Canthacur PS topical. At the time of hospital admission all medications were discontinued. The patient was observed for 2 days and then discontinued. Aldara cream was re-started ~ 2 weeks later for 21 days. At the end of the 21 days treatment there were no additional seizures reported.

¹⁰ AERS ISR # 4638791-7

¹¹ AERS ISR # 4635713-X

- 6 year old male hospitalized.¹² Four days after starting imiquimod for *molluscum contagiosum* the patient experienced two episodes of staring into space. Blood tests, urinalysis and CT scan were all negative. Aldara was discontinued, but later restarted. Approximately 22 days after re-starting Aldara, the patient experienced another episode of “clouded consciousness” and was taken to the ER and diagnosed with petit mal seizure. Aldara was discontinued again. Three days later the mother restarted Aldara and 10 days later the patient developed a grand mal seizure. An EEG was inconclusive and an MRI was negative.

Comment: Seizure is included in the product label as convulsion (including febrile convulsions) in the Post-Marketing Experience Section 6.5.

- 6 year old female hospitalized after receiving imiquimod three times weekly (11 days) to treat *venereal warts*.¹³ Ten days after starting imiquimod the patient experienced severe pain, weakened legs and temporary paralysis in the legs. The events resolved four days after discontinuation of imiquimod.

Comment: Temporary paralysis is included in the product label as paresis in the Post-Marketing Experience Section 6.5.

4.2.2.2 CONGENITAL ANOMALY (2)

There were two cases of congenital anomaly reported with imiquimod use. One case (US) reported multiple defects in a child whose mother used imiquimod one time weekly (viral warts) between gestational weeks nine and 16.¹⁴ The child was preterm at 34 weeks and was born with normal XY chromosomes but had undescended testicles, genitourinary reflux and small atrial and ventricular septal defects. Reportedly the child’s defects were corrected with surgery. The second case (foreign) described a child whose mother used imiquimod for four weeks from gestational weeks 14 to 18. The child was born with megacolon congenitum. The child’s physician did not see a relationship between the development of the megacolon to the use of the mother’s imiquimod.^{15,16}

Comment: Although, potentially, the developing fetuses may have been exposed to imiquimod through the mother, these two cases are not compelling in associating the mother’s use of imiquimod to the development of the children’s defects.

4.2.2.3 HEMATOLOGIC (1)

¹² AERS ISR # 3563013-8, US

¹³ AERS ISR # 4081945-1, US

¹⁴ AERS ISR # 3454265-3, US

¹⁵ AERS ISR # 3838059-2, Foreign. Megacolon congenitum (Hirschsprung’s disease) is a birth defect that affects the large intestine. A child born with Hirschsprung’s disease is missing nerve cells that stimulate muscles in the intestines to push stools through the intestine and out of the body. The disease is caused by the failure of the ganglion cells to migrate cephalocaudally through the neural crest during weeks 4 to 12 of gestation, causing an absence of ganglion cells in all or part of the colon. The disease can be hereditary and children born with Down’s syndrome are at a higher risk. The disease affects about 1 in every 5,000 newborns and is five times more frequent in males than in females. Hirschsprung’s Disease: Diagnosis and Management by J Kessmann, M.D. (American Family Physician October 15, 2006, <http://www.aafp.org/afp/20061015/1319.html>)

¹⁶ Imiquimod has a FDA pregnancy category C designation. There are no adequate and well-controlled studies in pregnant women. In embryofetal development studies in rats and rabbits, fetal effects noted at 20mg/kg/day (577xMRHD) included resorptions, ↓fetal body weights, delays in skeletal ossification, bent limb bones, exencephaly, protruding tongues and low-set ears. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 5mg/kg/day (98x MRHD).

One case described the development of thrombocytopenia purpura. A two year old male was hospitalized and diagnosed with immune thrombocytopenia purpura.¹⁷ This patient received Aldara to treat *molluscum contagiosum* 5 times weekly. Ten days after starting Aldara the patient developed bruising, petechiae and a bloody nose. The patient's platelet count was reportedly 4,000 (nl 200,000). The patient was recovering with treatment. Aldara was continued.

Comment: Thrombocytopenia purpura is not labeled, however, a decrease in platelet count is labeled (Adverse Events Section).

4.2.2.4 OTHER SERIOUS PEDIATRIC REPORTS (6)

Six US cases described labeled localized reactions including erosions and blistering, resulting in difficulty or painful urination in four of the five females in this subgroup. One female's inability to void was such that the patient had to be catheterized. Four children also experienced overlapping fatigue and/or flu-like symptoms in addition to the severe localized reactions.

- A 10 year old male developed an application site abscess requiring incision, drainage and antibiotics one month after starting imiquimod treat *molluscum contagiosum*.¹⁸ The patient had used imiquimod for four weeks; an unknown quantity was applied every other day for two weeks, followed by daily for two weeks.
- A 4 year old female hospitalized five days after starting imiquimod to treat *herpes*.¹⁹ The patient received imiquimod daily for 3 days and developed a fever, flu-like symptoms, burning pain and inability to void. No further information was provided.
- A 15 year old female applied ½ packet of imiquimod three times weekly for six applications to treat *genital warts*.²⁰ The patient applied the product at bedtime and washed it off eight hours later. Five days after starting the product the patient experienced skin burns, blisters, pain upon urination, fever and fatigue. Two days after the onset of symptoms the patient was hospitalized and treated with antibiotics for the skin burns and blisters. Concomitant medications were not provided.
- A 16 year old female applied one packet of imiquimod daily for three consecutive days (at night, and washed off in the AM) to treat *genital warts*.²¹ On the 3rd day the patient began to experience application site burning, erosions and ulcerations. The child was hospitalized after experiencing fever and increased WBC (14,000) and flu-like symptoms. There were no concomitant medications or a relevant medical history reported.
- A 7 year old female used two applications of imiquimod for *genital warts*.²² After the 2nd application, the child was diagnosed with a viral infection after experiencing a sore throat and a low grade fever. The child also experienced extreme swelling to the point of not being able to urinate. The child underwent a successful catheterization in the emergency room.

¹⁷ AERS ISR # 4352842-9, US

¹⁸ AERS ISR # 4008854-8, US

¹⁹ AERS ISR # 3276621-9, US

²⁰ AERS ISR # 3782506-6, US

²¹ AERS ISR # 5008775-5, US

²² AERS ISR # 3590699-4, US

- A 15 year old female applied one dose of imiquimod to treat *genital warts* and experienced burning, blisters, swelling and an inability to urinate due to swelling in the vaginal area.²³ The patient was treated with topical lidocaine. No other concomitant medications or medical history was reported.

5 CONCLUSION

Of the 1,566 imiquimod post-marketing reports in the AERS database from marketing to January 13, 2008, pediatric reports represented approximately 5.4% (84) of the total, with two pediatric reports submitted during the period of exclusivity. In contrast, during the three 12-month periods from January 1, 2005 to December 13, 2007 patients aged 0 to 16 years old accounted for ~ 21% of the total dispensed prescriptions for Aldara; and for ~ 22% of the total number of patients prescribed Aldara.²⁴

Overall, the two reports submitted during the period of exclusivity did not describe any new safety signals, but did continue to describe already known serious localized reactions. When the review was expanded to include the additional 82 pediatric reports submitted for imiquimod, DPV reviewed two congenital anomaly reports that did not provide compelling evidence to associate the mother's use of imiquimod during gestational development with the development of the children's congenital anomalies. Additionally, for the remainder of the pediatric post-marketing reports, the majority of the serious reports described already known flu-like and severe localized reactions. Among the severe localized reactions, a number of female children described painful urination or the inability to void as a consequence of the localized reactions. In particular, one female child's inability to void was treated by catheterization.

6 RECOMMENDATIONS

- DPV recommends enhancing the product label to identify that the inability to void or painful voiding may be particularly bothersome to female patients using imiquimod of genital warts.
- DPV will continue to continue monitoring of adverse events with the use of imiquimod pediatric patients.

7 REFERENCES

1. Borders-Hemphill V. Aldara™ (Imiquimod) Cream BPCA Drug Use Review, OSE RCM# 2008-714, July 17, 2008.
2. Papadopoulos EJ, DDDP, Clinical Executive Summary – Imiquimod 5% Cream, Three Times Weekly for Molluscum Contagiosum in Children 2 to 12; NDA 20-723, Submission SE8-020, March 15, 2007
3. Ahn HY, Clinical Pharmacology Executive Summary of Aldara for Molluscum Contagiosum, March 13, 2007.

²³ AERS ISR# 3635170-6, US

²⁴ Borders-Hemphill V. Aldara™ (Imiquimod) Cream BPCA Drug Use Review, OSE RCM# 2008-714, July 17, 2008.

4. Hirschsprung's Disease: Diagnosis and Management by J Kessmann, M.D. (American Family Physician October 15, 2006, <http://www.aafp.org/afp/20061015/1319.html>)

Appendix

Limitations of the Adverse Event Reporting System (AERS)

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Marilyn Pitts
9/3/2008 01:45:58 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
9/3/2008 05:38:17 PM
DRUG SAFETY OFFICE REVIEWER