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To: M. Dianne Murphy, MD
Director, Office of Pediatric Therapeutics (OPT), OIASI
Office of the Commissioner

CDR Lisa Mathis, M.D., USPHS
OND Associate Director
Pediatric and Maternal Health Team
Office of New Drugs

Felicia Collins, MD,
Medical Officer
Pediatric and Maternal Health Team
Office of New Drugs

Thru: Vicky Borders-Hemphill, Pharm.D., Acting Drug Use Data Analyst
Team Leader
Division of Epidemiology
Office of Surveillance and Epidemiology

From: LCDR Kendra Worthy, Pharm.D., Drug Use Data Analyst
Division of Epidemiology
Office of Surveillance and Epidemiology

Subject: Aldara[™] (Imiquimod) cream BPCA Drug Use Review

Drug Name(s): Aldara[™] (Imiquimod)

Application Type/Number: NDA 20-723

Applicant/sponsor: Graceway Pharmaceuticals

OSE RCM #: 2008-714

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EXECUTIVE SUMMARY

This review examines drug utilization patterns for Aldara™ (imiquimod) Cream, an immune response modifier for topical administration, in the pediatric population (patients aged 0-16 years) with a primary focus on patterns of use two years before and one year following the granting of Pediatric Exclusivity on December 13, 2006. Since approximately 92% of Aldara™ boxes were sold to U.S. retail settings and approximately 8% were sold to non-retail [mainly federal facilities (~34%)] settings during the pre- and post-exclusivity periods, this review focuses on the outpatient setting. Outpatient proprietary drug use databases licensed by FDA were used to examine the patterns of use for Aldara™ during the three 12-month periods from January 1, 2005 through December 31, 2007.

For each of the three 12-month periods from January 1, 2005 through December 31, 2007:

- Aldara™ Cream represented approximately 71% of the total projected number of dispensed prescriptions for selected products used to treat warts.
- Aldara™ prescriptions in the pediatric population (ages 0-16 years) accounted for approximately 21% of total dispensed Aldara™ prescriptions.
- Of the prescriptions dispensed to patients aged 0 to 16 years, around 40% were dispensed to patients aged 6-10 years and 38% dispensed to patients ages 11 to 16 years.
- Approximately 22% of total projected patients that filled a prescription for Aldara™ were aged 0 to 16 years.
- Dermatology was the top prescribing specialty for Aldara™ Cream.
- The top diagnosis code associated with the use of Aldara™ Cream for patients aged 0 to 16 years were “Viral Warts” (ICD-9 078.1) and “Molluscum Contagiosum” (ICD-9 078.0).

1 INTRODUCTION

Using the currently available proprietary drug use databases licensed by the Agency, this review describes outpatient drug use patterns for Aldara™ (imiquimod) cream in the pediatric population as well as in the adult population and includes data for three 12-month periods starting two years before and one year following the granting of pediatric exclusivity on December 13, 2006.

2 METHODS AND MATERIALS

IMS Health, IMS National Sales Perspectives™ data (*see Appendix 2*) were used to determine the setting in which Aldara™ cream was sold. Sales of this product by number of boxes (eaches) sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for three 12-month periods from January 1, 2005 through January 31, 2007 (*data not provided*).¹ During the three 12-month periods of this review, retail settings (chain stores, independent pharmacies, food stores, and mail service) accounted for the majority of Aldara™ sales (92%) and approximately 8% were sold to non-retail [mainly federal facilities (~34%)] settings. Thus, the examination of Aldara™ utilization patterns focused on the outpatient setting.

Outpatient use and patient demographics (stratified by ages 0-2 years, 3-5 years, 6-10 years, 11-16 years, and 17+ years for Aldara™ cream) were measured from Verispan, LLC: Vector One®: National (VONA) and Total Patient Tracker (TPT) (*Appendix 2*). Indications for use were obtained from the Verispan’s Physician’s Drug and Diagnosis Audit (PDDA) (*Appendix 2*). From these data sources, estimates of the number of prescriptions dispensed, the number of patients who received a prescription for Aldara™ cream, and the number of drug mentions by office-based physicians, were obtained from January 1, 2005 through

¹ IMS Health, IMS Nationals Sales Perspectives™, Data extracted 6-19-2008, Source file: NSPC 2008-714 6-19-06 Imiquimod 0806imiq.xls

December 31, 2007, inclusive. For comparative purposes, other select products used to treat warts were also examined, including: fluorouracil (Efudex[®], Carac[®], Fluoroplex[®]), interferon alfa-2b (Intron[®] A), and interferon alfa-n3 (Alferon[®] N).

3 RESULTS

During the three 12-month periods from January 1, 2005 through December 31, 2007, dispensed prescriptions for Aldara[™] Cream represented the majority (approximately 71%) of the projected number of prescriptions dispensed for products used to treat warts in the United States. The projected number of Aldara[™] dispensed prescriptions decreased approximately 5% from the pre-exclusivity period (January 1, 2005 through December 31, 2006) to the post-exclusivity period (January 1, 2007 through December 31, 2007) (*Table 1*).

Retail prescriptions for Aldara[™] dispensed from 2005-2007 accounted for the majority of prescriptions dispensed for products used to treat warts. On average, Aldara[™] prescriptions accounted for 71%, Efudex[®] prescriptions 16%, and Carac[®] prescriptions 12% (*Table 1, Figure 1*).

During the three 12-month periods from January 1, 2005 through December 31, 2007, dispensed prescriptions for Aldara[™] in the pediatric population (ages 0-16 years) accounted for approximately 21% of the total projected number of dispensed prescriptions for Aldara[™]. Of the prescriptions dispensed to patients aged 0 to 16 years, around 40% were dispensed to patients aged 6-10 years and 38% dispensed to patients ages 11 to 16 years (*Table 2*). Of the patients who filled a prescription for Aldara[™] in the outpatient retail pharmacy setting, approximately 22% of total projected patients were aged 0 to 16 years, and the proportion of projected pediatric patients aged 0 to 16 years were similar to the proportion of dispensed prescriptions for the same age groups (*Table 3*).

During the three 12-month periods from January 1, 2005 through December 31, 2007, Dermatology was the top prescribing specialty with approximately 45% of Aldara[™] prescriptions. General Practice was second with approximately 13% (*Table 4*).

According to office-based physician practices in the U.S., “Viral Warts” (ICD-9 078.1) and “Molluscum Contagiosum” (ICD-9 078.0) were the top diagnosis codes associated with the use of Aldara[™] for patients aged 0 to 16 years. Pediatric patients accounted for approximately 23% of office-based visits reportedly associated with the use of Aldara[™] during the three 12-month study periods (*Table 5*). “Viral Warts” (ICD-9 078.1) was also the top diagnosis for adults aged 17 years and older associated with the use of Aldara[™].

4 LIMITATIONS

Findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated that Aldara[™] is distributed primarily in outpatient settings based on the IMS Health, IMS National Sales Perspectives[™]. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use. Sales for the comparator products Intron[®] A and Alferon[®] N are distributed primarily in inpatient settings; therefore, estimates of these products are likely underestimated in this review.

Verispan’s Physician Drug & Diagnosis Audit (PDDA) data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly if use is not common in the pediatric population. Verispan recommends caution interpreting projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals.

5 CONCLUSIONS

Use of Aldara™ (imiquimod) cream in the pediatric and adult populations has been declining over the three 12-month study periods examined. Pediatric patients aged 0-16 years make up approximately 21% of all patients that fill a retail prescription for Aldara™. The majority of Aldara™ prescriptions dispensed to pediatric patients were dispensed to patients aged 6-10 years followed closely by 11-16 year-old age groups.

CONCURRENCE

Vicky Borders-Hemphill, Pharm.D.

Acting Team Leader

Division of Epidemiology (DEPi)

Solomon Iyasu, M D, MPH

Director

Division of Epidemiology (DEPi)

APPENDICES

APPENDIX 1: Tables

Table 1. Total number of retail prescriptions* dispensed for selected products used to treat warts, years 2005 - 2007

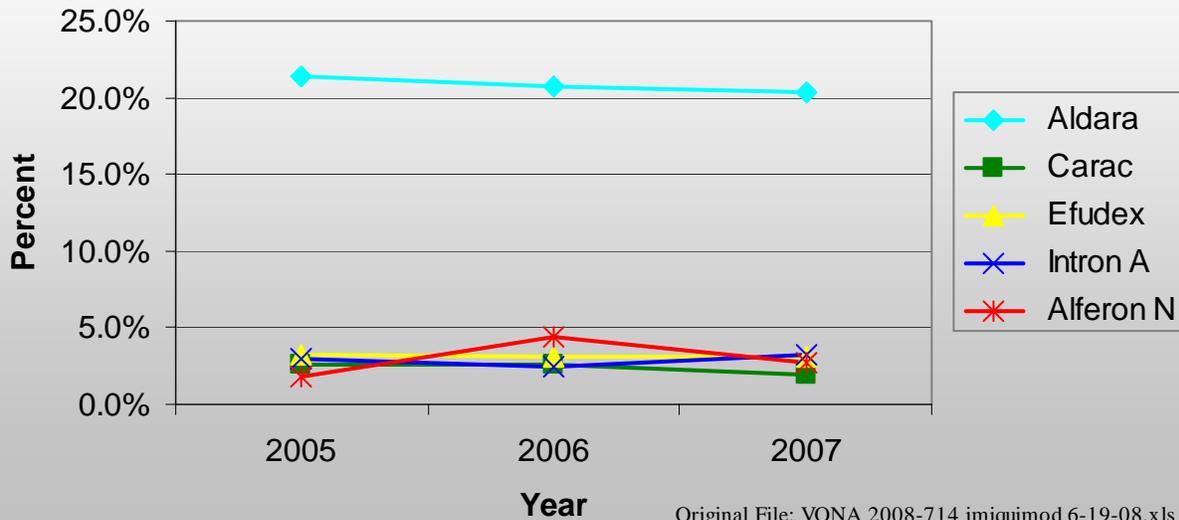
	2005		2006		2007	
	Retail TRxs N	Share %	Retail TRxs N	Share %	Retail TRxs N	Share %
TOTAL MARKET	1,779,875	100.0%	1,817,527	100.0%	1,623,092	100.0%
Aldara (imiquimod)	1,253,153	70.4%	1,257,177	69.2%	1,194,224	73.6%
Carac (flurouracil)	177,159	10.0%	195,159	10.7%	229,905	14.2%
Efudex (flurouracil)	317,597	17.8%	337,087	18.5%	173,308	10.7%
Intron A (interferon alfa-2b)	15,418	0.9%	13,683	0.8%	12,710	0.8%
Fluoroplex (flurouracil)	16,168	0.9%	13,983	0.8%	12,467	0.8%
Alferon N (interferon alfa-n3)	380	0.0%	438	0.0%	478	0.0%

Verispan, LLC, Vector One® National (VONA), Data extracted 6-2008. Source File: 2008-714 6-19-08 imiquimod comp.qry

*mail order pharmacies not included

Figure 1: Percentage of Retail Prescriptions Dispensed to Pediatric Patients, 2005 - 2007

Verispan Vector One®: National (VONA). Extracted 6/2008



Original File: VONA 2008-714 imiquimod 6-19-08.xls

Table 2. Total number of retail prescriptions* dispensed for imiquimod by age, years 2005 - 2007

	2005		2006		2007	
	Retail TRxs N	Share %	Retail TRxs N	Share %	Retail TRxs N	Share %
Aldara	1,253,105	100.0%	1,257,170	100.0%	1,194,218	100.0%
0-16	267,967	21.4%	259,980	20.7%	241,624	20.3%
0-2	10,364	0.8%	9,522	0.8%	8,732	0.7%
3-5	48,906	3.9%	47,755	3.8%	45,085	3.8%
6-10	103,900	8.3%	103,587	8.2%	97,433	8.2%
11-16	104,797	8.4%	99,116	7.9%	90,374	7.6%
17+	980,801	78.3%	994,170	79.1%	950,190	79.6%
UNSPEC.	4,337	0.3%	3,020	0.2%	2,404	0.2%

Verispan, LLC, Vector One® National (VONA), Data extracted 6-2008. Source File: 2008-714 imiquimod 6-19-08.qry

*mail order pharmacies not included

Table 3: Total number of patients*, by age, receiving a prescription from outpatient retail pharmacies for selected products used to treat warts , 2005-2007

	2005		2006		2007	
	Projected Patient Count N	Total Patient Share %	Projected Patient Count N	Total Patient Share %	Projected Patient Count N	Total Patient Share %
Grand Total	1,259,862	100.00%	1,302,572	100.00%	1,156,363	100.00%
ALDARA	849,039	67.39%	859,551	65.99%	823,780	71.24%
Product Total						
0 - 16	189,728	22.35%	185,239	21.55%	173,817	21.10%
17+	655,185	77.17%	671,006	78.06%	646,521	78.48%
Unknown Age	5,991	0.71%	5,080	0.59%	5,103	0.62%
CARAC	142,013	11.27%	156,891	12.04%	184,548	15.96%
Product Total						
0 - 16	4,137	2.91%	4,728	3.01%	4,309	2.33%
17+	136,693	96.25%	151,095	96.31%	179,002	97.00%
Unknown Age	1,360	0.96%	1,220	0.78%	1,404	0.76%
EFUDEX	278,602	22.11%	296,329	22.75%	153,030	13.23%
Product Total						
0 - 16	10,044	3.61%	10,200	3.44%	5,039	3.29%
17+	265,014	95.12%	283,265	95.59%	146,803	95.93%
Unknown Age	3,779	1.36%	3,042	1.03%	1,262	0.82%
INTRON A	3,937	0.31%	3,557	0.27%	3,395	0.29%
Product Total						
0 - 16	111	2.83%	92	2.60%	97	2.85%
17+	3,770	95.77%	3,420	96.15%	3,283	96.70%
Unknown Age	194	4.94%	84	2.36%	27	0.79%
ALFERON N	139	0.01%	173	0.01%	232	0.02%
Product Total						
0 - 16	5	3.79%	14	8.16%	9	3.71%
17+	120	86.21%	148	85.53%	170	73.44%
Unknown Age	37	26.32%	34	19.52%	110	47.44%

*Subtotals may not sum exactly, due to rounding. Due to aging of patients during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across age bands is not advisable and will result in overestimates of patient counts.

Source: Verispan, LLC: Total Patient Tracker, 2005 - 2007, Extracted June 2008. File: TPT 2008-714 Imiquimod 6-23-08 Custom Age Group Report.xls

Table 4. Total number of retail prescriptions* stratified by prescribing physician dispensed for imiquimod, years 2005 - 2007

	2005		2006		2007	
	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share
	N	%	N	%	N	%
imiquimod	1,253,161	100.0%	1,257,189	100.0%	1,194,237	100.0%
DERM	564,690	45.1%	563,178	44.8%	527,004	44.1%
GP/FM/DO	157,131	12.5%	165,364	13.2%	156,427	13.1%
OB/GYN	110,618	8.8%	112,709	9.0%	109,731	9.2%
UNSPEC	133,192	10.6%	106,828	8.5%	91,453	7.7%
PED	50,397	4.0%	53,589	4.3%	53,418	4.5%
All Others	237,133	18.9%	255,521	20.3%	256,204	21.5%

Verispan, LLC, Vector One[®] National (VONA), Data extracted 6-2008. Source File: 2008-714 imiquimod MD 6-19-08.qry

*mail order pharmacies not included; numbers may not match exactly due to rounding error.

Table 5: Projected Uses During Patient Visits in Office-Based Practices in the U.S. for Aldara[®] during years 2005- 2007.

	2005-2007	
	Uses (000)	Share %
Aldara	4,495	100.0%
0-16	1,035	23.0%
0781 VIRAL WARTS	636	61.5%
0780 MOLLUSCUM CONTAGIOSUM	357	34.5%
2280 HEMANGIOMA, ANY SITE	11	1.1%
7014 KELOID SCAR	8	0.8%
0794 H PAPILOMA VIRUS INF	8	0.8%
All Others	14	1.4%
17+	3,181	70.8%
0781 VIRAL WARTS	2,100	66.0%
7020 ACTINIC KERATOSIS	460	14.5%
1739 MALIG NEO SKIN NOS	208	6.5%
0794 H PAPILOMA VIRUS INF	54	1.7%
0780 MOLLUSCUM CONTAGIOSUM	52	1.6%
All Others	307	9.6%
UNSPEC.	280	6.2%
0781 VIRAL WARTS	175	62.3%
7020 ACTINIC KERATOSIS	44	15.7%
0780 MOLLUSCUM CONTAGIOSUM	18	6.5%
1739 MALIG NEO SKIN NOS	17	6.1%
0549 HERPES SIMPLEX NOS	7	2.7%
All Others	19	6.7%

Verispan, Physician Drug and Diagnosis Audit (PDDA), Data extracted 6-2008.

Source File: PDDA 2008-714 6-23-08 imiquimod.xls

APPENDIX 2: Database Descriptions

Verispan, LLC: Vector One®: National (VONA)

Verispan's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

Verispan, LLC: Vector One®: Total Patient Tracker (TPT)

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

Verispan, LLC: Physician Drug & Diagnosis Audit (PDDA)

Verispan's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Verispan uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

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Kendra Worthy
8/7/2008 10:27:21 AM
DRUG SAFETY OFFICE REVIEWER

Vicky Borders-Hemphill
8/7/2008 11:12:59 AM
DRUG SAFETY OFFICE REVIEWER