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Office of Surveillance and Epidemiology**

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Subject: BPCA Drug Use Review: Comparison of Elidel[®] cream and
Protopic[®] ointment utilization trends following 2006 labeling
changes

Drug Name(s): Elidel[®] (pimecrolimus) cream
Protopic[®] (tacrolimus) ointment

Application Type/Number: NDA 21-302
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Applicant/sponsor: Novartis Pharmaceutical Corp.
Astellas Pharma US, Inc.

OSE RCM #: 2009-772

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EXECUTIVE SUMMARY

This review examines drug utilization patterns for Elidel® (pimecrolimus) cream and Protopic® (tacrolimus) ointment, topical calcineurin inhibitors, in the pediatric population, patients age 0-1, 2-6, 7-12, 13-16 years. In year 2006, product labeling for pimecrolimus cream and tacrolimus ointment was updated with additional long-term safety information including a boxed warning and medication guide regarding possible malignancy risk. Drug utilization trends are compared for total dispensed prescriptions, total project patients, and prescriber specialties in the pediatric population for the two 12-month periods before and after year 2006 labeling changes. Since around 84% of both products were sold to U.S. outpatient retail settings and approximately 10% were sold to non-retail settings during the review period, this review focuses on the outpatient setting.

During the five years from January 1, 2004 through December 31, 2008:

- The total projected number of pimecrolimus cream and tacrolimus ointment dispensed prescriptions decreased by 74% from approximately 4.82 million prescriptions in year 2004 to approximately 1.27 million prescriptions in year 2008. Pimecrolimus cream accounted for the majority of the market from between 64% to nearly 80% of the market share in comparison to tacrolimus ointment. Dispensed prescriptions for pimecrolimus cream decreased 64% from year 2004 to 2006 compared to a decrease of 41% between year 2006 through 2008. Dispensed prescriptions for tacrolimus ointment followed similar trends and decreased 50% between years 2004 and 2006 compared to an 8% decrease from year 2006 to 2008.
- The total projected number of patients who filled a prescription for pimecrolimus cream and tacrolimus ointment decreased by 77% and 48%, respectively, for this review period. For pimecrolimus cream, total projected patients decreased approximately 62% between year 2004 and 2006 compared to 40% between year 2006 and 2008. Total projected patients for tacrolimus ointment decreased approximately 47% between year 2004 through 2006 compared to 35% between year 2006 and 2008. For pimecrolimus cream and tacrolimus ointment, the pediatric subgroup age 0-1 year experienced the largest decline in total number of projected patients.
- Dermatology was the top prescribing specialty for both pimecrolimus cream and tacrolimus ointment in year 2008
- The top diagnosis code associated with the use of pimecrolimus cream was “Dermatitis Nos” (ICD-9 692.9). The top diagnosis code associated with the use of tacrolimus ointment was “Dermatitis Nos” (ICD-9 692.9) in the pediatric subgroup age 0-1 year and patients age 17 years and greater. “Other Atopic Dermatitis” (ICD-9 691.8) was the top diagnosis code in the pediatric subgroup age 2-6 years. For the pediatric subgroups age 7-12 years and 13-16 years, “Dermatitis Nos” and “Other Atopic Dermatitis” were the top diagnoses codes associated with the use of tacrolimus ointment for the entire review period.

1 INTRODUCTION

Using the currently available proprietary drug use databases licensed by the Agency, this review describes outpatient drug use patterns for pimecrolimus cream and tacrolimus ointment in the pediatric population as well as in the adult population for years 2004 through 2008.

2 METHODS AND MATERIALS

IMS Health, IMS National Sales Perspectives™ data (*see Appendix 2*) were used to determine the setting in which pimecrolimus cream and tacrolimus ointment were sold. Sales of these products by number of packages and tube (eaches) sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for year 2008 (*data not provided*).¹ During the review period, retail settings (chain

¹ IMS Health, IMS Nationals Sales Perspectives™, Year 2008. Data extracted 1-2009, Source file: 0901fluc.DVR

stores, independent pharmacies, and food stores) accounted for the majority of pimecrolimus cream and tacrolimus ointment sales (84%) and approximately 9-10% were sold to non-retail settings. Thus, the examination of pimecrolimus cream and tacrolimus ointment utilization patterns focused on the outpatient setting, excluding mail order channels.

Outpatient use and patient demographics (stratified by ages 0-1, 2-6, 7-12, 13-16 and 17+ years) for pimecrolimus cream and tacrolimus ointment were measured from the SDI, Vector One[®]: National (VONA) and Total Patient Tracker (TPT) (*Appendix 2*). Indications for use were obtained from the SDI'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 pimecrolimus cream or tacrolimus ointments, and the number of drug mentions by office-based physicians, were obtained from January 1, 2004 through December 31, 2008 inclusive.

3 RESULTS

During the five 12-month periods from January 1, 2004 through December 31, 2008, the total projected number of pimecrolimus cream and tacrolimus ointment dispensed prescriptions decreased from approximately 4.82 million prescriptions in year 2004 to approximately 1.27 million prescriptions in year 2008, a decrease of 74%. *Figure 1 (Appendix 1)* shows the total number of dispensed prescriptions for pimecrolimus cream and tacrolimus ointment through U.S. outpatient retail pharmacies by month for years 2004 through 2008. Throughout the time period, pimecrolimus accounted for the majority of the market from between 64% to nearly 80% of the market share in comparison to tacrolimus ointment. Trends in use for both products, but especially for pimecrolimus, underwent a dramatic shift over the study period with the most dramatic changes occurring in March 2005 following the release of a Public Health Advisory. Dispensed prescriptions for pimecrolimus decreased by 64% from year 2004 to 2006 compared to a decrease of 41% between years 2006 through 2008. The pediatric age group 0-1 year accounted for the largest decline with a decrease of 87% between year 2004 and 2006 and a decrease of 52% between year 2006 and 2008 (*Figure 2, Table 1*). Tacrolimus ointment dispensed prescriptions followed similar trends and decreased 50% between year 2004 and 2006 compared to an 8% decrease from year 2006 to 2008 (*Figure 3, Table 1*) with the largest decreases seen in the younger pediatric age groups.

Similarly, the total projected number of patients who filled a prescription for pimecrolimus cream and tacrolimus ointment decreased by 77% and 48%, respectively, from January 1, 2004 through December 31, 2008. For pimecrolimus cream, total projected patients decreased approximately 62% between years 2004 through 2006 compared to 40% in year 2006 through 2008. The pediatric subgroup age 0-1 year using pimecrolimus cream decreased from 351,000 patients in year 2004 to approximately 23,000 patients by year 2008, a decrease of 93%. Total projected patients for tacrolimus ointment decreased approximately 47% between years 2004 through 2006 compared to 3.5% in year 2006 through 2008. The most dramatic decline for tacrolimus ointment occurred in the pediatric subgroup age 0-1 year between years 2004 through 2008, a decrease of nearly 85% (*Table 2*).

For pimecrolimus cream, Pediatricians were the most common prescribing specialty for years 2004 and 2005 accounting for roughly a quarter of dispensed prescriptions followed by Dermatology with approximately 20% of dispensed prescriptions. Beginning in year 2006, dispensed prescriptions by the Dermatology specialty surpassed dispensed prescriptions by Pediatrics. By year 2008, Dermatology accounted for approximately 26% of dispensed prescriptions followed by Pediatrics and General Practice/Family Medicine/Doctor of Osteopathy (GP/FM/DO) with approximately 19% of the market each. For tacrolimus ointment, Dermatology was the top prescribing specialty with approximately 48%-53% of dispensed prescriptions for the entire review period. Pediatricians were the second most common prescribing specialty with approximately 8% - 15% of dispensed prescriptions for the entire review period (*Table 3*).

According to office-based physician practices in the U.S., the top diagnosis code associated with the use of pimecrolimus cream for all pediatric age subgroups was "Dermatitis Nos" (ICD-9 692.9) for the combined years 2004 through 2008. For tacrolimus ointment, "Dermatitis Nos" (ICD-9 692.9) was the top diagnosis

code in the pediatric subgroup age 0-1 year. “Other Atopic Dermatitis” (ICD-9 691.8) was the top diagnosis code in pediatric patients age 2-6 years. For the pediatric subgroups age 7-12 years and 13-16 years, “Dermatitis Nos” and “Other Atopic Dermatitis” were the top diagnoses codes associated with the use of tacrolimus ointment for the entire review period (*Figure 4*).

4 LIMITATIONS

Findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated pimecrolimus cream and tacrolimus ointment were distributed primarily in the outpatient setting 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.

SDI’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. SDI 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

The total number of pimecrolimus cream and tacrolimus ointment dispensed prescriptions decreased by 74% from year 2004 to 2008. The largest decline in total dispensed prescriptions for pimecrolimus cream and tacrolimus ointment occurred prior to labeling changes made in year 2006, however, overall utilization for both products continued to decrease in year 2007 and 2008. The total projected number of patients who filled a prescription for pimecrolimus cream and tacrolimus ointment decreased by 77% and 48%, respectively, from year 2004 to 2008. In the pediatric subgroup age 0-1 year, patients using pimecrolimus cream decreased 93% from year 2004 through year 2008. Similarly, for tacrolimus ointment, the number of patients in the pediatric subgroup age 0-1 year declined by approximately 85% between year 2004 and 2008. Dermatology was the top prescribing specialty for pimecrolimus cream and tacrolimus ointment for year 2008. “Dermatitis Nos” and “Other Atopic Dermatitis” were the top diagnoses codes associated with the use of both products.

APPENDICES

APPENDIX 1: Figures and Tables

Figure 1. Total number of dispensed prescriptions for selected market through U.S. outpatient retail pharmacies by month, January 1, 2004 – December 31, 2008

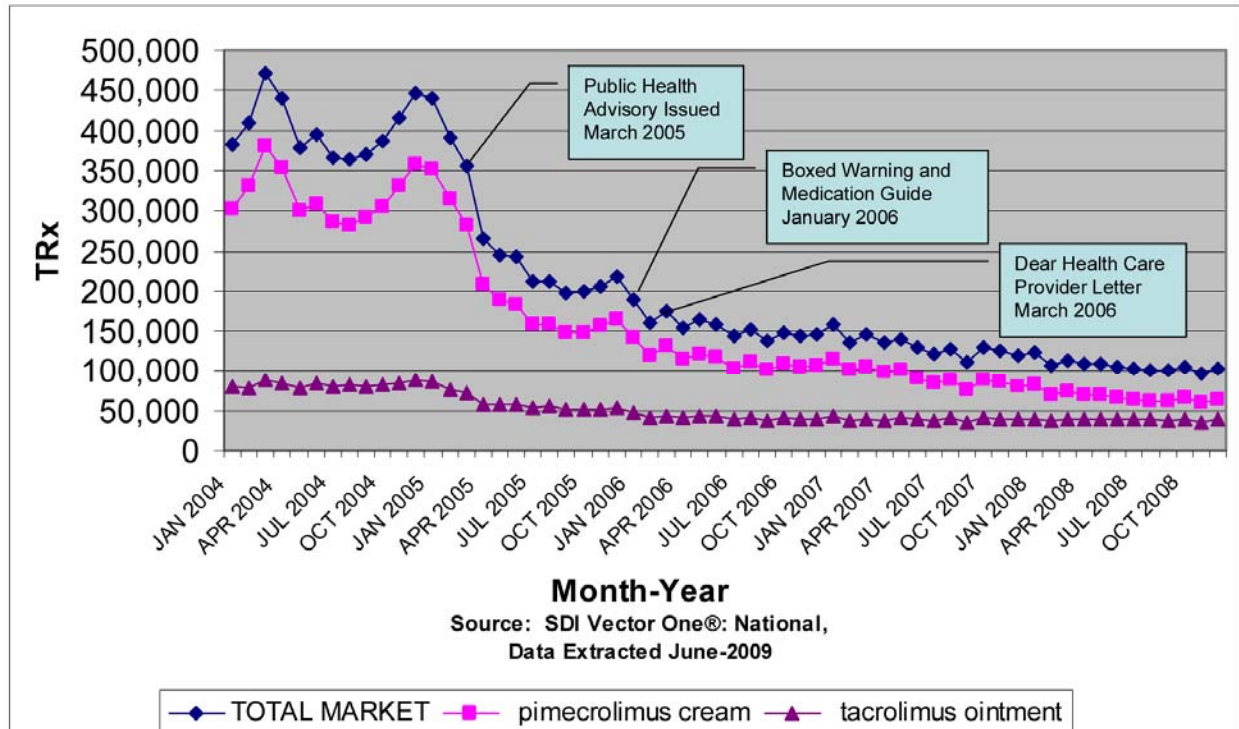


Table 1. Total number of dispensed prescriptions for selected market by patient age (0-1, 2-6, 7-12, 13-16, 17+) through U.S. outpatient retail pharmacies, January 1, 2004 - December 31, 2008

	2004		2005		2006		2007		2008	
	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share
	N	%	N	%	N	%	N	%	N	%
TOTAL MARKET	4,822,663	100.0%	3,186,110	100.0%	1,877,689	100.0%	1,580,946	100.0%	1,274,173	100.0%
pimecrolimus cream	3,829,776	79.4%	2,462,740	77.3%	1,379,138	73.4%	1,114,870	70.5%	813,539	63.8%
Age 0-1	525,801	13.7%	225,216	9.1%	66,173	4.8%	51,623	4.6%	31,575	3.9%
Age 2-6	849,342	22.2%	510,763	20.7%	249,218	18.1%	196,042	17.6%	134,459	16.5%
Age 7-12	454,685	11.9%	294,381	12.0%	164,789	11.9%	141,267	12.7%	105,866	13.0%
Age 13-16	201,369	5.3%	138,115	5.6%	83,062	6.0%	67,999	6.1%	50,781	6.2%
Age 17+	1,763,204	46.0%	1,266,870	51.4%	806,363	58.5%	651,859	58.5%	487,097	59.9%
UNSPEC.	35,375	0.9%	27,395	1.1%	9,533	0.7%	6,080	0.5%	3,761	0.5%
tacrolimus ointment	992,887	20.6%	723,370	22.7%	498,551	26.6%	466,076	29.5%	460,634	36.2%
Age 0-1	68,542	6.9%	30,903	4.3%	10,639	2.1%	8,832	1.9%	8,953	1.9%
Age 2-6	190,676	19.2%	120,246	16.6%	67,296	13.5%	53,191	11.4%	50,012	10.9%
Age 7-12	115,745	11.7%	79,158	10.9%	53,738	10.8%	51,919	11.1%	51,315	11.1%
Age 13-16	55,188	5.6%	41,283	5.7%	28,163	5.6%	25,519	5.5%	24,814	5.4%
Age 17+	553,900	55.8%	445,825	61.6%	335,213	67.2%	324,155	69.5%	323,211	70.2%
UNSPEC.	8,836	0.9%	5,955	0.8%	3,502	0.7%	2,460	0.5%	2,329	0.5%

Source: SDI Vector One®: National, Data Extracted June-2009. File: VONA 2009-772 Elidel Protopic 06-29-09.xls

Figure 2. Total number of dispensed prescriptions for pimecrolimus cream through U.S. outpatient retail pharmacies by patient age, January 1, 2004 – December 31, 2008

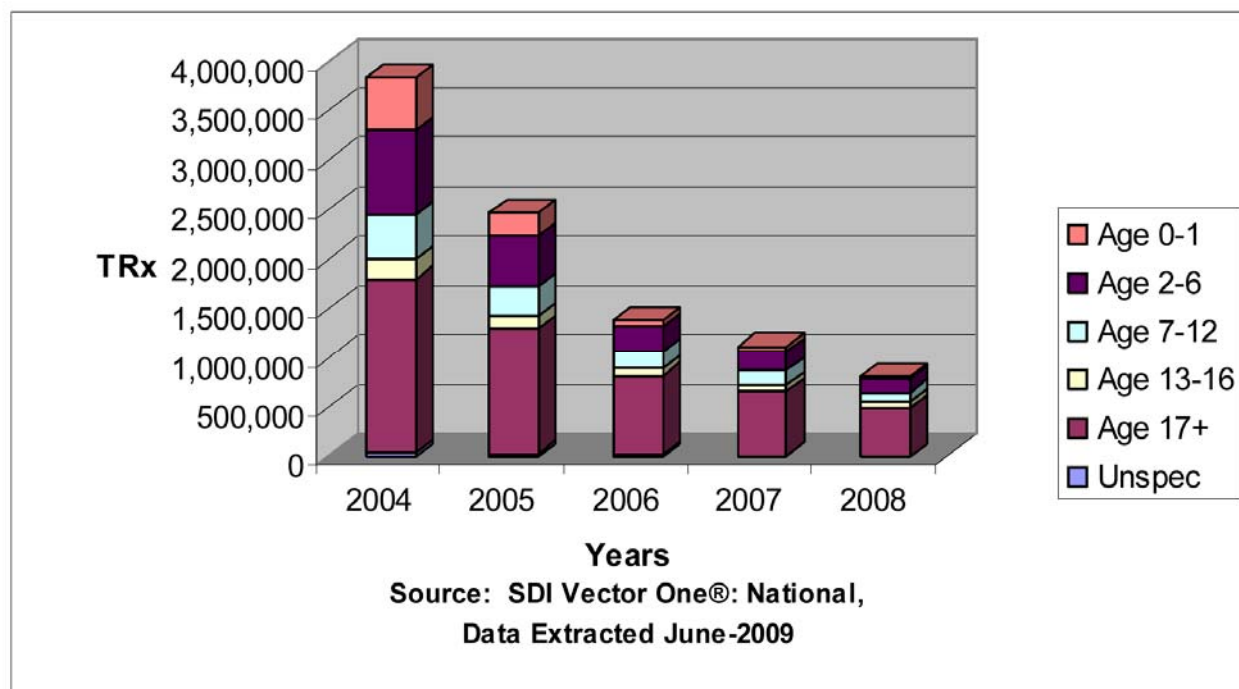


Figure 3. Total number of dispensed prescriptions for tacrolimus ointment through U.S. outpatient retail pharmacies by patient age, January 1, 2004 – December 31, 2008

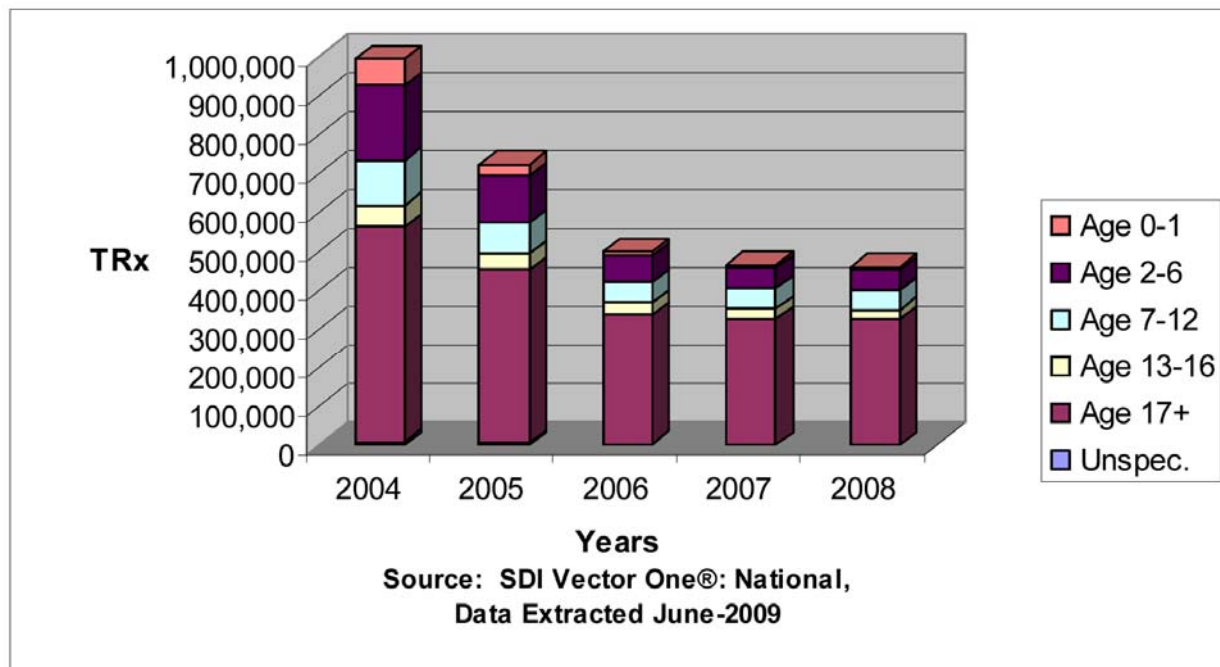


Table 2. Total number of projected patients (ages 0-1, 2-6, 7-12, 13-16, 17+) who filled a prescription for the selected market in U.S. outpatient retail pharmacies, January 1, 2004 - December 31, 2008

	2004		2005		2006		2007		2008	
	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share
	N	%	N	%	N	%	N	%	N	%
pimecrolimus cream	2,536,781	100.0%	1,689,284	100.0%	963,821	100.0%	778,241	100.0%	575,417	100.0%
Age 0 - 1	351,188	13.8%	169,977	10.1%	51,872	5.4%	39,600	5.1%	23,309	4.1%
Age 2 - 6	546,929	21.6%	347,514	20.6%	171,705	17.8%	135,184	17.4%	92,723	16.1%
Age 7 - 12	314,511	12.4%	209,152	12.4%	119,016	12.3%	101,307	13.0%	75,899	13.2%
Age 13 - 16	139,310	5.5%	96,590	5.7%	58,965	6.1%	48,302	6.2%	35,991	6.3%
Age 17+	1,189,221	46.9%	864,023	51.1%	562,096	58.3%	454,848	58.4%	348,182	60.5%
UNSPEC	31,718	1.3%	23,042	1.4%	9,211	1.0%	5,921	0.8%	4,108	0.7%
tacrolimus ointment	628,392	100.0%	474,930	100.0%	335,980	100.0%	321,295	100.0%	324,176	100.0%
Age 0 - 1	44,327	7.1%	21,696	4.6%	7,997	2.4%	6,590	2.1%	6,451	2.0%
Age 2 - 6	112,644	17.9%	73,985	15.6%	41,746	12.4%	34,953	10.9%	33,146	10.2%
Age 7 - 12	74,162	11.8%	52,740	11.1%	35,844	10.7%	34,885	10.9%	35,065	10.8%
Age 13 - 16	36,566	5.8%	27,857	5.9%	19,547	5.8%	17,923	5.6%	17,885	5.5%
Age 17+	360,050	57.3%	298,003	62.7%	229,791	68.4%	226,572	70.5%	230,537	71.1%
UNSPEC	7,457	1.2%	5,439	1.1%	3,513	1.0%	2,792	0.9%	2,819	0.9%

*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: SDI Total Patient Tracker. File: TPT 2009-772 Elidel 06-30-09.xls and TPT 2009-772 Protopic 06-30-09.xls

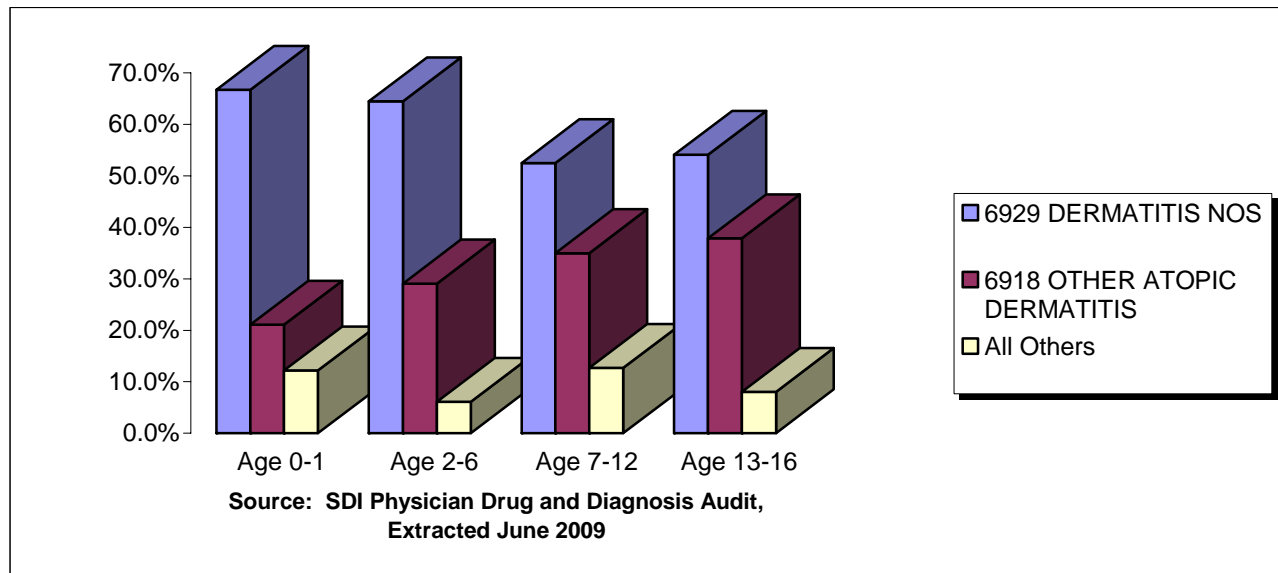
Table 3. Total number of dispensed prescriptions for selected market in outpatient retail pharmacies by top 10 prescribing specialties, January 1, 2004 - December 31, 2008

	2004		2005		2006		2007		2008	
	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share
	N	%	N	%	N	%	N	%	N	%
TOTAL MARKET	4,822,639	100.0%	3,186,121	100.0%	1,877,727	100.0%	1,581,010	100.0%	1,274,157	100.0%
pimecrolimus	3,829,768	79.4%	2,462,765	77.3%	1,379,145	73.4%	1,114,893	70.5%	813,531	63.8%
DERM	754,579	19.7%	499,761	20.3%	320,623	23.2%	274,769	24.6%	213,042	26.2%
PED	999,733	26.1%	569,921	23.1%	267,491	19.4%	220,285	19.8%	157,565	19.4%
GP/FM/DO	637,498	16.6%	469,221	19.1%	287,572	20.9%	220,395	19.8%	155,495	19.1%
IM	269,370	7.0%	199,516	8.1%	128,202	9.3%	97,930	8.8%	70,658	8.7%
UNSPEC	673,008	17.6%	370,845	15.1%	149,425	10.8%	110,160	9.9%	64,745	8.0%
PA	65,849	1.7%	53,451	2.2%	38,538	2.8%	37,014	3.3%	33,431	4.1%
NP	79,522	2.1%	58,588	2.4%	36,938	2.7%	35,632	3.2%	31,966	3.9%
ALLER/IMMU	68,623	1.8%	41,847	1.7%	27,763	2.0%	26,602	2.4%	21,525	2.6%
HOSP	76,896	2.0%	48,966	2.0%	27,078	2.0%	20,129	1.8%	13,892	1.7%
POD	34,869	0.9%	26,770	1.1%	19,587	1.4%	11,315	1.0%	6,511	0.8%
All Others	169,821	4.4%	123,879	5.0%	75,928	5.5%	60,662	5.4%	44,701	5.5%
tacrolimus	992,871	20.6%	723,356	22.7%	498,582	26.6%	466,117	29.5%	460,626	36.2%
DERM	478,876	48.2%	364,247	50.4%	260,617	52.3%	245,052	52.6%	244,307	53.0%
UNSPEC	167,827	16.9%	102,474	14.2%	55,283	11.1%	46,244	9.9%	40,508	8.8%
PED	143,567	14.5%	90,957	12.6%	49,782	10.0%	38,990	8.4%	38,143	8.3%
GP/FM/DO	43,727	4.4%	38,114	5.3%	32,687	6.6%	32,581	7.0%	30,576	6.6%
PA	14,218	1.4%	15,073	2.1%	14,399	2.9%	16,917	3.6%	21,975	4.8%
IM	25,275	2.5%	21,703	3.0%	18,482	3.7%	18,769	4.0%	18,069	3.9%
HOSP	36,593	3.7%	26,122	3.6%	17,760	3.6%	16,690	3.6%	14,445	3.1%
ALLER/IMMU	23,981	2.4%	16,537	2.3%	12,328	2.5%	12,001	2.6%	12,330	2.7%
NP	12,298	1.2%	10,861	1.5%	8,395	1.7%	9,229	2.0%	11,061	2.4%
OTHER	3,898	0.4%	3,532	0.5%	3,536	0.7%	3,914	0.8%	3,531	0.8%
All Others	42,611	4.3%	33,736	4.7%	25,313	5.1%	25,730	5.5%	25,681	5.6%

Source: SDI Vector One®: National, Data Extracted June-2009. File: VONA 2009-772 Elidel Protopic MD 06-29-09.xls

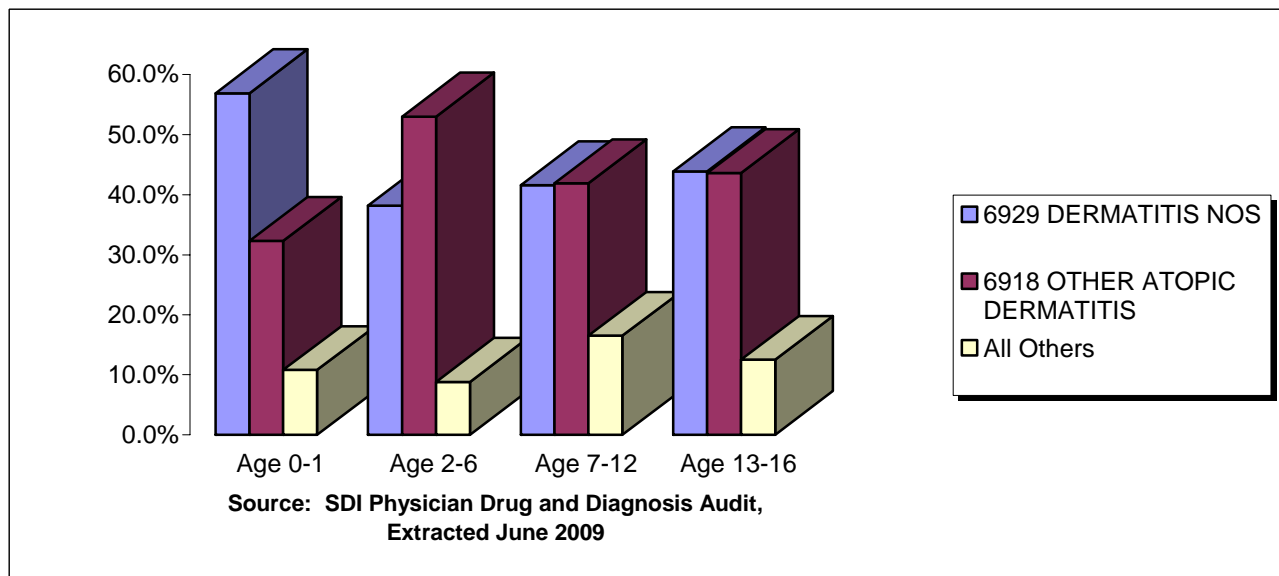
*GP/FM/DO – General Practice, Family Medicine, Doctor of Osteopathy

Figure 4. Diagnoses associated with the use* of pimecrolimus cream by patient age as reported by office-based physician practices, January 1, 2004 – December 31, 2008



*Use - SDI 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.

Figure 5. Diagnoses associated with the use* of tacrolimus ointment by patient age as reported by office-based physician practices, January 1, 2004 – December 31, 2008



*Use - SDI 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.

APPENDIX 2: Database Descriptions

SDI Vector One®: National (VONA)

SDI'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. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI Vector One®: Total Patient Tracker (TPT)

SDI'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.

SDI Physician Drug & Diagnosis Audit (PDDA)

SDI'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.

SDI 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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