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Subject: Lamisil<sup>®</sup> (terbinafine) tablets BPCA Drug Use Review

Drug Name(s): Lamisil<sup>®</sup> (terbinafine)

Application Type/Number: NDA 22-071

Applicant/sponsor: Novartis

OSE RCM #: 2008-701

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## EXECUTIVE SUMMARY

This review examines drug utilization patterns for Lamisil<sup>®</sup> (terbinafine), an allylamine antifungal agent, in the pediatric population, patients aged 0-3 years, 4-12 years, 13-16 years and 17+ years, with a primary focus on patterns of use two years before and one year following the granting of Pediatric Exclusivity on December 4, 2006. Since around 94% of Lamisil<sup>®</sup> bottles and packets of pills were sold to U.S. outpatient retail settings and approximately 6% were sold to non-retail 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 oral Lamisil<sup>®</sup> Tablets and Granules during the three 12-month periods from December 1, 2004 through November 30, 2007.

For each of the three 12-month periods from December 1, 2004 – November 30, 2007:

- Oral Lamisil<sup>®</sup> represented approximately 11% of the total projected number of select antifungal dispensed prescriptions.
- Oral Lamisil<sup>®</sup> prescriptions in the pediatric population (ages 0-16 years) accounted for approximately 2% of total dispensed oral Lamisil<sup>®</sup> prescriptions.
- Around 3% of total projected patients who filled a prescription for oral Lamisil<sup>®</sup>, were aged 0-16 years.
- General Practice/Family Medicine/Doctor of Osteopathy was the top prescribing specialty for terbinafine oral dosage forms.
- The top diagnosis code associated with the use of oral Lamisil<sup>®</sup> for patients aged 13-16 years and 17 years and greater was “dermatophytosis of nail” (ICD-9 110.1). Other nonspecific skin eruptions and dermatophytosis infections of body, scalp and foot were commonly reported for pediatric patients aged 0-3 years, and 4-12 years.

## 1 INTRODUCTION

Using the currently available proprietary drug use databases licensed by the Agency, this review describes outpatient drug use patterns for oral Lamisil<sup>®</sup> (terbinafine) 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 4, 2006.

## 2 METHODS AND MATERIALS

IMS Health, IMS National Sales Perspectives<sup>™</sup> data (*see Appendix 2*) were used to determine the setting in which oral Lamisil<sup>®</sup> was sold. Sales of this product by number of bottles and packets of tablets (eaches) sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for three 12-month periods from December 1, 2004 – November 30, 2007 (*data not provided*).<sup>1</sup> 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 oral Lamisil<sup>®</sup> sales (94%) and approximately 6% were sold to non-retail settings. Thus, the examination of oral Lamisil<sup>®</sup> utilization patterns focused on the outpatient setting, excluding mail order channels.

Outpatient use and patient demographics (stratified by ages 0-3 years, 4-12 years, 13-16 years and 17+ years for oral Lamisil<sup>®</sup> Tablets and Granules) were measured from Verispan, LLC: Vector One<sup>®</sup>: 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 oral Lamisil<sup>®</sup>, and the number of drug mentions by office-based physicians, were obtained from December 1,

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<sup>1</sup> IMS Health, IMS Nationals Sales Perspectives<sup>™</sup>, Data extracted 6-26-2008, Source file: 0806terb.DVR

2004 through November 30, 2007, inclusive. For comparative purposes, other select atypical antifungals were also examined: including fluconazole, ketoconazole, griseofulvin, and itraconazole.

### 3 RESULTS

During the three 12-month periods from December 1, 2004 – November 30, 2007, dispensed prescriptions for terbinafine products represented approximately 11% of the projected number of select antifungal prescriptions dispensed in the United States. The projected number of Lamisil<sup>®</sup> dispensed prescriptions decreased by close to 10% from roughly 2 million during the pre-exclusivity period (December 1, 2005 – November 30, 2006) to around 1.8 million during the post-exclusivity period (December 1, 2006 – November 30, 2007) (*Table 1*). No prescriptions for Lamisil<sup>®</sup> Oral Granules were recorded during the entire study period.

During the three 12-month periods from December 1, 2004 – November 30, 2007, dispensed prescriptions for Lamisil<sup>®</sup> in the pediatric population (ages 0-16 years) accounted for approximately 2% of the total projected number of dispensed prescriptions for Lamisil<sup>®</sup>. Of the roughly 40 thousand prescriptions dispensed to patients aged 0-16 years, around 5% were dispensed to patients aged 0-3 years, 38% were dispensed to patients aged 4-12 years, and 57% dispensed to patients ages 13-16 years (*Table 2*). Of the patients who filled a prescription for Lamisil<sup>®</sup> in the outpatient retail pharmacy setting, approximately 3% of total projected patients were aged 0-16 years, and the proportion of projected pediatric patients aged 0-3, 4-12, and 13-16 years were similar to the proportion of dispensed prescriptions for the same age groups (*Table 3*).

During the three 12-month periods from December 1, 2004 – November 30, 2007, General Practice/Family Medicine/Doctor of Osteopathy was the top prescribing specialty for terbinafine products with approximately 32% of dispensed prescriptions. Podiatry was the second most common prescribing specialty with approximately 23% of dispensed prescriptions. Pediatrics accounted for less than 2% of dispensed prescription over the entire study period (*Table 4*).

According to office-based physician practices in the U.S., “dermatophytosis of nail” (ICD-9 110.1) was the most common diagnosis code associated with the use of oral terbinafine for patients aged 13-16 years and 17 years and greater. Other nonspecific skin eruptions and dermatophytosis infections of body, scalp and foot were commonly reported for pediatric patients aged 0-3 years, and 4-12 years (*Table 5*).

### 4 LIMITATIONS

Findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated that oral Lamisil<sup>®</sup> is distributed primarily in outpatient settings based on the IMS Health, IMS National Sales Perspectives<sup>™</sup>. 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.

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 Lamisil<sup>®</sup> (terbinafine) oral formulations in the pediatric and adult populations has been declining over the three 12-month study periods examined. There were no dispensed prescriptions for Lamisil<sup>®</sup> Oral Granules in either the adult or pediatric populations during the entire study period.

## APPENDICES

### APPENDIX 1: Tables

**Table 1. Total number of dispensed prescriptions through U.S. outpatient retail pharmacies for the selected antifungal agents, December 1, 2004 - November 30, 2007**

	DEC 2004 – NOV 2005		DEC 2005 – NOV 2006		DEC 2006 – NOV 2007	
	Baseline		Pre-Exclusivity		Post-Exclusivity	
	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share
	N	%	N	%	N	%
<b>TOTAL MARKET</b>	19,100,100	100.0%	18,922,386	100.0%	19,325,270	100.0%
<b>Fluconazole</b>	11,889,382	62.2%	11,997,288	63.4%	12,537,430	64.9%
Regular Tab	11,656,924	98.0%	11,727,947	97.8%	12,261,064	97.8%
Suspension	232,458	2.0%	269,341	2.2%	276,343	2.2%
All Others	--	--	--	--	23	0.0%
<b>Ketoconazole</b>	3,773,635	19.8%	3,773,794	19.9%	3,906,071	20.2%
Cream	1,848,110	49.0%	1,901,316	50.4%	1,937,430	49.6%
Shampoo	1,196,961	31.7%	1,154,055	30.6%	1,216,161	31.1%
Regular Tab	728,564	19.3%	717,718	19.0%	713,298	18.3%
Gel	--	--	705	0.0%	36,595	0.9%
Other Topical	--	--	--	--	1,405	0.0%
Test Kit	--	--	--	--	1,182	0.0%
<b>terbinafine hcl</b>	2,215,135	11.6%	2,024,853	10.7%	1,816,148	9.4%
Regular Tab	2,210,451	99.8%	2,022,084	99.9%	1,811,054	99.7%
Cream	1,262	0.1%	816	0.0%	3,200	0.2%
Solution	3,422	0.2%	1,953	0.1%	1,894	0.1%
<b>Griseofulvin</b>	904,631	4.7%	848,022	4.5%	811,132	4.2%
Regular Tab	417,883	46.2%	416,654	49.1%	420,982	51.9%
Suspension	486,739	53.8%	431,362	50.9%	390,144	48.1%
Regular Cap	9	0.0%	6	0.0%	6	0.0%
<b>Itraconazole</b>	317,317	1.7%	278,429	1.5%	254,489	1.3%
Regular Cap	298,416	94.0%	261,302	93.8%	238,493	93.7%
Solution	18,806	5.9%	17,016	6.1%	15,895	6.2%
Other Injectable	95	0.0%	111	0.0%	101	0.0%

Source: Verispan Vector One®: National, Data Extracted 6-2008. File: VONA 2008-701 6-25-08 terbinafine market.qry

**Table 2. Total number of dispensed prescriptions (in thousands, add 3 zeros) for terbinafine by patient age (0-3, 4-12, 13-16, 17+) through U.S. outpatient retail pharmacies, December 1, 2004 - November 30, 2007**

	DEC 2004 – NOV 2005		DEC 2005 – NOV 2006		DEC 2006 – NOV 2007		<i>Baseline to Post-Exclusivity</i>	<i>Pre-Exclusivity to Post-Exclusivity</i>
	Baseline		Pre-Exclusivity		Post-Exclusivity			
	Retail TRxs N (000)	Share %	Retail TRxs N (000)	Share %	Retail TRxs N (000)	Share %		
<b>terbinafine hcl</b>	<b>2,215</b>	<b>100.0%</b>	<b>2,025</b>	<b>100.0%</b>	<b>1,816</b>	<b>100.0%</b>	<b>-18%</b>	<b>-10%</b>
<b>Ages 0-16</b>	47	2.1%	42	2.1%	39	2.1%	-17%	-7%
<b>0-3</b>	2	4.3%	2	4.8%	2	5.1%	0%	0%
<b>4-12</b>	18	38.3%	16	38.1%	15	38.5%	-17%	-6%
<b>13-16</b>	27	57.4%	24	57.1%	22	56.4%	-19%	-8%
<b>Ages 17+</b>	2,159	97.5%	1,978	97.7%	1,774	97.7%	-18%	-10%
<b>UNSPEC.</b>	9	0.4%	5	0.2%	4	0.2%	-56%	-20%

Source: Verispan Vector One®: National, Data Extracted 6-2008. File: VONA 2008-701 6-9-08 terbinafine Age.qry

**Table 3. Total number of projected patients (ages 0-3, 4-12, 13-16, 17+) who filled a prescription for terbinafine in U.S. outpatient retail pharmacies, December 1, 2004 - November 30, 2007**

	DEC 2004 – NOV 2005		DEC 2005 – NOV 2006		DEC 2006 – NOV 2007		<i>Baseline to Post-Exclusivity</i>	<i>Pre-Exclusivity to Post-Exclusivity</i>
	Baseline		Pre-Exclusivity		Post-Exclusivity			
	Projected Patient Count N	Total Patient Share %	Projected Patient Count N	Total Patient Share %	Projected Patient Count N	Total Patient Share %		
<b>Grand Total</b>	<b>1,097,028</b>	<b>100.0%</b>	<b>999,441</b>	<b>100.0%</b>	<b>901,212</b>	<b>100.0%</b>	<b>-18%</b>	<b>-10%</b>
<b>Ages 0 - 16</b>	31,406	2.9%	27,071	2.7%	25,050	2.8%	-20%	-7%
<b>Ages 0 - 3</b>	1,464	4.7%	1,196	4.4%	1,297	5.2%	-11%	8%
<b>Ages 4 - 12</b>	12,629	40.2%	11,039	40.8%	10,398	41.5%	-18%	-6%
<b>Ages 13 - 16</b>	17,558	55.9%	15,117	55.8%	13,543	54.1%	-23%	-10%
<b>Ages 17+</b>	1,060,837	96.7%	969,878	97.0%	874,013	97.0%	-18%	-10%
<b>UNKNOWN AGE</b>	9,120	0.8%	5,083	0.5%	4,097	0.5%	-55%	-19%

\*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, Vector One®: Total Patient Tracker. File: TPT 2008-701 terbinafine patients 7-1-08.xls

**Table 4. Total number of dispensed prescriptions for terbinafine in outpatient retail pharmacies by top 10 prescribing specialties, December 1, 2004 - November 30, 2007**

	DEC 2004 – NOV 2005		DEC 2005 – NOV 2006		DEC 2006 – NOV 2007	
	Baseline		Pre-Exclusivity		Post-Exclusivity	
	Retail TRxs N (000)	Share %	Retail TRxs N (000)	Share %	Retail TRxs N (000)	Share %
<b>terbinafine hcl</b>	2,215	100.0%	2,025	100.0%	1,816	100.0%
GP/FM/DO*	693	31.3%	653	32.2%	588	32.4%
POD	478	21.6%	460	22.7%	419	23.1%
IM	357	16.1%	322	15.9%	282	15.5%
DERM	233	10.5%	213	10.5%	198	10.9%
UNSPEC	183	8.2%	121	6.0%	98	5.4%
PA	37	1.7%	40	2.0%	41	2.2%
NP	33	1.5%	36	1.8%	37	2.0%
PEDIATRICS	34	1.5%	32	1.6%	30	1.6%
HOSP	31	1.4%	28	1.4%	21	1.2%
EM	14	0.7%	14	0.7%	12	0.7%
All Others	121	5.5%	108	5.3%	90	5.0%

Source: Verispan Vector One®: National, Data Extracted 6-2008. File: VONA 2008-701 6-9-08 terbinafine MD.qry

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

**Table 5. Diagnoses associated with the use\* of oral terbinafine by patient age (0-3, 4-12, 13-16, 17+) as reported by office-based physician practices, December 1, 2004 - November 30, 2007**

	DEC 2004 – NOV 2005		DEC 2005 – NOV 2006		DEC 2006 – NOV 2007	
	Baseline		Pre-Exclusivity		Post-Exclusivity	
	Uses N	Share %	Uses N	Share %	Uses N	Share %
<b>terbinafine hcl</b>	2,962,197	100.0%	2,576,341	100.0%	2,051,486	100.0%
<b>0-3</b>	--	--	13,300	0.5%	6,038	0.3%
1105 DERMATOPHYTOSIS OF BODY	--	--	--	--	6,038	100.0%
1104 DERMATOPHYTOSIS OF FOOT	--	--	13,300	100.0%	--	--
<b>4-12</b>	29,526	1.0%	27,314	1.1%	16,882	0.8%
7821 NONSPECIF SKIN ERUPT NEC	--	--	--	--	6,924	41.0%
1100 DERMATOPHYT SCALP/BEARD	--	--	27,314	100.0%	5,992	35.5%
1101 DERMATOPHYTOSIS OF NAIL	21,874	74.1%	--	--	3,966	23.5%
1104 DERMATOPHYTOSIS OF FOOT	7,651	25.9%	--	--	--	--
<b>13-16</b>	45,646	1.5%	28,058	1.1%	45,226	2.2%
1101 DERMATOPHYTOSIS OF NAIL	16,534	36.2%	7,547	26.9%	45,226	100.0%
1179 MYCOSES NEC & NOS	3,903	8.6%	--	--	--	--
1103 DERMATOPHYTOSIS OF GROIN	2,652	5.8%	--	--	--	--
1105 DERMATOPHYTOSIS OF BODY	5,727	12.5%	8,123	29.0%	--	--
1109 DERMATOPHYTOSIS SITE NOS	3,959	8.7%	--	--	--	--
All Others	12,871	28.2%	12,388	44.2%	--	--
<b>17+</b>	2,813,900	95.0%	2,389,519	92.7%	1,968,929	96.0%
1101 DERMATOPHYTOSIS OF NAIL	2,395,298	85.1%	2,020,180	84.5%	1,637,864	83.2%
1104 DERMATOPHYTOSIS OF FOOT	130,651	4.6%	95,953	4.0%	85,837	4.4%
1179 MYCOSES NEC & NOS	37,110	1.3%	40,335	1.7%	75,899	3.9%
1105 DERMATOPHYTOSIS OF BODY	43,486	1.5%	44,201	1.8%	44,179	2.2%
1109 DERMATOPHYTOSIS SITE NOS	13,735	0.5%	12,601	0.5%	29,152	1.5%
All Others	193,620	6.9%	176,249	7.4%	95,998	4.9%
<b>UNSPEC.</b>	73,125	2.5%	118,150	4.6%	14,410	0.7%
1101 DERMATOPHYTOSIS OF NAIL	54,898	75.1%	91,974	77.8%	10,450	72.5%
1179 MYCOSES NEC & NOS	--	--	--	--	3,961	27.5%
1104 DERMATOPHYTOSIS OF FOOT	3,388	4.6%	22,751	19.3%	--	--
1109 DERMATOPHYTOSIS SITE NOS	--	--	3,425	2.9%	--	--
4659 ACUTE URI NOS	5,489	7.5%	--	--	--	--
All Others	9,349	12.8%	--	--	--	--

Source: Verispan Physician Drug and Diagnosis Audit, Extracted 1-2008. File: PDDA 2008-701 terbinafine AgDx4 6-27-08.qry

\* Use - Projected uses for a product linked to a diagnosis. The projected number of times a product has been reported for treatment of a particular disease.

## **APPENDIX 2: Database Descriptions**

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### ***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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