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Subject:	Lamictal® (lamotrigine) BPCA Drug Use Review
Drug Name(s):	Lamictal® (lamotrigine)
Application Type/Number:	NDA 20-241
Applicant/sponsor:	GlaxoSmithKlein
OSE RCM #:	2007-388

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CONTENTS

EXECUTIVE SUMMARY

This review examines drug utilization patterns for Lamictal® (lamotrigine), a anti-seizure agent, in the pediatric population, patients aged 0-1-, 2-5, 6-11, 12-16 and 17+ years, with a primary focus on patterns of use two years before and one year following the granting of Pediatric Exclusivity in March of 2007. Since around 74% of lamotrigine was sold to U.S. retail settings and 13% to mail order pharmacies 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 lamotrigine during the three 12-month periods from March 1, 2005 through February 29, 2008.

The primary findings of this review are summarized below:

- Lamotrigine dispensed prescriptions rose by 22% from the pre-exclusivity year to the post-exclusivity year.
- Lamotrigine was the 3rd most commonly dispensed anti-seizure agent, accounting for roughly 18% of dispensing within the market during the post-exclusivity period.
- Lamotrigine was primarily dispensed to adult patients who accounted for approximately 90% of patients who received a retail lamotrigine prescription during the pre and post exclusivity years.
- Sustentative changes in the use among any of the examined pediatric age bands were not seen when comparing the pre to the post exclusivity years.
- Off-label use for 0 to 2 year old patients is very low. We observed that this age group accounted for less than 0.1% of overall use, or between 30 and 40 patients during the pre and post exclusivity years.
- The most commonly mentioned indications for use of lamotrigine in adults and pediatrics were Epilepsy (ICD-9 345.9), Bipolar Affective Disorder (ICD-9 296.7), and Convulsions (ICD-9 780.3).

1 INTRODUCTION

Using the currently available proprietary drug use databases licensed by the Agency, this review describes outpatient drug use patterns for oral Lamictal® (lamotrigine) 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 in March of 2007.

2 METHODS AND MATERIALS

IMS Health, IMS National Sales Perspectives™ data (*see Appendix 2*) were used to determine the setting in which lamotrigine was sold. Sales of this product by number of extended units (tablets, capsules, milliliters) of product sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for three 12-month periods from March 1, 2005 through February 29, 2008.[1] During the three 12-month periods of this review, retail settings (chain stores, independent pharmacies, food stores) accounted for the majority of lamotrigine sales (74%), 13% of sales were into mail order pharmacies and 13% were sold to non-retail [mainly long-term care) settings. Thus, this review will focus on lamotrigine utilization patterns in outpatient retail pharmacies.

Outpatient use and patient demographics (stratified by ages 0-1 years, 2-5 years, 6-11 years,12-16 years and 17+ years) were measured from Verispan, LLC: Vector One®: National (VONA) and Total Patient Tracker (TPT) (***Appendix 1***). Indications for use were obtained from the Verispan's Physician's Drug and Diagnosis Audit (PDDA) (***Appendix 1***). From these data sources, estimates of the number of prescriptions dispensed, the number

[1] IMS Health, IMS Nationals Sales Perspectives™, Data extracted 7-31-2008, Source file: 0807lamo.DVR

of patients who received a prescription for lamotrigine, and the number of drug mentions by office-based physicians, were obtained from March 1, 2005 through February 29, 2008, inclusive. For comparative purposes, other select anti-seizure agents were also examined: including carbamazepine, divalproex, phenytoin, levetiracetam, oxcarbazepine, topiramate, and zonisamide.

3 RESULTS

Over the 3 years examined, the total number of prescriptions dispensed in the selected anti-seizure market increased by 11% from 35.9 million during March 2005 – February 2006 to 39.8 million during March 2007-February 2008 (Appendix 1, Table 1). The most commonly dispensed agents in this market were divalproex, topiramate and lamotrigine which accounted for 20%, 19% and 18% of March 2007-February 2008 dispensing, respectively.

Among the products examined, lamotrigine had the second largest increase in the number of prescriptions dispensed during the 3 years examined with 4.7 million prescriptions dispensed during March 2005- February 2006 to 7.2 million during March 2007- February 2008, an increase of 53%. From the pre-exclusivity year to the post exclusivity year (March 2006 through February 2008), lamotrigine dispensing increased by 22% rising from 5.9 million prescriptions dispensed to 7.2 million prescriptions dispensed.

Lamotrigine is used primarily in adult patients who accounted for approximately 90% of retail prescriptions during the pre and post exclusivity years (Appendix 1, Table 2). Dispensing for patients 0-1 and 2-5 years of age remained stable from the pre- to post-exclusivity year, accounting for less than 0.5% and around 6% of dispensing for 0-16 year olds, respectively. Patients age 6-11 years and 12-16 years accounted for a larger proportion of dispensing for 0-16 year olds, approximately 34% and 60%, respectively, during the pre- and post-exclusivity years.

We examined lamotrigine dispensing by physician specialty (Appendix 1, Table 3). The top provider specialties were Psychiatry and Neurology. Pediatricians accounted for approximately 1% of lamotrigine dispensing during each of the three years examined.

The projected number of patients who received a lamotrigine prescription through outpatient retail pharmacies was obtained using Verispan's Total Patient Tracker (Appendix 1, Table 4). The number of patients receiving a lamotrigine prescription rose from 443,757 during the pre-exclusivity year to 536,613 during the post-exclusivity year, a 21% increase. The number of projected patients aged 0-1 and 2-5 years remained stable from pre-to post-exclusivity year with less than 0.05% of patients in the 0-1 year old group, 0.2% in the 2-5 year group, and approximately 2% in the 6-11 year old group. Adults age 17 and older accounted for 91% of lamotrigine patients during the pre-exclusivity year and 92% of patients during the post-exclusivity year.

We examined the relative frequency of diagnoses associated with a mention of lamotrigine by U.S. office based physicians using Verispan's Physician Drug and Diagnosis Audit (Appendix 1, Table 5). Due to the relatively low use in pediatric patients, the age groups examined were 0-16 years old and age 17 years and older. For pediatric patients, commonly mentioned diagnoses included Epilepsy (ICD-9 345.9), Bipolar Affective Disorder (ICD-9 296.7), and Convulsions (ICD-9 780.3). For adult patients, the top three diagnoses were the same (epilepsy, bipolar and convulsions).

4 LIMITATIONS

Findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated that lamotrigine 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.

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 as was seen in this review. Verispan recommends caution interpreting data trends when projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals.

5 CONCLUSIONS

Use of lamotrigine is primarily in the adult population which accounted for roughly 90% of the lamotrigine prescriptions dispensed. Use within the 0-2 year old age group is very low, accounting for less than 0.1% of annual prescriptions and patient counts for this product.

CONCURRENCE

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APPENDICES

Appendix 1 – Figures and Tables

Table 1: Projected Number Retail Prescriptions Dispensed By U.S. Pharmacies for Lamotrigine and Other Selected Anti-Seizure Agents March 2005-February 2008

	Mar 2005 - Feb 2006		Mar 2006 - Feb 2007		Mar 2007 - Feb 2008	
	Retail TRxs	***(%)***	**Retail TRxs**	***(%)***	**Retail TRxs**	***(%)***
TOTAL MARKET	35,904,678	*(100)*	37,784,689	*(100)*	39,824,821	*(100)*
divalproex sodium	7,726,683	*(21.5)*	7,687,245	*(20.3)*	7,819,820	*(19.6)*
topiramate	6,161,099	*(17.2)*	6,824,284	*(18.1)*	7,495,960	*(18.8)*
lamotrigine	4,694,749	*(13.1)*	5,896,721	*(15.6)*	7,185,734	*(18)*
Phenytoin	6,664,886	*(18.6)*	6,550,064	*(17.3)*	6,214,469	*(15.6)*
carbamazepine	5,219,208	*(14.5)*	4,996,658	*(13.2)*	4,616,762	*(11.6)*
levetiracetam	1,838,252	*(5.1)*	2,239,279	*(5.9)*	2,857,482	*(7.2)*
oxcarbazepine	2,752,087	*(7.7)*	2,742,251	*(7.3)*	2,754,204	*(6.9)*
zonisamide	847,714	*(2.4)*	848,187	*(2.2)*	880,390	*(2.2)*

Source: **Vector One®:National** Data Extracted 6-2008 File: 2007-288 lamotrigine market figure 1

Table 2: Projected Number Retail Prescriptions Dispensed By U.S. Pharmacies for Lamotrigine by Patient Age, March 2005-February 2008

	Mar 2005 - Feb 2006		Mar 2006 - Feb 2007		Mar 2007 - Feb 2008	
	Retail TRxs	***(%)***	**Retail TRxs**	***(%)***	**Retail TRxs**	***(%)***
Lamotrigine	4,694,733	*(100.0)*	5,896,719	*(100.0)*	7,185,722	*(100.0)*
0-16	519,237	*(11.1)*	576,878	*(9.8)*	648,773	*(9.0)*
0-1	2,044	*(0.4)*	1,294	*(0.2)*	1,149	*(0.2)*
2-5	38,400	*(7.4)*	36,400	*(6.3)*	36,370	*(5.6)*
6-11	181,219	*(34.9)*	197,673	*(34.3)*	215,054	*(33.1)*
12-16	297,574	*(57.3)*	341,511	*(59.2)*	396,200	*(61.1)*
17+	4,094,968	*(87.2)*	5,276,559	*(89.5)*	6,494,739	*(90.4)*
UNSPEC.	80,528	*(1.7)*	43,282	*(0.7)*	42,210	*(0.6)*

Source: **Vector One®:National**, Data Extracted 6-2008 File: 2007-388 lamotrigine age figure3

Table 3: Projected Number Retail Prescriptions Dispensed By U.S. Pharmacies for Lamotrigine by Physician Specialty March 2005-February 2008

	Mar 2005 - Feb 2006		Mar 2006 - Feb 2007		Mar 2007 - Feb 2008	
	Retail TRxs	*(%)*	Retail TRxs	*(%)*	Retail TRxs	*(%)*
Lamotrigine	4,694,776	*(100)*	5,896,744	*(100)*	7,185,741	*(100)*
Psychiatry	2,195,151	*(46.8)*	2,966,485	*(50.3)*	3,619,486	*(50.4)*
Neurology	1,021,217	*(21.8)*	1,178,690	*(20)*	1,311,913	*(18.3)*
Unspec	534,816	*(11.4)*	391,068	*(6.6)*	453,351	*(6.3)*
Gp/Fm/Do	242,750	*(5.2)*	370,775	*(6.3)*	501,642	*(7)*
Nurse Pract	215,100	*(4.6)*	348,815	*(5.9)*	512,078	*(7.1)*
Internal Med	143,534	*(3.1)*	200,420	*(3.4)*	257,561	*(3.6)*
Hospitalist	81,763	*(1.7)*	103,094	*(1.7)*	108,476	*(1.5)*
Other	68,469	*(1.5)*	91,874	*(1.6)*	116,870	*(1.6)*
Pediatrics	63,765	*(1.4)*	70,386	*(1.2)*	82,585	*(1.1)*
Physician Assist	31,579	*(0.7)*	56,126	*(1)*	81,685	*(1.1)*
All Others	96,632	*(2.1)*	119,011	*(2)*	140,094	*(1.9)*

Source: **Vector One®:National**, Data Extracted 6-2008 File: 2007-388 MD Figure 4

Figure 4: Projected Number of Patients Receiving a Retail Prescription Dispensed By U.S. Pharmacies for Lamotrigine, March 2005-February 2008

	Mar 2005 - Feb 2006		Mar 2006 - Feb 2007		Mar 2007 - Feb 2008	
	Retail TRxs	*(%)*	Retail TRxs	*(%)*	Retail TRxs	*(%)*
Grand Total	358,265	*(100.0)*	443,757	*(100.0)*	536,613	*(100.0)*
0-16	89,798	*(25.1)*	93,680	*(21.1)*	102,130	*(19.0)*
0 - 1	58	*(0.1)*	40	*(0.04)*	36	*(0.03)*
2 - 5	1,563	*(1.7)*	1,185	*(1.3)*	1,192	*(1.2)*
6 - 11	11,030	*(12.3)*	10,838	*(11.6)*	11,507	*(11.3)*
12 - 16	21,632	*(24.1)*	23,774	*(25.4)*	27,736	*(27.2)*
17+	319,486	*(89.2)*	404,609	*(91.2)*	493,003	*(91.9)*
Unknown	4,980	*(1.4)*	3,643	*(0.8)*	3,461	*(0.6)*

Source: Verispan Total Patient Tracker, Extracted 6-2008 and 8-4-08, 2007-388 TPT Lamotrigine and 2007-388 lamotrigine 8-4-08 age 0-16.xls

Table 5: Projected Number of "Uses" Associated with a Office Based Physician Lamotrigine Mention, by Diagnosis Code March 2005-February 2008

	Mar 2005 - Feb 2006		Mar 2006 - Feb 2007		Mar 2007 - Feb 2008	
	Uses	***(%)***	**Uses**	***(%)***	**Uses**	***(%)***
Lamotrigine	3,140	*(100)*	3,332	*(100)*	4,185	*(100)*
0-16	96	*(3)*	119	*(3.6)*	110	*(2.6)*
3459 Epilepsy Nos	3	*(3.2)*	10	*(8.5)*	18	*(16)*
2967 Bipolar Affective Nos	14	*(14.9)*	18	*(15)*	16	*(14.5)*
7803 Convulsions	37	*(38.5)*	25	*(21.3)*	15	*(13.4)*
2968 Manic-Depressive Nec/Nos	--	--	--	--	11	*(10.1)*
3455 Partial Epilepsy Nec	5	*(5.1)*	6	*(5.2)*	10	*(8.8)*
3450 Gen Nonconvuls Epilepsy	--	--	16	*(13.7)*	9	*(8.6)*
2989 Psychosis Nos	--	--	--	--	7	*(5.9)*
5589 Noninf Gastroenterit Nec	--	--	--	--	6	*(5.6)*
3454 Psychomotor Epilepsy	--	--	--	--	6	*(5.5)*
2966 Bipolar Affective, Mixed	24	*(25.6)*	--	--	5	*(4.2)*
All Others	12	*(12.7)*	43	*(36.2)*	8	*(7.4)*
17+	2,880	*(91.7)*	3,075	*(92.3)*	3,964	*(94.7)*
2967 Bipolar Affective Nos	868	*(30.1)*	874	*(28.4)*	1,178	*(29.7)*
2968 Manic-Depressive Nec/Nos	416	*(14.4)*	585	*(19)*	928	*(23.4)*
7803 Convulsions	317	*(11)*	368	*(12)*	311	*(7.8)*
3459 Epilepsy Nos	112	*(3.9)*	198	*(6.4)*	236	*(6)*
2966 Bipolar Affective, Mixed	270	*(9.4)*	114	*(3.7)*	234	*(5.9)*
2965 Bipolar Affect, Depress	155	*(5.4)*	165	*(5.4)*	158	*(4)*
2957 Schizoaffective Type	107	*(3.7)*	139	*(4.5)*	120	*(3)*
3110 Depressive Disorder Nec	155	*(5.4)*	72	*(2.3)*	120	*(3)*
2969 Affect Psychoses Nec/Nos	59	*(2.1)*	69	*(2.2)*	78	*(2)*
2962 Depr Psych, Singl Episod	88	*(3.1)*	91	*(3)*	76	*(1.9)*
All Others	334	*(11.6)*	399	*(13)*	523	*(13.2)*
Unspec.	164	*(5.2)*	138	*(4.1)*	111	*(2.6)*

Source: Verispan Physician Drug and Diagnosis Audit, Extracted 6-2008, File: 2007-288 PDDA Lamictal.xl

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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