

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

Drug Use Review

Date: October 31, 2012

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Drug Name(s): Lamictal XR (lamotrigine)

Application Type/Number: NDA 022115/6, 022509

Applicant/sponsor: SmithKline Beecham

OSE RCM #: 2012-1803

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EXECUTIVE SUMMARY

In preparation for the March 2013 Pediatric Advisory Committee (PAC) meeting, this review provides U.S. outpatient retail pharmacy drug utilization patterns for Lamictal® XR™ (lamotrigine) in the pediatric population (0-12 and 13-16 years) and the adult population (17 years and older) from July 2009 through June 2012.

Summary of outpatient utilization from July 2009 through June 2012:

- Approximately 602,500 Lamictal® XR™ prescriptions were dispensed and 74,000 unique patients received Lamictal® XR™ prescriptions from outpatient retail pharmacies from July 2009 to June 2012.
- Pediatric patients aged 0-16 years accounted for about 12% (9,200 patients) of patients who received dispensed prescriptions of Lamictal® XR™
 - Off-label use in patients age 0-12 years accounted for approximately 40% (3,600 patients) of all pediatric patients that received a dispensed prescription for Lamictal® XR™.
- Neurology was the top prescribing specialty for Lamictal® XR™, accounting for approximately 64% of prescriptions dispensed.
- Diagnoses for “Epilepsy” and “Affective Personality” were the only diagnoses captured associated with the use of Lamictal® XR™ in the pediatric population ages 0-16 years.

1 INTRODUCTION

The Office of Pediatric Therapeutics (OPT) and Pediatric and Maternal Health Staff (PMHS) requested a review of drug utilization patterns for Lamictal® XR™ following changes made to the label in 2011 about lactation warnings. In support of these efforts, this review provides a description of pediatric drug utilization patterns for Lamictal® XR™ from July 2009 through June 2012.

2 BACKGROUND

2.1 PRODUCT LABELING

Lamictal® XR™ (lamotrigine) is an antiepileptic drug (AED) approved under NDA 022115 on May 29, 2009. Lamictal XR® is indicated for:

- Adjunctive therapy for primary generalized tonic-clonic (PGTC) seizures and partial onset seizures with or without secondary generalization in patients \geq 13 years of age
- Conversion to monotherapy in patients \geq 13 years of age with partial seizures who are receiving treatment with a single AED

Lamictal® XR™ is supplied as a tablet with the following strengths: 25mg, 50mg, 100mg, 200mg, 250mg, and 300mg. It is also supplied as the following:

- Lamictal XR® Patient Titration Kit for Patients Taking Valproate (Blue XR Kit, blisterpack of 21/25mg tablets, and 7/50mg tablets)
- Lamictal XR® Patient Titration Kit for Patients Taking Carbamazepine, Phenytoin, Phenobarbital, or Primidone, and Not Taking Valproate (Green XR Kit, blisterpack of 14/50mg tablets, 14/100mg tablets, and 7/200mg tablets)

- Lamictal® XR™ Patient Titration Kit for Patients Not Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate (Orange XR Kit, blisterpack of 14/25mg tablets, 14/50mg tablets, and 7/100mg tablets).¹

3 METHODS AND MATERIALS

3.1 DETERMINING SETTINGS OF CARE

Proprietary drug use databases were used to conduct this analysis.

The IMS Health, IMS National Sales Perspectives™ data (see Appendix 2 for full database description) was used to determine the settings in which Lamictal® XR™ were sold. From July 2009 to June 2012, sales data for Lamictal® XR™ by number of bottles sold from the manufacturer to various channels of distribution indicated that approximately 74% of Lamictal® XR™ was distributed to outpatient retail pharmacies, 20% to mail-order/specialty pharmacies, and 6% to non-retail settings. As a result, outpatient retail pharmacy drug utilization patterns were examined for this review. Inpatient, mail-order/specialty pharmacy and clinic data were excluded in this analysis.

3.2 DATA SOURCES USED

The IMS, Vector One®: National (VONA) and Total Patient Tracker (TPT) databases were used to obtain the nationally estimated number of prescriptions and patients receiving prescriptions for Lamictal® XR™, stratified by patient age (0-12 years, 13-16 years, 17 years and older), from July 2009 through June 2012. The number of prescriptions dispensed by the top ten prescribing specialties of Lamictal® XR™ were also obtained for the same aggregate time period. Diagnoses associated with the use of Lamictal® XR™, stratified by patient age (0-12 years, 13-16 years, and 17 years and older), were obtained from the Encuity Research, LLC., Physician Drug and Diagnosis Audit™ (PDDA) with Pain Panel, from July 2009 through June 2012, in aggregate.

4 RESULTS

4.1 OUTPATIENT DISPENSED PRESCRIPTIONS FOR LAMICTAL® XR™ BY PATIENT AGE

Figure 1 and **Table 1** shows the nationally estimated number of prescriptions for Lamictal® XR™, stratified by patient age, dispensed from U.S. outpatient retail pharmacies, July 2009 through June 2012. There were approximately 602,500 total prescriptions dispensed for Lamictal® XR™ from U.S. outpatient retail pharmacies during the specified time period. Approximately 15% (89,500 prescriptions) of the total prescriptions were dispensed to pediatric patients aged 0-16 years. Approximately 34,500 prescriptions (38.5% of pediatric prescriptions) were dispensed off-label to patients aged 0-12 years during the examined time.

¹ LAMICTAL XR (lamotrigine) tablet. U.S. National Library of Medicine: DailyMed. Accessed September 2012. Available at: <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=3e2c9a35-6a39-41d7-ad84-3c0bb8894b09#nmlm34069-5>

4.2 NUMBER OF PATIENTS RECEIVING DISPENSED PRESCRIPTIONS FOR LAMICTAL® XR™ BY PATIENT AGE

Figure 1 and **Table 2** displays the nationally estimated number of patients who received prescriptions dispensed for Lamictal® XR™ from U.S. outpatient retail pharmacies from July 2009 through June 2012. A total of approximately 74,000 unique patients received a dispensed prescription for Lamictal® XR™ during the specified time period. Pediatric patients aged 0-16 years accounted for about 12% (9,200 patients) of total patients who received dispensed prescriptions of Lamictal® XR™. Off-label use in pediatric patients aged 0-12 years accounted for approximately 40% (3,600 patients) of all pediatric patients during the study period.

4.3 TOP 10 PRESCRIBING SPECIALTIES

Table 3 provides the nationally estimated number of outpatient retail dispensed prescriptions for Lamictal® XR™ by the top 10 prescribing specialties. From July 2009 through June 2012, Neurology was the top prescribing specialty with approximately 64% (383,000 prescriptions) of total prescriptions dispensed for Lamictal® XR™. Pediatricians accounted for approximately 1.4% of total Lamictal® XR™ prescriptions dispensed.

4.4 INDICATIONS FOR LAMICTAL® XR™ USE BY PATIENT AGE

Table 4 provides the top diagnoses associated with the use of Lamictal® XR™ by drug use mentions², stratified by patient age, as reported by U.S. office-based physician surveys from July 2009 through June 2012, aggregate. Drug use mentions were coded according to the International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were applied to the estimates. “Epilepsy NOS” (ICD-9 code 345.9) and “Partial Epilepsy NEC” (ICD-9 code 345.5) with 4,000 drug use mentions (95% CI : 500-14,000) each, were the only diagnoses associated with the use of Lamictal® XR™ among the 0-12 years pediatric age group. “Affective Personality” (ICD-9 code 301.1) with 5,000 drug use mentions (95% CI: 500-15,000) was the only diagnosis associated with the use of Lamictal® XR™ for the 13-16 years pediatric age group, from July 2009 through June 2012. However, the number of drug use mentions for Lamictal® XR™ reported for the pediatric population from office-based physician visits was very low and were below the acceptable count allowable to provide a reliable estimate of national use.

5 DISCUSSION

The pediatric population of 0-16 year olds accounted for approximately 12% (9,200 patients) of all patients who received dispensed prescriptions for Lamictal® XR™ from U.S. outpatient retail pharmacies during July 2009 through June 2012. Off-label use in patients 0-12 years occurred in approximately 40% (3,600 patients) of all pediatric patients.

The top prescribing specialty for dispensed prescriptions of Lamictal® XR™ was Neurology. Diagnoses related to “Epilepsy” (ICD-9 codes 345.9 and 345.5) were the only diagnosis codes associated with the use of Lamictal® XR™ in pediatric patients ages 0-12 years. “Affective

² Encuity Research, LLC., 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.

Personality” (ICD-9 code 301.1) was the only diagnosis code associated with the use of Lamictal® XR™ in pediatric patients ages 13-16 years. However, the number of drug use mentions for Lamictal® XR™ among the pediatric population from office-based physician visits was below the acceptable count allowable to provide a reliable estimate of national use, and should therefore be interpreted with caution.

In a recent study examining six anticonvulsant drugs (including lamotrigine) in the pediatric population (aged 0-17 years), it was found that the proportion of psychiatric diagnosis visits increased by 1.7 fold from 1996 to 2009, while proportion of seizure-related visits remained unchanged³. This demonstrates the growth in off-label use of anticonvulsants in the pediatric population. Specific to lamotrigine, off-label use has been observed in the pediatric population for bipolar disorder⁴, convulsions in the newborn⁵, and refractory epilepsy^{6,7,8}. Lamotrigine has been studied for use in autistic disorder, but treatment effect was not found to be significantly different from placebo.⁹

Findings from this review should be interpreted in the context of the known limitations of the databases used. Based on the IMS Health, IMS National Sales Perspectives™ sales data from July 2011 to June 2012, the majority of Lamictal® XR™ packages were being distributed to outpatient retail pharmacies. These data sets do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer to 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, assuming that facilities purchase drugs in quantities reflective of actual patient use.

Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and outpatient prescription data are best used to evaluate utilization trends over time. Results should not be overstated when nationally projected

³ Tran AR, Zito JM, Safer DJ, Hundley SD. National Trends in Pediatric Use of Anticonvulsants. *Psychiatr Serv.* 2012, Sept 15.

⁴ Kowatch RA, Fristad M, Birmaher, et al. Treatment Guidelines for Children and Adolescents With Bipolar Disorder: Child Psychiatric Workgroup on Bipolar Disorder. *J Am Acad Child Adolesc Psychiatry.* 2005;44(3):213-235.

⁵ Barr PA, Buettiker VE, Anthony JH. Efficacy of lamotrigine in refractory neonatal seizures. *Pediatr Neurol.* 1999;2:161-3.

⁶ Celebi A, Yalnmzoqlu D, Turanli G, et al. Lamotrigine in children with refractory epilepsy. *Turk. J Pediatr.* 2008;50(5):426-31.

⁷ Fallah R, Islami Z, Tavakoli N. Efficacy and safety of lamotrigine in refractory epilepsy of children. *Eastern J of Medicine.* 2008;13:7-12

⁸ Coppola G, Pascotto. Lamotrigine as add-on drug in children and adolescents with refractory epilepsy and mental delay: an open trial. *Brain and Development.* 1997;19(6):398-402.

⁹ Belsito KM, Law PA, Kirk KS, et al. Lamotrigine Therapy for Austistic Disorder: A Randomized, Double-Blind Placebo-Controlled Trial. *J Autism and Developmental Disorders.* 2001;31(2):175-181.

estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

6 CONCLUSIONS

There were a nationally estimated number of 602,500 prescriptions and 74,000 unique patients who received dispensed prescriptions for Lamictal® XR™ from U.S. outpatient retail pharmacies from July 2009 through June 2012. The pediatric population (0-16 years) accounted for approximately 12% (9,200 patients) of total patients who received dispensed prescriptions for Lamictal® XR™.

Although the majority of use in pediatric patients was among those aged 13-16 years old, there was off-label use in patients aged 0-12 years (3,600 patients) for Lamictal® XR™ during the examined time period. The top prescribing specialty of Lamictal® XR™ was Neurology. Diagnoses for “Epilepsy” and “Affective Personality” were the only diagnoses captured associated with the use of Lamictal® XR™ in the pediatric population. However, these data were below the acceptable count allowable to provide a reliable estimate of national use, and should therefore be interpreted with caution.

7 APPENDICES

7.1 APPENDIX 1: TABLES AND FIGURES

Table 1. Nationally Estimated Number of Dispensed Lamictal XR® Prescriptions from U.S. Outpatient Retail Pharmacies, July 2009 - June 2012								
	July 2009 - June 2010		July 2010 - June 2011		July 2011 - June 2012		July 2009 - June 2012, Aggregated	
	Prescriptions (N)	Share (%)	Prescriptions (N)	Share (%)	Prescriptions (N)	Share (%)	Prescriptions (N)	Share (%)
Lamictal XR	103,437	100.0%	222,996	100.0%	276,094	100.0%	602,527	100.0%
0-16 years	16,364	15.8%	33,632	15.1%	39,503	14.3%	89,499	14.9%
0-12 years	6,724	41.1%	12,820	38.1%	14,926	37.8%	34,470	38.5%
13-16 years	9,639	58.9%	20,812	61.9%	24,577	62.2%	55,028	61.5%
17+ years	86,923	84.0%	188,913	84.7%	236,588	85.7%	512,424	85.0%
Unknown Age	151	0.1%	450	0.2%	--	--	601	0.1%

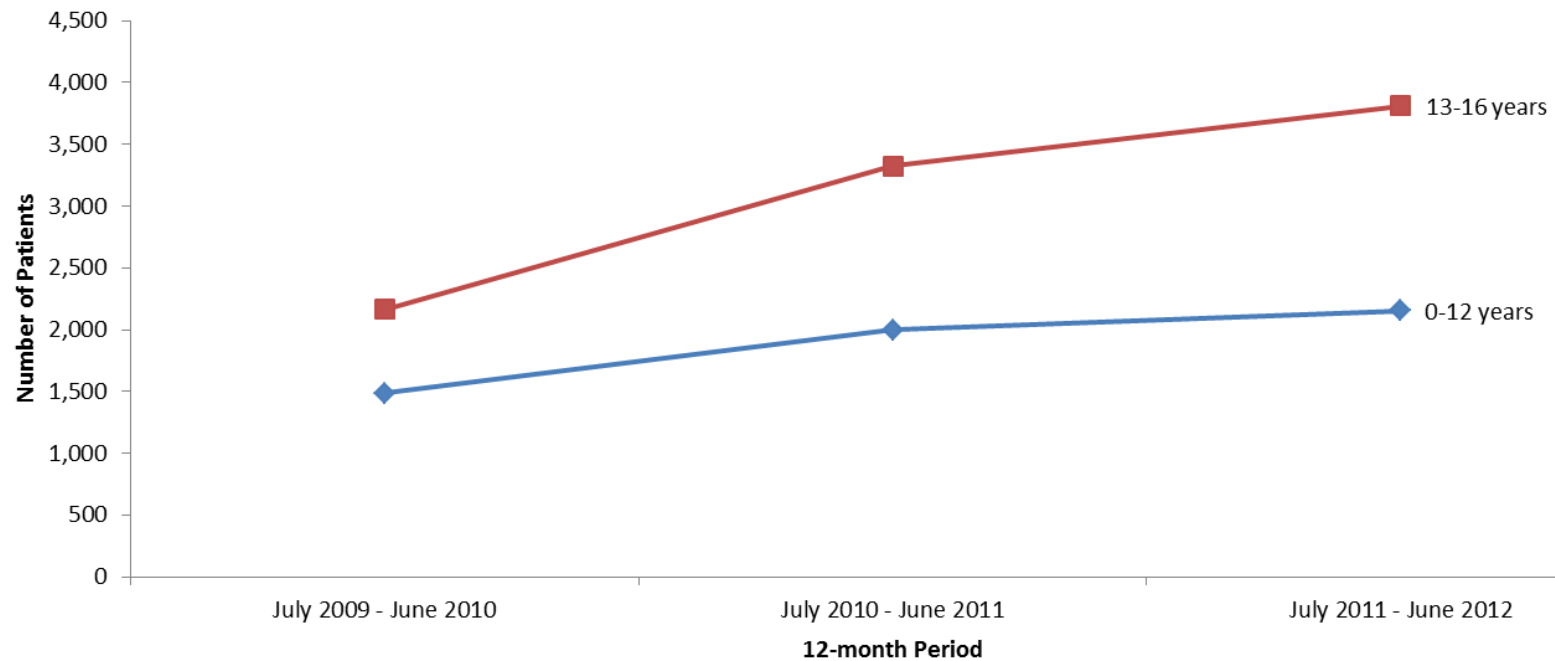
Source:IMS, Vector One®: National (VONA). Extracted September-October 2012. Files: VONA 2012-1803 Lamictal XR BPCA, by age, 9-04-2012.xls and VONA 2012-1803 Lamictal XR BPCA, by age (0-16, 17up, MAT, 10-01-12.xls

Table 2. Nationally Estimated Number of Patients Who Received Prescriptions for Lamictal XR® from U.S. Outpatient Retail Pharmacies, July 2009 – June 2012								
	July 2009 - June 2010		July 2010 - June 2011		July 2011 - June 2012		July 2009 - June 2012, Aggregated	
	Patients (N)	Share (%)	Patients (N)	Share (%)	Patients (N)	Share (%)	Patients (N)	Share (%)
Lamictal XR	25,967	100.0%	39,161	100.0%	45,828	100.0%	73,893	100.0%
0-16 years	3,547	13.7%	5,081	13.0%	5,687	12.4%	9,158	12.4%
0-12 years	1,483	41.8%	1,997	39.3%	2,152	37.8%	3,631	39.6%
13-16 years	2,164	61.0%	3,326	65.5%	3,811	67.0%	6,239	68.1%
17+ years	22,578	86.9%	34,463	88.0%	40,662	88.7%	66,067	87.0%
Unknown Age	72	0.3%	114	0.3%	--	--	124	0.0%

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

Source:IMS, Vector One®: Total Patient Tracker (TPT). Extracted October 2012. Files: TPT 2012-1803 Lamictal XR BPCA, by age, by MAT, 10-01-2012.xls; TPT 2012-1803 Lamictal BPCA, by age (0-16, 17up), aggregate, 10-01-2012.xls; TPT 2012-1803 Lamictal XR BPCA, by age (0-12, 13-16, 17up), aggregate, 10-01-2012.xls

Figure 1. Nationally Estimated Number of Pediatric Patients That Received a Prescription for Lamictal XR® from U.S. Outpatient Retail Pharmacies, stratified by age, from July 2009 through June 2012



Source: IMS, Vector One®: Total Patient Tracker (TPT). Extracted October 2012. File: TPT 2012-1803 Lamictal XR BPCA, by age, by MAT, 10-01--2012.xls

Table 3. Top 10 Prescribing Specialties for Lamictal XR® by the Nationally Estimated Number of Prescriptions Dispensed from U.S. Outpatient Retail Pharmacies, July 2009 – June 2012, Aggregated		
	Specialties (N)	Share (%)
Lamictal XR	602,524	100.0%
Neurology	382,562	63.5%
Other	48,129	8.0%
Nurse Practitioner	36,791	6.1%
Psychiatrist	35,049	5.8%
Unspecified	27,473	4.6%
General Practitioner/ Family Medicine/ Osteopathic Medicine	19,370	3.2%
Internal Medicine	16,066	2.7%
Physician Assistant	15,207	2.5%
Pediatrician	8,493	1.4%
Hospitalist	3,666	0.6%
All Others	9,718	1.6%
Source: IMS, Vector One®: National (VONA). Extracted September 2012. File: VONA 2012-1803 Lamictal XR BPCA, by specialty, 9-04--2012.xls		

Table 4. Diagnoses Associated with Lamictal XR® Drug Mentions (Stratified by Age) as Reported by Office-Based Physician Practices, July 2009 through June 2012, Aggregated			
	July 2009 through June 2012		
	Drug Use Mentions	Share %	95% Confidence Interval
Lamictal XR	341,000	100.0%	253,000 - 428,000
0-12 years	9,000	2.6%	<500 - 23,000
3459 Epilepsy NOS	4,000	50.0%	<500 - 14,000
3455 Partial Epilepsy NEC	4,000	50.0%	<500 - 14,000
13-16 years	5,000	1.5%	<500 - 15,000
3011 Affective Personality	5,000	100.0%	<500 - 15,000
17+ years	319,000	93.8%	235,000 - 404,000
3459 Epilepsy NOS	109,000	34.2%	60,000 - 159,000
3455 Partial Epilepsy NEC	61,000	19.2%	24,000 - 98,000
2967 Bipolar Affective NOS	46,000	14.3%	14,000 - 78,000
All Others	103,000	32.3%	55,000 - 151,000
Unspecified age	7,000	2.2%	<500 - 20,000
<p>1 Encuity Research, LLC. Recommends caution interpreting projected annual uses or mentions below 100,000, as the sample size is very small with correspondingly large confidence intervals.</p> <p>2 NOS: unspecified</p> <p>3 NEC: not elsewhere classified</p> <p>Source: Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA) with Pain Panel. Extracted August 2012. July 2009 – July 2012. File: 2012-1803 PDDA Lamotrigine ICD-9 Aug12.xls</p>			

7.2 APPENDIX 2: DRUG USE DATABASE DESCRIPTIONS

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 manufactures 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.

IMS, Vector One®: National (VONA)

The IMS, Vector One®: National (VONA) database 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 includes prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. There are over 800,000 physicians in the VECTOR One database, which supplies VONA, TPT, & DET. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. IMS receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

IMS, Vector One®: Total Patient Tracker (TPT)

The IMS, Vector One®: 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 over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Encuity Research, LLC., Physician Drug and Diagnosis Audit™ (PDDA) with Pain Panel

The Encuity Research, LLC., Physician Drug and Diagnosis Audit™ (PDDA) with Pain Panel 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 over 3,200 office-based physicians representing 30 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 Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

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/s/

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