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Office of Surveillance and Epidemiology**

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

CDR Lisa L. Mathis, USPHS, MD
Pediatric and Maternal Health Team
Office of New Drugs

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

Thru: Laura Governale, Pharm.D., MBA, Drug Use Data Analyst Team Leader
Division of Epidemiology
Office of Surveillance and Epidemiology

From: Vicky Borders-Hemphill, Pharm.D./ Drug Use Data Analyst
Division of Epidemiology
Office of Surveillance and Epidemiology

Subject: Zyprexa[®] (Olanzapine) tablets BPCA Drug Use Review

Drug Name(s): Zyprexa[®] (Olanzapine)

Application Type/Number: NDA 20-592

Applicant/sponsor: Eli Lilly

OSE RCM #: 2007-1386

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CONTENTS

EXECUTIVE SUMMARY	1
1 Introduction.....	1
2 Methods and Materials.....	1
3 Results.....	2
4 Limitations	2
5 CONCLUSIONS	2
Concurrence.....	3
Appendices	3

EXECUTIVE SUMMARY

This review examines drug utilization patterns for Zyprexa[®] (Olanzapine), an atypical antipsychotic agent, in the pediatric population, patients aged 0-12, 13-17, and 18+ years, with a primary focus on patterns of use two years before and one year following the granting of Pediatric Exclusivity on January 10, 2007. Since around 68% of Zyprexa[®] bottles and packets of pills were sold to U.S. retail settings and approximately 32% were sold to non-retail [mainly long-term care (~22%)] 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 Zyprexa[®] during the three 12-month periods from February 1, 2005 through January 31, 2008.

For each of the three 12-month periods from February 1, 2005 – January 31, 2008:

- Oral Zyprexa[®] represented approximately 15% of the total projected number of select oral atypical antipsychotic dispensed prescriptions.
- Oral Zyprexa[®] prescriptions in the pediatric population (ages 0-17 years) accounted for approximately 4.7% of total dispensed oral Zyprexa[®] prescriptions.
- Around 5.7% of total projected patients who filled a prescription for oral Zyprexa[®], were aged 0 to 17 years.
- Psychiatry was the top prescribing specialty for olanzapine oral dosage forms.
- The top diagnosis code associated with the use of oral Zyprexa[®] for patients aged 0 to 12 years were “Anxiety States” (ICD-9 300.0) and “Early Child Psychoses, NEC” (ICD-9 299.8). For patients aged 13 to 17 years, “Depressive Disorder, NEC” (ICD-9 311.0) was the top diagnosis code associated with the use of oral Zyprexa[®].

1 INTRODUCTION

Using the currently available proprietary drug use databases licensed by the Agency, this review describes outpatient drug use patterns for oral Zyprexa[®] (olanzapine) 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 January 10, 2007.

2 METHODS AND MATERIALS

IMS Health, IMS National Sales PerspectivesTM data (*see Appendix 2*) were used to determine the setting in which oral Zyprexa[®] 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 February 1, 2005 through January 31, 2008 (*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 oral Zyprexa[®] sales (68%) and approximately 32% were sold to non-retail [mainly long-term care (~22%)] settings. Thus, the examination of oral Zyprexa[®] utilization patterns focused on the outpatient setting.

Outpatient use and patient demographics (stratified by ages 0-12 years, 13-17 years, and 18+ years for oral Zyprexa[®]) 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 oral Zyprexa[®], and the number of drug mentions by office-based physicians, were obtained from February 1, 2005 through January 31, 2008, inclusive. For

¹ IMS Health, IMS Nationals Sales PerspectivesTM, Data extracted 5-12-2008, Source file: 0805ola.DVR

comparative purposes, other select atypical antipsychotics (oral, solid, liquid dosage forms only) were also examined: including quetiapine fumarate, risperidone, aripiprazole, ziprasidone, clozapine, and paliperidone.

3 RESULTS

During the three 12-month periods from February 1, 2005 through January 31, 2008, dispensed prescriptions for Zyprexa[®] represented approximately 15% of the projected number of select atypical antipsychotic prescriptions dispensed in the United States. The projected number of Zyprexa[®] dispensed prescriptions decreased by close to 5% from the pre-exclusivity period (February 1, 2005 through January 31, 2006) to the post-exclusivity period (February 1, 2007 through January 31, 2008) (*Table 1*).

During the three 12-month periods from February 1, 2005 through January 31, 2008, dispensed prescriptions for Zyprexa[®] in the pediatric population (ages 0-17 years) accounted for approximately 4.7% of the total projected number of dispensed prescriptions for Zyprexa[®]. Of the prescriptions dispensed to patients aged 0 to 17 years, around 43% were dispensed to patients aged 12 years or younger and 57% dispensed to patients ages 13 to 17 years (*Table 2*). Of the patients who filled a prescription for Zyprexa[®] in the outpatient retail pharmacy setting, 5.7% of total projected patients were aged 0 to 17 years, and the proportion of projected pediatric patients aged 0 to 12 years and 13 to 17 years coincided with the proportion of dispensed prescriptions for the same age groups (*Table 3*).

During the three 12-month periods from February 1, 2005 through January 31, 2008, Psychiatry was the top prescribing specialty for olanzapine oral dosage forms. Among the Psychiatry specialty, around 9.8% of oral Zyprexa[®] prescriptions were prescribed by Child Psychiatry (*Table 4*).

According to office-based physician practices in the U.S., “anxiety states” (ICD-9 300.0) and “early child psychoses, NEC” (ICD-9 299.8) were the top diagnosis codes associated with the use of oral solid and liquid dosage forms of olanzapine for patients aged 0 to 12 years, and “depressive disorder, NEC” (ICD-9 311.0) was the top diagnosis code associated with the use for patients aged 13 to 17 years. Adults aged 18 years and older accounted for the majority (~93%) of office-based physician visits reportedly associated with the use of oral Zyprexa[®] during the three 12-month study periods (*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 Zyprexa[®] is distributed primarily in outpatient settings based on the IMS Health, IMS National Sales Perspectives[™]. Long-term care (~22%) is the second most common distribution channel. 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 Zyprexa[®] (olanzapine) oral formulations in the pediatric and adult populations has been declining over the three 12-month study periods examined.

CONCURRENCE

Laura Governale, Pharm D., MBA.
Team Leader
Division of Epidemiology (DEPi)
Solomon Iyasu, M D, MPH
Director
Division of Epidemiology (DEPi)

APPENDICES

APPENDIX 1: Tables

Table 1. Projected Number of Select Atypical Antipsychotic Prescriptions (In Thousands) Dispensed from U.S Retail Pharmacies, MAT February 1, 2005 – January 31, 2008

	MAT/JAN/2006		MAT/JAN/2007		MAT/JAN/2008	
	Retail TRxs (000)	Share %	Retail TRxs (000)	Share %	Retail TRxs (000)	Share %
TOTAL MARKET	26,820	100.0%	28,487	100.0%	30,950	100.0%
quetiapine fumarate	8,538	31.8%	9,693	34.0%	11,105	35.9%
risperidone	7,462	27.8%	7,669	26.9%	7,819	25.3%
aripiprazole	3,121	11.6%	3,741	13.1%	4,272	13.8%
olanzapine	4,677	17.4%	4,246	14.9%	4,032	13.0%
ziprasidone hcl	1,654	6.2%	1,996	7.0%	2,230	7.2%
clozapine	1,368	5.1%	1,141	4.0%	1,129	3.6%
paliperidone	--	--	1	0.0%	364	1.2%

Verispan, LLC: Vector One[®]: National (VONA) Data extracted 5-12-2008. Source File: 2007-1386 VONA 5-12-08 olanzapine comparators BPCA.qry

For Oral Solid, Liquid Dosage forms Only

Table 2. Projected Number of Olanzapine Prescriptions (In Thousands) Dispensed from U.S Retail Pharmacies stratified by age, MAT February 1, 2005 – January 31, 2008

	MAT/JAN/2006		MAT/JAN/2007		MAT/JAN/2008	
	Retail TRxs (000)	Share %	Retail TRxs (000)	Share %	Retail TRxs (000)	Share %
olanzapine	4,677	100.0%	4,246	100.0%	4,032	100.0%
0-17	246	5.2%	189	4.5%	174	4.3%
0-12	109	2.3%	80	1.9%	73	1.8%
13-17	137	2.9%	109	2.6%	101	2.5%
18+	4,295	91.8%	4,011	94.5%	3,826	94.9%
UNSPEC.	136	2.9%	45	1.1%	33	0.8%

Verispan, LLC: Vector One[®]: National (VONA) Data extracted 5-12-2008. Source File: 2007-1386 VONA 5-12-08 olanzapine age BPCA.qry
 For Oral Solid, Liquid Dosage forms Only

Table 3. Projected Number of Patients who filled a Zyprexa® Prescription at a U.S. Retail Pharmacy, MAT February 1, 2005 – January 31, 2008

	MAT Ending 01-06		MAT Ending 01-07		MAT Ending 01-08	
	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share
Zyprexa Total	929,106	100.00%	787,402	100.00%	729,209	100.00%
0-17	59,033	6.35%	43,040	5.47%	38,202	5.24%
0 - 12	26,069	2.81%	18,490	2.35%	16,218	2.22%
13 - 17	34,487	3.71%	25,770	3.27%	23,052	3.16%
18 - 85	841,056	90.52%	735,256	93.38%	684,936	93.93%
UNKNOWN AGE	69,412	7.47%	31,812	4.04%	24,993	3.43%

Verispan, Total Patient Tracker, data extracted 5-12-08 and 5-13-08. Source Files: 2007-1386 TPT 5-12-08 zyprexa age.xls and 2007-1386 TPT 5-13-08 zyprexa age.xls

*Subtotals may not sum exactly due to rounding. Because of patients aging during the study period (“the cohort effect”), patients may be counted more than once in the individual age categories. For this reason, summing across years is not advisable and will result in overestimates of patient counts. – means no data

Table 4. Total Number of Olanzapine Prescriptions Dispensed (*In Thousands*) from U.S. Retail Pharmacies by Prescriber Specialty (Top 10), MAT February 1, 2005 – January 31, 2008

	MAT/JAN/2006		MAT/JAN/2007		MAT/JAN/2008	
	Retail TRxs (000)	Share %	Retail TRxs (000)	Share %	Retail TRxs (000)	Share %
olanzapine	4,677	100.0%	4,246	100.0%	4,032	100.0%
PSYCHIATRY	2,115	45.2%	2,222	52.3%	2,123	52.6%
PSYCHIATRY	1,863	88.1%	1,971	88.7%	1,887	88.9%
CHILD PSYCHIATRY	220	10.4%	214	9.6%	198	9.3%
PSYCHIATRY, GERIATRIC	31	1.5%	37	1.7%	38	1.8%
GP/FM/DO[†]	646	13.8%	643	15.1%	593	14.7%
INTERNAL MEDICINE	433	9.3%	406	9.6%	365	9.1%
UNSPECIFIED	909	19.4%	376	8.9%	354	8.8%
NURSE PRACTITIONER	197	4.2%	230	5.4%	255	6.3%
HOSPITAL	77	1.7%	79	1.9%	67	1.7%
NEUROLOGY	55	1.2%	53	1.3%	49	1.2%
NEUROLOGY	49	89.2%	48	90.1%	44	89.9%
CHILD NEUROLOGY	6	10.8%	5	9.9%	5	10.1%
PHYSICIAN ASSISTANT	33	0.7%	38	0.9%	42	1.0%
PEDIATRICS	34	0.7%	31	0.7%	29	0.7%
PEDIATRICS	22	67.1%	21	67.4%	19	65.1%
PEDIATRICS, INTERNAL MEDICIN	9	26.5%	9	28.6%	9	31.6%
PEDIATRIC HEMATOLOGY	0	0.9%	0	1.2%	0	1.4%
PEDIATRIC, OTHER	1	2.5%	0	1.0%	0	0.8%
PEDIATRIC CARDIOLOGY	0	0.7%	0	0.4%	0	0.3%
PEDIATRIC NEPHROLOGY	0	0.1%	0	0.3%	0	0.3%
PEDIATRIC SURGERY	0	0.6%	0	0.2%	0	0.2%
PEDIATRIC ALLERGY	0	0.5%	0	0.2%	0	0.1%
PEDIATRIC PULMONOLOGY	0	0.1%	0	0.3%	0	0.1%
PEDIATRIC ENDOCRINOLOGY	0	0.6%	0	0.3%	0	0.1%
PEDIATRIC EMERGENCY MED.	0	0.0%	0	0.1%	0	0.0%
PEDIATRIC RADIOLOGY	0	0.3%	0	0.0%	0	0.0%
PEDIATRIC OTOLARYNGOLOGY	0	0.1%	--	--	--	--
OTHER	179	3.5%	165	3.6%	156	3.6%

Source: Verispan, LLC: Vector One®: National (VONA) Data extracted 5-12-2008. File: 2007-1386 VONA 5-12-08 olanzapine specialty BPCA.qry

[†]GP/FM/DO = General Practice, Family Medicine, Doctors of Osteopathy

For Oral Solid, Liquid Only

Table 5. Physician Reports of the Top Diagnosis Associated with the Use of Olanzapine, MAT February 1, 2005 – January 31, 2008

	MAT/JAN/2006		MAT/JAN/2007		MAT/JAN/2008	
	Uses (000)	Share %	Uses (000)	Share %	Uses (000)	Share %
olanzapine	3,538	100.0%	2,684	100.0%	2,239	100.0%
0-12	25	0.7%	6	0.2%	12	0.5%
3000 ANXIETY STATES	--	--	--	--	6	50.0%
2998 EARLY CHLD PSYCHOSES NEC	--	--	--	--	6	50.0%
2966 BIPOLAR AFFECTIVE, MIXED	11	44.2%	--	--	--	--
2959 SCHIZOPHRENIA NOS	--	--	6	100.0%	--	--
3140 ATTENTION DEFICIT DIS	3	13.8%	--	--	--	--
Others (2)	10	42.0%	--	--	--	--
13-17	58	1.7%	37	1.4%	56	2.5%
3110 DEPRESSIVE DISORDER NEC	5	8.9%	--	--	14	24.4%
3129 CONDUCT DISTURBANCE NOS	--	--	--	--	8	14.4%
2971 PARANOIA	--	--	--	--	8	14.4%
2998 EARLY CHLD PSYCHOSES NEC	--	--	--	--	8	13.7%
2953 PARANOID SCHIZOPHRENIA	--	--	--	--	8	13.7%
Others (9)	53	91.20%	37	100%	11	19.4%
18+	3,247	91.8%	2,536	94.5%	2,078	92.8%
2967 BIPOLAR AFFECTIVE NOS	419	12.9%	373	14.7%	394	19.0%
2959 SCHIZOPHRENIA NOS	402	12.4%	277	10.9%	356	17.1%
2957 SCHIZOAFFECTIVE TYPE	386	11.9%	204	8.0%	307	14.8%
2953 PARANOID SCHIZOPHRENIA	379	11.7%	334	13.2%	215	10.4%
2989 PSYCHOSIS NOS	173	5.3%	122	4.8%	127	6.1%
Others (74)	1,490	46.1%	1,224	48.2%	681	32.8%
UNSPEC.	208	5.9%	104	3.9%	93	4.2%
2959 SCHIZOPHRENIA NOS	36	17.3%	11	10.8%	30	31.9%
2967 BIPOLAR AFFECTIVE NOS	24	11.7%	25	23.7%	22	23.8%
2989 PSYCHOSIS NOS	6	3.1%	--	--	12	13.3%
3098 OTHER ADJUST REACTION	12	5.6%	--	--	12	12.9%
2957 SCHIZOAFFECTIVE TYPE	21	10.3%	29	28.2%	11	11.8%
Others (18)	110	51.9%	38	37.4%	6	6.2%

Verispan, LLC. Physician Drug and Diagnosis Audit, Extracted 5-13-08; File: 2007-1386 PDDA 5-13-08 olanzapine diagnosis BPCA.xls

-- means no data

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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Laura Governale
6/27/2008 10:34:07 AM
DRUG SAFETY OFFICE REVIEWER