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Office of Surveillance and Epidemiology**

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Subject: Ambien<sup>®</sup> (zolpidem) tablets BPCA Drug Use Review

Drug Name(s): Ambien<sup>®</sup> (zolpidem)

Application Type/Number: NDA 19-908

Applicant/sponsor: Sanofi Aventis

OSE RCM #: 2007-256

**\*\*This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.\*\***

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## EXECUTIVE SUMMARY

This review examines drug utilization patterns for Ambien<sup>®</sup> (zolpidem), a non-benzodiazepine hypnotic agent, in the pediatric population, patients aged 0-5, 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 on November 20, 2006. Since approximately 80% of Ambien<sup>®</sup> tablets were sold to U.S. retail settings and about 10% 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 Ambien<sup>®</sup> 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:

- Ambien<sup>®</sup> represented approximately 64% of the total projected number of dispensed prescriptions for the selected sedative hypnotic agents.
- Ambien<sup>®</sup> prescriptions in the pediatric population (ages 0-16 years) accounted for less than 1% (51,365 TRx) of total dispensed Ambien<sup>®</sup> prescriptions.
- Similarly, less than 1% of the 8.3 million total projected patients who filled a prescription for Ambien<sup>®</sup> were pediatric patients.
- General Practice/Family Medicine/Doctors of Osteopathy was the top prescribing specialty for Ambien<sup>®</sup>.
- The top diagnosis code associated with the use of Ambien<sup>®</sup> for patients aged 6 to 11 years was “Depressive Disorder, NEC” (ICD-9 311.0). For patients aged 12 to 16 years, “Sleep Disturbances” (ICD-9 780.5) and “Depressive Disorder, NEC” (ICD-9 311.0) was the top diagnosis code associated with the use of Ambien<sup>®</sup>.
- Use of Ambien<sup>®</sup> (zolpidem) in the pediatric population has been declining over the three 12-month study periods examined. However, use of zolpidem in the adult population has been gradually increasing.

## 1 INTRODUCTION

Using the currently available proprietary drug use databases licensed by the Agency, this review describes outpatient drug use patterns for Ambien<sup>®</sup> (zolpidem) 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 November 20, 2006.

## 2 METHODS AND MATERIALS

IMS Health, IMS National Sales Perspectives<sup>™</sup> data (see Appendix 2 for full database description) were used to determine the setting in which Ambien<sup>®</sup> was sold. Sales of this product by number of tablets (extended units) 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 through November 30, 2007 (data not provided).<sup>1</sup> During the three 12-month periods of this review, retail settings (chain stores, independent pharmacies, and food stores) accounted for the majority of Ambien<sup>®</sup> sales at 80% and approximately 10% were sold to non-retail settings. Thus, the examination of Ambien<sup>®</sup> utilization patterns focused on the outpatient setting.

Outpatient use and patient demographics (stratified by ages 0-5 years, 6-11 years, 12-16 years and 17+ years for Ambien<sup>®</sup>) 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

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<sup>1</sup> IMS Health, IMS Nationals Sales Perspectives<sup>™</sup>, Data extracted 5-16-2008, Source file: 0805zolp.DVR

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 Ambien<sup>®</sup>, and the number of drug mentions by office-based physicians, were obtained from December 1, 2004 through November 30, 2007, inclusive. For comparative purposes, other select short-term insomnia agents were also examined: including temazepam, eszopiclone, ramelteon, zaleplon, flurazepam, pentobarbital, and estazolam.

### 3 RESULTS

During the three 12-month periods from December 1, 2004 through November 30, 2007, dispensed prescriptions for Ambien<sup>®</sup> represented approximately 64% of the projected number of prescriptions dispensed for the selected sedative hypnotic agents in the United States. The projected number of Ambien<sup>®</sup> dispensed prescriptions increased by close to 16% from the pre-exclusivity period (December 1, 2005 through November 30, 2006) to the post-exclusivity period (December 1, 2006 through November 30, 2007) (Appendix 1 Table 1).

During the three 12-month periods from December 1, 2004 through November 30, 2007, dispensed prescriptions for Ambien<sup>®</sup> in the pediatric population (ages 0-16 years) accounted for less than 1% of the total projected number of dispensed prescriptions for Ambien<sup>®</sup>. Of the prescriptions dispensed to patients aged 0 to 16 years, around 78% were dispensed to patients aged 12 to 16 years, and 14% dispensed to patients ages 6 to 11 years (Appendix 1 Table 2). Of the 8.3 million patients who filled a prescription for Ambien<sup>®</sup> in the outpatient retail pharmacy setting, less than 1% of total projected patients were aged 0 to 16 years. Similar proportions were seen for patients as that of dispensed prescriptions (Appendix 1 Table 3).

During the three 12-month periods from December 1, 2004 through November 30, 2007, General Practice/Family Medicine/Doctors of Osteopathy was the top prescribing specialty for zolpidem with approximately 31% followed by Internal Medicine and Psychiatry with 26% and 11%, respectively. Among the Psychiatry specialty, around 9.5% of Ambien<sup>®</sup> prescriptions (approximately 300,000 TRx) were prescribed by Child Psychiatry (Appendix 2 Table 4). Pediatricians accounted for approximately 1% (approximately 296,000 TRx) of overall dispensed prescriptions for Ambien<sup>®</sup>.

According to office-based physician practices in the U.S., “sleep disturbances” (ICD-9 780.5) was the top diagnosis code associated with the use of zolpidem for patients aged 6 to 11 years, and “depressive disorder, NEC” (ICD-9 311.0) and “sleep disturbances:” (ICD-9 780.5) were the top diagnosis codes associated with the use for patients aged 12 to 16 years. Adults aged 17 years and older accounted for the majority (~97%) of office-based physician visits reportedly associated with the use of Ambien<sup>®</sup> during the three 12-month study periods (Appendix 2 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 Ambien<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 Ambien® (zolpidem) in the pediatric population has been declining over the three 12-month study periods examined. However, use of zolpidem in the adult population has been gradually increasing.

## CONCURRENCE

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## APPENDICES

### APPENDIX 1: Tables and Figures

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

	Dec 2004-Nov 2005		Dec 2005-Nov 2006		Dec 2006-Nov 2007	
	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share
	N	%	N	%	N	%
<b>TOTAL MARKET</b>	<b>36,399,205</b>	<b>100.0%</b>	<b>42,627,889</b>	<b>100.0%</b>	<b>47,910,774</b>	<b>100.0%</b>
zolpidem tartrate	23,697,163	65.1%	26,477,034	62.1%	30,657,677	64.0%
temazepam	7,922,598	21.8%	7,659,829	18.0%	8,071,847	16.8%
eszopiclone	2,532,491	7.0%	5,825,236	13.7%	6,339,013	13.2%
ramelteon	82,678	0.2%	890,888	2.1%	1,298,799	2.7%
zaleplon	1,280,708	3.5%	1,003,892	2.4%	813,149	1.7%
flurazepam hydrochloride	645,127	1.8%	576,926	1.4%	539,646	1.1%
estazolam	238,263	0.7%	193,927	0.5%	190,560	0.4%
pentobarbital sodium	177	0.0%	157	0.0%	83	0.0%

Source: Verispan Vector One®: National, Data Extraced 6/08. File: VONA 2007-256 Ambien BPCA TRx Comparators.xls

**Table 2. Total number of dispensed prescriptions for zolpidem by patient age through U.S. outpatient retail pharmacies, December 1, 2004-November 30, 2007**

	DEC 2004-NOV 2005		DEC 2005-NOV 2006		DEC 2006-NOV 2007		Pre- Baseline to	Pre- Exclusivity
	Baseline		Pre-Exclusivity		Post-Exclusivity		Post- Exclusivity	to Post- Exclusivity
	Retail TRxs N	Share %	Retail TRxs N	Share %	Retail TRxs N	Share %	% change	% change
<b>zolpidem tartrate</b>	23,697,202	100.0%	26,476,963	100.0%	30,657,696	100.0%	29.37%	15.79%
<b>age 0-16</b>	59,211	0.2%	54,058	0.2%	51,365	0.2%	-13.25%	-4.98%
<b>age 0-5</b>	6,472	10.9%	3,769	7.0%	2,667	5.2%	-58.79%	-29.24%
<b>age 6-11</b>	7,733	13.1%	7,577	14.0%	7,745	15.1%	0.16%	2.22%
<b>age 12-16</b>	45,006	76.0%	42,712	79.0%	40,953	79.7%	-9.01%	-4.12%
<b>age 17+</b>	23,467,957	99.0%	26,349,271	99.5%	30,548,516	99.6%	30.17%	15.94%
<b>age UNSPEC.</b>	170,034	0.7%	73,634	0.3%	57,815	0.2%	-66.00%	-21.48%

Source: Verispan Vector One®: National, Data Extraced 5/08. File: VONA 2007-256 Ambien BPCA TRx by Age 5-29-08.xls

**Table 3. Projected Number of Patients Who Filled a Zolpidem Prescription at a U.S. Retail Pharmacy, Dec 1, 2004-Nov 30, 2007**

	Dec 2004-Nov 2005		Dec 2005-Nov 2006		Dec 2006-Nov 2007	
	Projected Patient Count	Share %	Projected Patient Count	Share %	Patient Count	Share %
<b>Zolpidem Total</b>	<b>7,249,858</b>	<b>100.00%</b>	<b>7,780,510</b>	<b>100.00%</b>	<b>8,322,990</b>	<b>100.00%</b>
<b>Age 0-5</b>	3,115	0.04%	2,135	0.03%	1,518	0.02%
<b>Age 6-11</b>	4,214	0.06%	3,623	0.05%	3,467	0.04%
<b>Age 12-16</b>	25,957	0.36%	22,005	0.28%	19,855	0.24%
<b>Age 17+</b>	7,142,042	98.51%	7,710,073	99.09%	8,265,938	99.31%
<b>Age Unspec.</b>	165,899	2.29%	114,357	1.47%	101,002	1.21%

Verispan, Vector One: Total Patient Tracker, Data Extracted 6/08. File: TPT 2007-256 Ambien BPCA Patient Count.xls

**Table 4. Total Number of Zolpidem Prescriptions Dispensed from U.S. Retail Pharmacies by Prescriber Specialty (Top 15), MAT December 1, 2004-November 30, 2007**

	MAT/NOV/2005		MAT/NOV/2006		MAT/NOV/2007	
	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share
	N	%	N	%	N	%
<b>zolpidem tartrate</b>	<b>23,697,201</b>	<b>100.0%</b>	<b>26,477,059</b>	<b>100.0%</b>	<b>30,657,660</b>	<b>100.0%</b>
<b>GP/FM/DO*</b>	6,840,702	28.9%	8,183,387	30.9%	9,826,225	32.1%
<b>INTERNAL MEDICINE</b>	6,195,832	26.1%	7,046,574	26.6%	8,096,322	26.4%
<b>PSYCHIATRY</b>	2,485,578	10.5%	2,897,100	10.9%	3,308,244	10.8%
<b>PSYCHIATRY</b>	2,212,665	89.0%	2,581,783	89.1%	2,954,301	89.3%
<b>CHILD PSYCHIATRY</b>	242,781	9.8%	276,211	9.5%	304,101	9.2%
<b>PSYCHIATRY, GERIATRIC</b>	30,132	1.2%	39,106	1.3%	49,842	1.5%
<b>UNSPECIFIED</b>	1,722,997	7.3%	1,135,057	4.3%	1,208,796	3.9%
<b>NURSE PRACTITIONER</b>	575,044	2.4%	798,317	3.0%	1,076,979	3.5%
<b>OB/GYN</b>	655,533	2.8%	716,185	2.7%	826,388	2.7%
<b>PHYSICIAN ASSISTANT</b>	328,010	1.4%	450,605	1.7%	607,708	2.0%
<b>CARDIOVASCULAR DISEASES</b>	486,463	2.1%	503,572	1.9%	529,953	1.7%
<b>NEUROLOGY</b>	387,215	1.6%	426,336	1.6%	467,186	1.5%
<b>NEUROLOGY</b>	380,253	98.2%	418,122	98.1%	458,513	98.1%
<b>CHILD NEUROLOGY</b>	6,962	1.8%	8,214	1.9%	8,673	1.9%
<b>RHEUMATOLOGY</b>	327,074	1.4%	361,377	1.4%	385,636	1.3%
<b>PULMONARY DISEASES</b>	302,214	1.3%	331,667	1.3%	381,842	1.2%
<b>ANESTHESIOLOGY</b>	285,783	1.2%	331,779	1.3%	377,575	1.2%
<b>ORTHOPEDIC SURGERY</b>	356,131	1.5%	350,112	1.3%	365,649	1.2%
<b>ORTHOPEDIC SURGERY</b>	315,673	88.6%	305,670	87.3%	313,118	85.6%
<b>ORTHOPEDIC SURGERY, OTHER</b>	20,129	5.7%	22,489	6.4%	26,978	7.4%
<b>ORTHO SURG, SPORTS MEDICINE</b>	19,485	5.5%	21,233	6.1%	24,936	6.8%
<b>ORTHO SURG, PED ORTHOPEDICS</b>	844	0.2%	720	0.2%	617	0.2%
<b>PEDIATRICS</b>	207,478	0.9%	243,326	0.9%	296,433	1.0%
<b>PEDIATRICS, INTERNAL MEDICINE</b>	110,175	53.1%	139,918	57.5%	184,601	62.3%
<b>PEDIATRICS</b>	86,255	41.6%	92,594	38.1%	99,732	33.6%
<b>PEDIATRIC, OTHER</b>	2,481	1.2%	2,640	1.1%	2,998	1.0%
<b>PEDIATRIC HEMATOLOGY</b>	2,134	1.0%	1,889	0.8%	1,972	0.7%
<b>PEDIATRIC CARDIOLOGY</b>	1,092	0.5%	1,289	0.5%	1,425	0.5%
<b>PEDIATRIC PULMONOLOGY</b>	1,269	0.6%	974	0.4%	1,319	0.4%
<b>PEDIATRIC ENDOCRINOLOGY</b>	842	0.4%	856	0.4%	956	0.3%
<b>PEDIATRIC RADIOLOGY</b>	671	0.3%	691	0.3%	856	0.3%
<b>PEDIATRIC NEPHROLOGY</b>	505	0.2%	692	0.3%	801	0.3%
<b>PEDIATRIC SURGERY</b>	860	0.4%	725	0.3%	613	0.2%
<b>PEDIATRIC EMERGENCY MED.</b>	342	0.2%	415	0.2%	569	0.2%
<b>PEDIATRIC ALLERGY</b>	730	0.4%	531	0.2%	428	0.1%
<b>PEDIATRIC OTOLARYNGOLOGY</b>	122	0.1%	112	0.0%	163	0.1%
<b>HOSPITAL</b>	245,147	1.0%	275,308	1.0%	289,640	0.9%
<b>All Others</b>	2,296,000	9.7%	2,426,357	9.2%	2,613,084	8.5%

Source: Verispan Vector One®: National, Data Extracted 5/08. File: VONA 2007-256 zolpidem specialty BPCA.xls

\*GP/FM/DO = General Practice, Family Medicine, Doctors of Osteopathy

**Table 5. Diagnosis associated with the use\* of zolpidem by patient age 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 (000)	Share %	Uses (000)	Share %	Uses (000)	Share %
<b>zolpidem tartrate</b>	4,524	100.0%	4,528	100.0%	4,788	100.0%
<b>6-11</b>	7	0.1%	--	--	--	--
7805 SLEEP DISTURBANCES	7	100.0%	--	--	--	--
<b>12-16</b>	29	0.6%	5	0.1%	13	0.3%
3110 DEPRESSIVE DISORDER NEC	--	--	--	--	7	52.6%
7805 SLEEP DISTURBANCES	12	42.1%	--	--	6	47.4%
7291 MYALGIA AND MYOSITIS NOS	5	18.0%	--	--	--	--
6441 THREATENED LABOR NEC	--	--	5	100.0%	--	--
3372 REFLEX SYMPATH DYSTROPHY	5	18.0%	--	--	--	--
2963 DEPR PSYCH, RECUR EPISOD	6	21.8%	--	--	--	--
<b>17+</b>	4,383	96.9%	4,412	97.4%	4,625	96.6%
7805 SLEEP DISTURBANCES	2,178	49.7%	2,483	56.3%	2,320	50.2%
2963 DEPR PSYCH, RECUR EPISOD	216	4.9%	130	2.9%	289	6.2%
2962 DEPR PSYCH, SINGL EPISOD	300	6.8%	201	4.5%	247	5.3%
3000 ANXIETY STATES	295	6.7%	150	3.4%	237	5.1%
3110 DEPRESSIVE DISORDER NEC	230	5.3%	266	6.0%	223	4.8%
2967 BIPOLAR AFFECTIVE NOS	103	2.4%	54	1.2%	130	2.8%
3098 OTHER ADJUST REACTION	78	1.8%	53	1.2%	115	2.5%
3004 NEUROTIC DEPRESSION	104	2.4%	61	1.4%	73	1.6%
2968 MANIC-DEPRESSIVE NEC/NOS	40	0.9%	61	1.4%	55	1.2%
3530 BRACHIAL PLEXUS LESIONS	--	--	--	--	53	1.1%
7291 MYALGIA AND MYOSITIS NOS	23	0.5%	58	1.3%	50	1.1%
3050 ALCOHOL ABUSE	12	0.3%	13	0.3%	45	1.0%
V670 SURGERY FOLLOW-UP	10	0.2%	34	0.8%	44	1.0%
2959 SCHIZOPHRENIA NOS	48	1.1%	7	0.2%	38	0.8%
2965 BIPOLAR AFFECT, DEPRESS	27	0.6%	13	0.3%	36	0.8%
3003 OBSESSIVE-COMPULSIVE DIS	56	1.3%	30	0.7%	32	0.7%
8404 SPRAIN ROTATOR CUFF	10	0.2%	7	0.2%	26	0.6%
2953 PARANOID SCHIZOPHRENIA	25	0.6%	13	0.3%	24	0.5%
V723 GYNECOLOGIC EXAMINATION	19	0.4%	5	0.1%	22	0.5%
3099 ADJUSTMENT REACTION NOS	5	0.1%	6	0.1%	20	0.4%
All Others	605	13.8%	768	17.4%	546	11.8%
<b>UNSPEC.</b>	104	2.3%	111	2.4%	151	3.1%

Source: Verispan Physician Drug and Diagnosis Audit, Extracted 6/08. File: PDDA 2007-256 Ambien BPCA Dx4 by Age2.xls

\*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. --means no data

## **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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