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Subject: One Year Post-Pediatric Exclusivity Post-marketing Adverse Event Review  
Drug Utilization Analysis  
Pediatric Exclusivity Grant Date: March 21, 2006

Drug Name(s): Provigil® (modafinil)

Submission Number: SE5/S-021

Application Type/Number: NDA 20-717

Applicant/sponsor: Cephalon, Inc.

OSE RCM #: 2007-251

**\*\*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 the drug utilization patterns for modafinil, Provigil<sup>®</sup>, two years before and one year following the granting of Pediatric Exclusivity on March 21, 2006, with a primary focus on the use in the pediatric population, ages 0 through 17 years. Modafinil is a wakefulness-promoting agent that is similar in action to sympathomimetic agents such as amphetamine and methylphenidate. Outpatient drug use patterns for modafinil and other selected drug products used for the treatment of ADHD were examined for the three 12-month periods from April 1 2004 through March 31, 2007, using proprietary drug use databases licensed by FDA.

The total number of retail prescriptions dispensed in the selected ADHD market, including clonidine and guanfacine, rose approximately 7% from the 12-month period April 2004 – March 2005 to the 12-month period ending March 2007. Excluding clonidine and guanfacine, methylphenidate and amphetamine/dextroamphetamine products accounted for over 75% of the ADHD market during the post-exclusivity period. Atomoxetine accounted for approximately 8% of the market followed by modafinil with nearly 5% of the market.

Modafinil is primarily used in adult patients. The number of prescriptions and patients receiving a prescription for modafinil in the outpatient retail pharmacy setting increased for the adult (ages 18 and above) and the 6-17 year age groups, and fell for the 0-5 year age group between the pre- and post-exclusivity periods. The relative proportion of patients in each age group remained constant throughout the study period. Adults accounted for greater than 97% of total dispensed prescriptions and patients for modafinil during each year of this analysis, whereas children accounted for less than 3%.

Psychiatry was the most common prescribing specialty for modafinil, and pediatricians accounted for less than 1% of all dispensed prescriptions.

Data from office-based physician practices in the U.S. indicates no recorded use of modafinil within the pediatric population during the post-exclusivity period. However, during the pre-exclusivity period and the year prior, Attention Deficit Disorder was reported among the 6-17 year age group.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

On January 4, 2002, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of that Act requires the review of adverse events associated with the use of a drug in children during the one year following the date on which the drug received marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Committee on the drug utilization patterns and adverse events associated with the use of the drug soon after the one-year anniversary of granting exclusivity. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

### **1.2 REGULATORY HISTORY**

Modafinil is a wakefulness-promoting agent that is similar in action to sympathomimetic agents such as amphetamine and methylphenidate. This similarity to sympathomimetics, however, does not extend to the pharmacologic level, and the precise mechanism of action is as yet unknown for modafinil.

Modafinil or Provigil<sup>®</sup> (trade name) was approved on December 24, 1998, to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy under NDA 20-717. Additional indications for the treatment of obstructive sleep apnea/hypopnea (OSA) syndrome, and shift work sleep disorder were approved January 23, 2004. The Agency issued the first Pediatric Written Request (WR) on June 17, 2004, for studies in pediatric patients with obstructive sleep apnea/hypopnea and narcolepsy. The WR was amended several times over the course of the year and the final WR was issued on August 10, 2005, which removed the requirement for studies in pediatric patients with OSAH.

Cephalon, Inc. also submitted an application for the indication of pediatric attention deficit and hyperactivity disorder (ADHD) under NDA 20-717, SE1/S-019 on December 20, 2004. However, on August 9, 2006, the FDA issued a Not Approvable letter based on the decision from the Pharmacological Drugs Advisory Committee (PDAC) meeting which was held on March 23, 2006, due to safety concerns with severe skin reactions.

A supplemental NDA was submitted under NDA 20-717, SE5/S-021 for the treatment of excessive sleepiness associated with narcolepsy in children and adolescents (ages 6-16 years) on December 21, 2005. Based on those submitted studies, Pediatric Exclusivity was granted for Provigil<sup>®</sup> (modafinil) on March 21, 2006. However, the studies failed to demonstrate efficacy on both primary endpoints and the application was deemed Not Approvable on September 21, 2006. The sponsor, Cephalon, subsequently withdrew the application for pediatric narcolepsy on October 17, 2006. However, S-019 for ADHD is still active.

### **1.3 PRODUCT LABELING**

Currently, there are no approved pediatric indications for modafinil. The Provigil<sup>®</sup> (modafinil) product labeling contains the following information on Indications and Usage, and Pediatric Use sections.

#### **INDICATIONS AND USAGE<sup>1</sup>**

PROVIGIL is indicated to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder.

In OSAHS, PROVIGIL is indicated as an adjunct to standard treatment(s) for the underlying obstruction. If continuous positive airway pressure (CPAP) is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating PROVIGIL. If PROVIGIL is used adjunctively with CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary.

In all cases, careful attention to the diagnosis and treatment of the underlying sleep disorder(s) is of utmost importance. Prescribers should be aware that some patients may have more than one sleep disorder contributing to their excessive sleepiness.

#### **PEDIATRIC USE<sup>1</sup>**

Safety and effectiveness in individuals below 16 years of age have not been established. Leukopenia has been reported in pediatric patients taking PROVIGIL.

## **2 METHODS AND MATERIALS**

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<sup>1</sup> PDR <sup>®</sup> Electronic Library<sup>™</sup>, accessed June 2007.

## 2.1 INTRODUCTION

Using the currently available data resources, this review describes the outpatient drug use patterns for modafinil in the pediatric population as well as in the adult population in the years prior to and subsequent to the granting of pediatric exclusivity on March 21, 2006. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

## 2.2 DETERMINING SETTING OF CARE

IMS Health, IMS National Sales Perspectives™ data (see Appendix) were used to determine the setting in which modafinil is sold. Sales of this product by number of tablets sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for three 12-month periods from April 2004 through March 2007. From these data, it was clear that this product is distributed to outpatient settings of care (chain, independent, food store, and mail order pharmacies) which accounted for over 91% of the modafinil tablets sold in each of the three 1-year periods in this analysis<sup>2</sup>, and the remaining 9% were distributed to inpatient settings of care (data not shown). Mail order pharmacies accounted for approximately 18% of the overall distribution of modafinil.

Because the bulk of drug product sales of modafinil tablets during this time period was into outpatient retail settings, we examined the utilization patterns for modafinil focusing on the outpatient setting only. We also examined selected products used for the treatment of attention deficit hyperactivity disorder (ADHD) since modafinil is used off-label for this indication.

## 2.3 DATA SOURCES USED

Outpatient use and patient demographics were measured with two data sources from Verispan, LLC: Vector One®: National (VONA) and Total Patient Tracker (TPT) (see Appendix). From these two sources, nationally projected estimates of the number of prescriptions dispensed by retail pharmacies and the number of patients<sup>3</sup> who received a dispensed prescription for Provigil® (modafinil) were obtained. Indications for use were obtained from the Verispan, Physician Drug and Diagnosis Audit (see Appendix). Outpatient drug utilization patterns were examined for three twelve-month periods from April 1, 2004 through March 31, 2007.

## 2.4 PRODUCTS INCLUDED

We examined prescriptions dispensed for Provigil® (modafinil) as well as selected products used for the treatment of ADHD based on discussions with the Pediatric and Maternal Health Staff. There are no products approved for the treatment of narcolepsy in the pediatric population. Comparator products were analyzed at the molecule level and those included: methylphenidate, amphetamine/dextroamphetamine, atomoxetine, dexmethylphenidate, d-amphetamine sulfate, methamphetamine and caffeine. Also included in the analysis were guanfacine and clonidine, two anti-hypertensive agents that are also used off-label for the treatment of ADHD.

## 3 RESULTS

### 3.1 DISPENSED PRESCRIPTIONS

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<sup>2</sup> IMS Health, IMS National Sales Perspectives™, Data extracted 5-7-2007, File: 0705moda.dvr

<sup>3</sup> Note that data concerning the total number of patients based on Verispan's Total Patient Tracker may not be summed due to aging of patients during the study period.

### 3.1.1 Modafinil

Total prescriptions dispensed for modafinil increased by 17% between the pre- (April 2005 – March 2006) and post-exclusivity periods (April 2006 – March 2007), from almost 2 million prescriptions to 2.3 million prescriptions, respectively (Table 1).

### 3.1.2 Selected ADHD Market

The total number of retail prescriptions dispensed in the selected ADHD market including clonidine and guanfacine rose approximately 7% from 46.3 million in the 12-month period April 2004 – March 2005 to 49.5 million in the 12-month period ending March 2007 (Table 1, Appendix 2: Figure 1). Excluding clonidine and guanfacine, the market rose approximately 6% from 34.5 million dispensed prescriptions to 36.6 million dispensed prescriptions during the same time period.

Again excluding clonidine and guanfacine, methylphenidate and amphetamine/dextroamphetamine products accounted for over 75% of the ADHD market during the post-exclusivity period, April 2006 – March 2007. Atomoxetine accounted for approximately 8% of the market followed by modafinil with nearly 5% of the market.

The two anti-hypertensive agents, clonidine and guanfacine accounted for 24% and 2%, respectively, for the entire market analyzed. However, it is unknown what percentage of these dispensed prescriptions were specifically for the treatment of ADHD or narcolepsy versus other indications, such as hypertension.

**Table 1. Total number of prescriptions dispensed by retail pharmacies for Modafinil and the selected ADHD market\*, Moving Annual Total March 2004 through March 2007 (mail order pharmacies not included)**

	April 2004 - March 2005		April 2005 - March 2006		April 2006 - March 2007	
	TRxs	Share	TRxs	Share	TRxs	Share
	N	%	N	%	N	%
<b>TOTAL MARKET</b>	46,362,495	100.0%	48,634,062	100.0%	49,532,415	100.0%
<b>methylphenidate hcl</b>	14,054,139	30.3%	14,620,707	30.1%	14,219,947	28.7%
<b>amphetamine/dextroamphetamine</b>	11,700,143	25.2%	12,759,168	26.2%	13,323,666	26.9%
<b>clonidine hcl</b>	10,872,760	23.5%	11,492,222	23.6%	11,993,287	24.2%
<b>atomoxetine hydrochloride</b>	5,600,228	12.1%	4,693,188	9.7%	3,692,037	7.5%
<b>modafinil</b>	1,720,279	3.7%	1,986,208	4.1%	2,320,925	4.7%
<b>dexmethylphenidate</b>	344,392	0.7%	1,042,427	2.1%	1,980,986	4.0%
<b>d-amphetamine sulfate</b>	1,096,619	2.4%	1,065,464	2.2%	1,021,926	2.1%
<b>guanfacine hcl</b>	946,240	2.0%	948,950	2.0%	954,875	1.9%
<b>methamphetamine hcl</b>	21,637	0.0%	19,816	0.0%	19,261	0.0%
<b>caffeine</b>	6,058	0.0%	5,912	0.0%	5,505	0.0%

Verispan, LLC, Vector One® National (VONA), Data extracted 6-2007.

Source File: 2007-251 6-1-07 ADHD market AgSx.qry

\*Selected ADHD market = methylphenidate, amphetamine/dextroamphetamine, atomoxetine, dexmethylphenidate, d-amphetamine sulfate, methamphetamine and caffeine, guanfacine, clonidine.

## 3.2 PATIENT DEMOGRAPHICS

### 3.2.1 Modafinil

Modafinil is primarily used in adult patients. Adults accounted for greater than 97% of total dispensed prescriptions for modafinil during each year of this analysis; whereas, prescriptions dispensed to children aged 0-5 years and 6-17 years accounted for less than 1% and 2% of total dispensed prescriptions, respectively (Table 3).

Prescriptions dispensed to children aged 0-5 years was similar (486 prescriptions and 494 prescriptions, respectively) during the pre- and post-exclusivity periods. However, there was a decline of approximately 36% from the year prior to the pre-exclusivity period (April 2004 – March 2005) to the post-exclusivity period from 766 dispensed prescriptions to 494 dispensed prescriptions. Dispensed prescriptions for the 6-17 year age group increased by approximately 20% during the pre- and post-exclusivity period and the over 18 year population experienced a 17% increase during the same time period.

**Table 3. Total number of prescriptions dispensed by retail pharmacies for modafinil by patient age, Moving Annual Total March 2004 through March 2007 (mail order pharmacies not included)**

	April 2004 - March 2005		April 2005 - March 2006		April 2006 - March 2007	
	TRxs	Share	TRxs	Share	TRxs	Share
	N	%	N	%	N	%
<b>Modafinil</b>	<b>1,720,279</b>	<b>100.0%</b>	<b>1,986,208</b>	<b>100.0%</b>	<b>2,320,925</b>	<b>100.0%</b>
<b>0-5</b>	766	0.0%	486	0.0%	494	0.0%
<b>6-17</b>	35,157	2.0%	41,645	2.1%	50,147	2.2%
<b>18+</b>	1,673,728	97.3%	1,933,465	97.3%	2,264,702	97.6%
<b>UNSPEC.</b>	10,628	0.6%	10,612	0.5%	5,582	0.2%

Verispan, LLC, Vector One® National (VONA), Data extracted 6-2007. Source File: 2007-251 6-1-07 ADHD market AgSx.qry

Similar to dispensed prescriptions, the number of patients receiving a prescription for modafinil in outpatient retail pharmacies increased for the adult (ages 18 and above) and the 6-17 year age groups, and fell slightly for the 0-5 year age group between the 1-year prior to the exclusivity period and the post-exclusivity period (Table 4). The relative proportion of patients in each age group remained constant during the entire study period.

**Table 4. Total number of patients\* receiving a prescription for modafinil in outpatient retail pharmacies by patient age, Moving Annual Total March 2004 through March 2007 (mail order pharmacies not included)**

	April 2004 - March 2005		April 2005 - March 2006		April 2006 - March 2007	
	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share
<b>Grand Total</b>	<b>467,617</b>	<b>100.00%</b>	<b>524,455</b>	<b>100.00%</b>	<b>594,631</b>	<b>100.00%</b>
<b>0 - 5</b>	384	0.08%	258	0.05%	235	0.04%
<b>6-17</b>	11,802	2.52%	14,057	2.68%	15,205	2.56%
<b>18+</b>	452,742	96.82%	507,424	96.75%	577,855	97.18%
<b>Unknown Age</b>	7,119	1.52%	7,046	1.34%	5,255	0.88%

\*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 Total Patient Tracker. File: 2007-251 TPT 6-11-07 modafinil age.xls

### 3.2.2 Selected ADHD Market

Examination of the selected ADHD market, including clonidine and guanfacine, revealed that methylphenidate is the most commonly dispensed prescription for the 0-5 year and 6-17 year age groups, accounting for 28% and 42% of use in these age groups during the post-exclusivity period (Appendix 2: Table 2, Figure 2). Clonidine accounted for nearly 26% of dispensed prescriptions for the 0-5 year age group followed by the amphetamine/dextroamphetamine salts with approximately 23% of dispensed prescriptions. For the 6-17 year age group, methylphenidate was followed by the amphetamine/dextroamphetamine salts, with nearly 29% of dispensed prescriptions, followed by atomoxetine and clonidine at 11% and 8% of the market share, respectively. Guanfacine accounted for approximately 5% and 2% of dispensed prescriptions for the 0-5 year age group and 6-17 year age group, respectively. Modafinil accounted for less than 1% of dispensed prescriptions for both pediatric age groups. Excluding clonidine and guanfacine from the analysis, the combination salt products amphetamine/dextroamphetamine were the most commonly dispensed prescription for the adult population (age 18 years and above) during the post-exclusivity period with nearly 43% of the ADHD market share. This was followed by methylphenidate and modafinil at 29% and 15%, respectively.

### 3.3 PRESCRIBER SPECIALTY

Psychiatry was the most common prescribing specialty for modafinil, accounting for over a quarter of dispensed prescriptions during each year of the study period (Table 5). Neurology was the second most common prescribing specialty during the first 2 years of this study period with approximately 18% and 17% of dispensed prescriptions, respectively, then dropped to third in rank during the post-exclusivity period with 15%, surpassed by the General Practice specialty at 17% of the market share. Prescriptions by pediatricians accounted for less than 1% of all dispensed prescriptions for modafinil during each year of this analysis.

**Table 5: Total number of prescriptions dispensed for modafinil by top 10 prescriber specialties, Moving Annual Total March 2004 through March 2007 (mail order pharmacies not included)**

	April 2004 - March 2005		April 2005 - March 2006		April 2006 - March 2007	
	TRxs	Share	TRxs	Share	TRxs	Share
	N	%	N	%	N	%
<b>modafinil</b>	<b>1,720,325</b>	<b>100.0%</b>	<b>1,986,217</b>	<b>100.0%</b>	<b>2,320,925</b>	<b>100.0%</b>
<b>PSYCH</b>	498,281	29.0%	551,436	27.8%	632,218	27.2%
<b>GP/FM/DO*</b>	216,503	12.6%	292,621	14.7%	385,439	16.6%
<b>NEURO</b>	316,698	18.4%	328,597	16.5%	352,681	15.2%
<b>IM</b>	171,293	10.0%	222,631	11.2%	272,452	11.7%
<b>PUD</b>	88,391	5.1%	104,456	5.3%	126,514	5.5%
<b>UNSPEC</b>	128,552	7.5%	113,138	5.7%	96,311	4.1%
<b>NP</b>	46,343	2.7%	62,402	3.1%	89,660	3.9%
<b>ANES</b>	47,884	2.8%	56,979	2.9%	69,382	3.0%
<b>PM&amp;R</b>	30,171	1.8%	37,281	1.9%	44,361	1.9%
<b>RHEUM</b>	29,680	1.7%	33,367	1.7%	38,792	1.7%
<b>PED (13<sup>th</sup>)</b>	11,500	0.7%	13,421	0.7%	18,784	0.8%
<b>All Others</b>	135,029	7.8%	169,888	8.6%	194,331	8.4%

\*GP/FM/DO – General Practice, Family Medicine, Doctors of Osteopathy  
Verispan, LLC, Vector One® National (VONA), Data extracted 6-2007  
Source File: 2007-251 6-1-07 Modafinil MD.gry

### 3.4 INDICATION FOR USE

According to office-based physician practices in the U.S., no use was recorded for the pediatric population during the post-exclusivity period, April 2006 – March 2007 (Appendix 2: Table 6). However, during the pre-exclusivity period, April 2005 – March 2006, the following diagnoses associated with the use of modafinil in the 6-17 year age group were recorded: “attention deficit disorder” (ICD-9 314.0), “cataplexy and narcolepsy” (ICD-9 347.0), “major depressive disorder, single episode” (ICD-9 296.2), and “urinary tract infection, not otherwise specified” (ICD-9 599.0). For adults (ages 18 years and above), the top three most common diagnoses associated with the use of modafinil during the post-exclusivity period were “malaise and fatigue” (ICD-9 780.7) 16.4%, “sleep disturbances” (ICD-9 780.5) 12.9%, and “cataplexy and narcolepsy” (ICD-9 347.0) 10.4%.

Examining product usage by diagnosis, modafinil was the most commonly mentioned drug product associated with the indication “cataplexy and narcolepsy” in the adult population during the entire study period (data not shown).<sup>4</sup>

## 4 DISCUSSION

Although Provigil<sup>®</sup> (modafinil) is indicated for the treatment of narcolepsy in patients over the age of 17 years, the data show that it is also used off-label for the treatment of ADHD in the pediatric population. The FDA recently considered the pediatric ADHD indication under Supplement S-019, however, this application was deemed Not Approvable based on the decision of the PDAC meeting which was held on March 23, 2005, citing safety concerns with serious skin reactions. The treatment of narcolepsy, however, appears to be exclusive to the adult population.

The two anti-hypertensive agents, clonidine and guanfacine were found to be used in the pediatric population, however, it is unknown what percentage of these dispensed prescriptions were specifically for the treatment of ADHD or narcolepsy versus other indications such as hypertension.

Prescriptions written by General Practice specialty surpassed in volume over Neurologists during the most recent 12-months of the study period, reflecting a growing comfort level in prescribing habits for this product.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that modafinil products are 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.

While we conducted a comprehensive analysis of the use of this product in the outpatient settings, in which the majority of use occurred, a substantial proportion of wholesale sales of modafinil products were to mail order pharmacies, a distribution channel not currently captured by Verispan’s retail prescription audits.

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

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<sup>4</sup> Verispan Physician Drug and Diagnosis Audit , Extracted June 2007. File: DDA 2007-251 Dx narcolepsy ADHD.xls

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 and trending variability. For instance, the diagnoses associated with the use of modafinil in the pediatric age group should be viewed without regard to extent of use.

## **5 CONCLUSIONS**

While no indications are approved for use in the pediatric population, these databases show that modafinil is being used in a small but growing number of pediatric patients. In the most recent 12-months of this analysis, Psychiatry was the most common prescribing specialty for modafinil, followed by General Practice specialty at 17% and Neurologists at 15%. Prescriptions by pediatricians accounted for less than 1% of all dispensed prescriptions for modafinil during each year of this analysis. Examining product usage by diagnosis, modafinil was the most commonly mentioned drug product associated with the indication “cataplexy and narcolepsy” in the adult population during the entire study period. In the pediatric population, however, ADHD (an off-label use) appears to be the most common indication for modafinil.

## **APPENDICES**

### ***APPENDIX 1: 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 billion prescription claims, representing over 160 million unique patients.

Prescriptions are captured from a sample of approximately 54,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent approximately 50% 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, Non-Retail or Combined (NSP)***

The IMS Health, IMS National Sales Perspective 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. 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 National Sales Perspectives™ measures the volume of drug products moving from manufacturer into retail and non-retail settings in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections.

APPENDIX 2: Tables and Figures

Table 2. Total number of prescriptions dispensed for the selected ADHD market\* by patient age (0-5, 6-17, 18+) in outpatient retail pharmacies in the U.S., Moving Annual Total March 2004 through March 2007 (mail order pharmacies not included)

	April 2004 - March 2005		April 2005 - March 2006		April 2006 - March 2007	
	TRxs	Share	TRxs	Share	TRxs	Share
	N	%	N	%	N	%
<b>TOTAL MARKET</b>	<b>46,362,495</b>	<b>100.0%</b>	<b>48,634,062</b>	<b>100.0%</b>	<b>49,532,415</b>	<b>100.0%</b>
<b>0-5</b>	568,539	1.2%	512,649	1.1%	470,331	0.9%
methylphenidate hcl	167,655	29.5%	154,171	30.1%	132,368	28.1%
clonidine hcl	120,975	21.3%	123,398	24.1%	120,655	25.7%
amphetamine/dextroamphetamine	160,462	28.2%	127,732	24.9%	108,522	23.1%
dexmethylphenidate	12,284	2.2%	30,315	5.9%	44,270	9.4%
guanfacine hcl	23,632	4.2%	23,707	4.6%	25,267	5.4%
Atomoxetine hydrochloride	63,800	11.2%	35,555	6.9%	23,159	4.9%
d-amphetamine sulfate	13,295	2.3%	11,755	2.3%	10,382	2.2%
Caffeine	5,639	1.0%	5,480	1.1%	5,171	1.1%
<b>Modafinil</b>	<b>766</b>	<b>0.1%</b>	<b>486</b>	<b>0.1%</b>	<b>494</b>	<b>0.1%</b>
methamphetamine hcl	31	0.0%	50	0.0%	43	0.0%
<b>6-17</b>	23,515,553	50.7%	23,534,326	48.4%	22,765,503	46.0%
methylphenidate hcl	9,812,224	41.7%	10,005,317	42.5%	9,562,546	42.0%
amphetamine/dextroamphetamine	7,046,925	30.0%	6,973,416	29.6%	6,517,565	28.6%
Atomoxetine hydrochloride	4,016,905	17.1%	3,190,946	13.6%	2,467,472	10.8%
clonidine hcl	1,567,188	6.7%	1,723,763	7.3%	1,778,493	7.8%
dexmethylphenidate	267,781	1.1%	847,914	3.6%	1,659,885	7.3%
guanfacine hcl	432,938	1.8%	458,738	1.9%	488,193	2.1%
d-amphetamine sulfate	334,707	1.4%	291,229	1.2%	240,353	1.1%
<b>Modafinil</b>	<b>35,157</b>	<b>0.1%</b>	<b>41,645</b>	<b>0.2%</b>	<b>50,147</b>	<b>0.2%</b>
methamphetamine hcl	1,719	0.0%	1,354	0.0%	816	0.0%
Caffeine	9	0.0%	4	0.0%	33	0.0%
<b>18+</b>	21,645,824	46.7%	23,939,140	49.2%	25,971,064	52.4%
clonidine hcl	9,015,769	41.7%	9,484,966	39.6%	10,020,027	38.6%
amphetamine/dextroamphetamine	4,347,261	20.1%	5,494,897	23.0%	6,611,028	25.5%
methylphenidate hcl	3,901,813	18.0%	4,280,160	17.9%	4,433,607	17.1%
<b>Modafinil</b>	<b>1,673,728</b>	<b>7.7%</b>	<b>1,933,465</b>	<b>8.1%</b>	<b>2,264,702</b>	<b>8.7%</b>
Atomoxetine hydrochloride	1,421,434	6.6%	1,380,883	5.8%	1,166,810	4.5%
d-amphetamine sulfate	737,302	3.4%	751,985	3.1%	765,875	2.9%
guanfacine hcl	473,048	2.2%	448,874	1.9%	431,799	1.7%
dexmethylphenidate	55,628	0.3%	145,537	0.6%	258,864	1.0%
methamphetamine hcl	19,602	0.1%	18,140	0.1%	18,131	0.1%
Caffeine	239	0.0%	233	0.0%	221	0.0%
<b>UNSPEC.</b>	632,579	1.4%	647,947	1.3%	325,517	0.7%

Verispan, LLC, Vector One® National (VONA), Data extracted 6-2007.

Source File: 2007-251 6-8-07 ADHD market AgSx molecule.qry

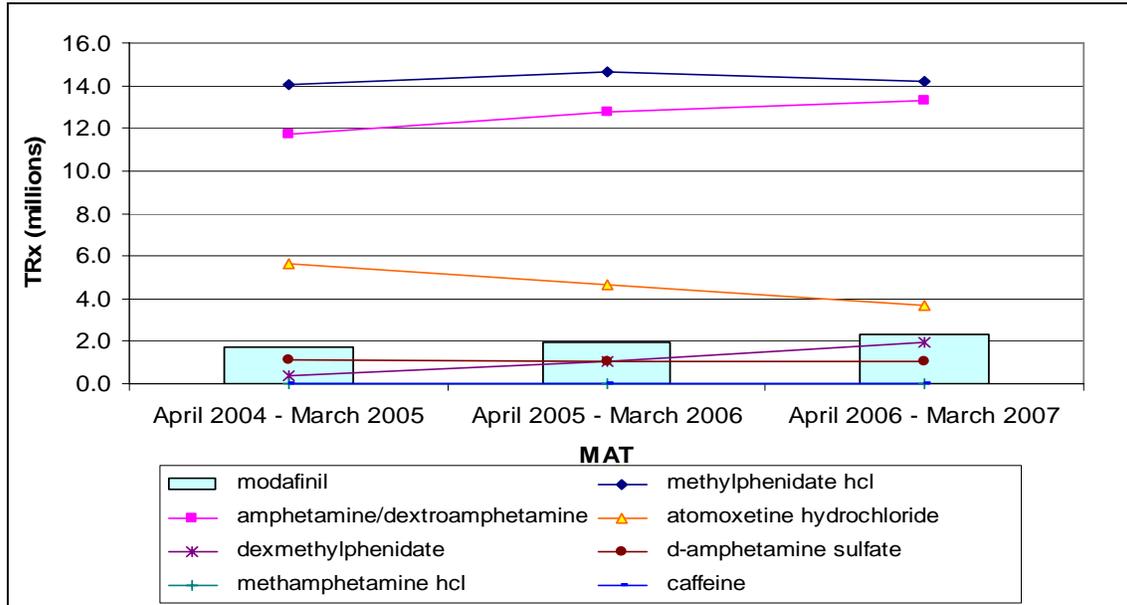
\*Selected ADHD market = methylphenidate, amphetamine/dextroamphetamine, atomoxetine, dexmethylphenidate, d-amphetamine sulfate, methamphetamine, caffeine, guanfacine, and clonidine.

**Table 6. Diagnoses associated with the use of modafinil as reported by U.S. office-based physician practices, Moving Annual Total March 2004 through March 2007**

	April 2004 - March 2005		April 2005 - March 2006		April 2006 - March 2007	
	Uses (000)	Share %	Uses (000)	Share %	Uses (000)	Share %
<b>modafinil</b>	873	100.0%	800	100.0%	1,019	100.0%
<b>6-17</b>	7	0.8%	31	3.8%	--	--
3470 CATAPLEXY AND NARCOLEPSY	--	--	6	21.1%	--	--
2962 DEPR PSYCH, SINGL EPISOD	--	--	6	18.0%	--	--
5990 URIN TRACT INFECTION NOS	--	--	3	11.3%	--	--
3140 ATTENTION DEFICIT DIS	7	100.0%	15	49.5%	--	--
<b>18+</b>	840	96.2%	749	93.6%	997	97.9%
7807 MALAISE & FATIGUE	82	9.8%	45	6.0%	164	16.4%
7805 SLEEP DISTURBANCES	85	10.1%	61	8.1%	128	12.9%
3470 CATAPLEXY AND NARCOLEPSY	72	8.6%	48	6.4%	103	10.4%
2962 DEPR PSYCH, SINGL EPISOD	82	9.8%	69	9.2%	97	9.7%
3400 MULTIPLE SCLEROSIS	116	13.8%	132	17.7%	82	8.2%
3110 DEPRESSIVE DISORDER NEC	61	7.2%	74	9.9%	68	6.8%
3140 ATTENTION DEFICIT DIS	11	1.3%	46	6.1%	35	3.5%
2967 BIPOLAR AFFECTIVE NOS	29	3.5%	22	3.0%	32	3.2%
2968 MANIC-DEPRESSIVE NEC/NOS	6	0.7%	6	0.9%	32	3.2%
3098 OTHER ADJUST REACTION	--	--	12	1.6%	31	3.1%
2963 DEPR PSYCH, RECUR EPISOD	69	8.2%	34	4.5%	22	2.2%
7800 ALTER OF CONSCIOUSNESS	--	--	--	--	20	2.0%
4349 CEREBR ARTERY OCCLUS NOS	--	--	--	--	19	1.9%
3272 ORGANIC SLEEP APNEA	3	0.3%	2	0.3%	16	1.6%
V078 PROPHYLACTIC MEASURE NEC	--	--	--	--	15	1.5%
2959 SCHIZOPHRENIA NOS	--	--	--	--	14	1.4%
V728 EXAMINATION NEC	--	--	--	--	12	1.2%
3004 NEUROTIC DEPRESSION	35	4.1%	18	2.4%	12	1.2%
3320 PARALYSIS AGITANS	13	1.6%	9	1.2%	10	1.0%
<b>All Others</b>	177	21.1%	171	22.8%	86	8.6%
<b>UNSPEC.</b>	26	2.9%	21	2.6%	21	2.1%

Source: Verispan Physician Drug and Diagnosis Audit , Extracted June 2007. File: PDDA 2007-251 modafinil AgDx.qry

**Figure 1: Total number of prescriptions dispensed for the selected ADHD market\* by patient age (0-5, 6-17, 18+) in outpatient retail pharmacies in the U.S., Moving Annual Total March 2004 through March 2007 (mail order pharmacies not included)**

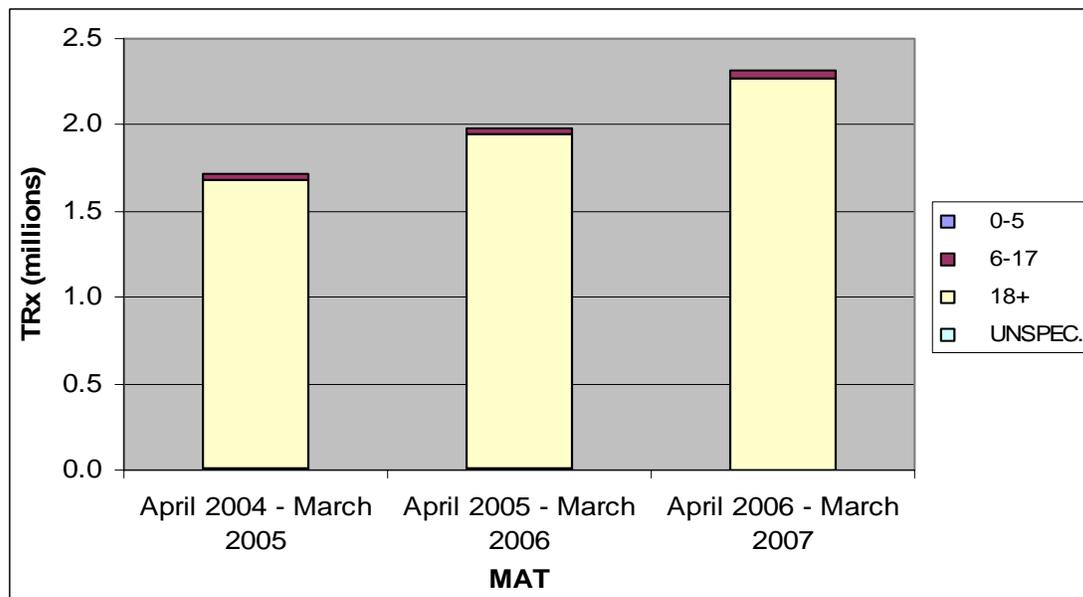


Verispan, LLC, Vector One® National (VONA), Data extracted 6-2007.

Source File: 2007-251 6-8-07 ADHD market AgSx molecule.qry

\*Selected ADHD market = methylphenidate, amphetamine/dextroamphetamine, atomoxetine, dexmethylphenidate, d-amphetamine sulfate, methamphetamine and caffeine.

**Figure 2: Total number of prescriptions dispensed for modafinil by patient age (0-5, 6-17, 18+) in outpatient retail pharmacies in the U.S., Moving Annual Total March 2004 through March 2007 (mail order pharmacies not included)**



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/s/

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Laura Governale  
6/20/2007 02:10:17 PM  
DRUG SAFETY OFFICE REVIEWER

Please sign for Solomon.

Toni Piazza Hepp  
6/20/2007 04:26:12 PM  
DRUG SAFETY OFFICE REVIEWER  
for Solomon Iyasu