MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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SUBJECT: Adderall XR® (mixed amphetamine salts, NDA 21-303)
One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review:
Drug Utilization Data
Pediatric Exclusivity Grant Date: October 28, 2004

****This document contains proprietary data which cannot be shared outside of FDA without clearance from the data vendor obtained through the Office of Drug Safety.****

EXECUTIVE SUMMARY

This consult examines the drug utilization patterns for Adderall XR® in the pediatric population (ages 0-16 years), with primary focus on patterns of use one year before and one year following the granting of Pediatric Exclusivity for Adderall XR® on October 28, 2004. Adderall XR® is a combination product, containing a mixture of 4 salts: amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate.

Proprietary drug use databases licensed by FDA were used to conduct this analysis. The IMS Health, National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution. Since the majority of use for this product occurs in the outpatient setting,

we examined the utilization patterns for Adderall XR®, focusing on the outpatient setting. Outpatient use was measured by IMS Health's audit, the National Disease and Therapeutic Index™ (NDTI™), along with audits from Verispan, LLC, Vector One®: National (VONA) and Total Patient Tracker (TPT). Outpatient drug utilization patterns were examined for the 3-year period from November 1, 2002 through October 31, 2005.

We examined prescriptions dispensed for Adderall XR®, as well as for other single ingredient or combination products that are used to treat Attention Deficit/Hyperactivity Disorder (ADHD) to compare Adderall XR® use with the use of other products in this therapeutic class.
Seven (7) single ingredient drug substances were included in this analysis: atomoxetine, dexmethylphenidate, dextroamphetamine, methamphetamine, methylphenidate, modafinil, and pemoline. The combination agents were amphetamine- and dextroamphetamine-containing products.

During the one-year pre-exclusivity period (November 2003 to October 2004), 32.7 million prescriptions were dispensed by retail pharmacies in the U.S. for these eight (8) substances used to treat ADHD. During the post-exclusivity period (November 2004 to October 2005), over 36 million prescriptions were dispensed. The two (2) most frequently dispensed drug substances were methylphenidate products and amphetamine/ dextroamphetamine combination products.

For Adderall XR®, the number of dispensed prescriptions increased from approximately 7.3 million prescriptions in the pre-exclusivity period (November 2003 to October 2004) to approximately 8.6 million prescriptions in the post-exclusivity period (November 2004 to October 2005).

Psychiatrists and pediatricians were the most frequent prescribers of Adderall XR®. In the post-exclusivity period (November 2004 to October 2005), psychiatrists prescribed over 2.7 million (31.8%) of the Adderall XR® prescriptions dispensed in the retail setting. Pediatricians were the second most frequent prescribers, with over 2.5 million dispensed prescriptions (29.7%) for the same period.

Retail prescriptions for Adderall XR® dispensed to the pediatric population (ages 0 – 16 years) increased by 8%, from approximately 5.1 million prescriptions dispensed during the pre-exclusivity period (November 2003 to October 2004) to approximately 5.5 million prescriptions dispensed during the post-exclusivity period (November 2004 to October 2005). Adderall XR® prescriptions dispensed to the pediatric population aged 0-16 years old accounted for 63.8% of the total dispensed Adderall XR® prescriptions during the post-exclusivity period.

The projected number of unique pediatric patients (aged 0 to 12 years) who received a dispensed prescription for Adderall XR® remained relatively constant over the three-year period, at approximately 800,000 patients annually. The number of adults ages 18 and older receiving prescriptions for Adderall XR® nearly doubled over the three-year period. The number of children between the ages of 13 and 17 years who received a dispensed Adderall XR® prescription increased by 11.4% between the pre- and post-exclusivity periods.

The indication for use most frequently linked to Adderall XR® in the pediatric population (0-16 years) during November 2002 through October 2005 was Attention Deficit Disorder (ICD-9 code 314.0), accounting for over 97% of all Adderall XR® mentions during office-based physicians visits.

INTRODUCTION

On January 3, 2001, 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 reporting 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 on a quarterly basis. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

Adderall XR® (NDA 21-303) is a once daily, extended-release amphetamine-containing product. This product consists of 4 different salts: amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate. Adderall XR™ was approved on October 11, 2001, for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The safety and efficacy of Adderall XR® have not been established in children less than six years of age. Adderall XR® extended-release capsules are available in 5 mg, 10 mg, 15 mg, 20mg, 25mg, and 30 mg dosage strengths. The product is administered orally once daily in the morning.

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Adderall XR® (NDA 21-303/S-009) on October 28, 2004.

This review describes outpatient drug use patterns for Adderall XR® and 7 other drug substances that are used to treat ADHD in adults and children. The period of observation was three (3) years, from the year prior to and including the year after the granting of pediatric exclusivity (i.e., November 1, 2002 through October 31, 2005). Proprietary drug use databases licensed by the FDA were used to conduct this analysis.

METHODS

IMS Health, National Sales Perspectives™ data (see Appendix) were used to determine the setting in which Adderall XR® is sold. Sales of this product by number of extended-release capsules sold from the manufacturer to retail and non-retail channels of distribution were analyzed for three 12-month periods from November 2002 through October 2005 (Table 1). From these data, it was clear that this product is sold primarily to retail settings. Approximately 95% of all capsules were sold to outpatient pharmacies.

Table 1. Total Number of Adderall XR® Extended-Release Capsules (in thousands) Sold to U.S. Distribution Channels During November 1, 2002 through October 31, 2005

	November 1, 2002 – October 31, 2003		November 1, 2003 – October 31, 2004		November 1, 2004 – October 31, 2005	
	N (000)	***%***	**N (000)**	***%***	**N (000)**	***%***
Total	**248720**	***100.0***	**297994**	***100.0***	**339972**	***100***
Retail*	236142	*94.9*	282115	*94.7*	321299	*94.5*
Non-Retail**	12578	*5.1*	15879	*5.3*	18673	*5.5*

*** Retail includes chain, independent, mail order, long term care, and food store pharmacies.**
****Non-Retail includes non-federal hospitals, federal facilities, clinics, HMOs, home health care, prisons, universities, and other.**
Source: IMS Health, IMS National Sales Perspectives™ Combined, MAT November 2002 to October 2005. Data extracted December 20, 2005. (Original file: 0512AXRc.dvr & 0512AXRc.xls).

Because the bulk of drug product sales of Adderall XR® for this time period were to retail settings, we examined the utilization patterns for Adderall XR® and seven (7) other drug substances used to treat ADHD by focusing on the outpatient setting only. The 7 single ingredient drug substances included in this analysis were the following: atomoxetine, dexmethylphenidate, dextroamphetamine, methamphetamine, methylphenidate, modafinil, and pemoline. The combination agents were amphetamine- and dextroamphetamine-containing products.

Outpatient use was measured by IMS Health's National Disease and Therapeutic Index™ (NDTI™), along with audits from Verispan, LLC, Vector One®: National (VONA) and Total Patient Tracker (TPT) (see Appendix). Estimates of the number of drug mentions by office-based physicians, the number of dispensed prescriptions by retail pharmacies and the number of patients[1] who received a dispensed Adderall XR® retail prescription were obtained. Outpatient drug utilization patterns were examined for the 3-year period from November 1, 2002 through October 31, 2005.

RESULTS

I. Dispensed Prescriptions

There was an overall increase in the volume of prescriptions dispensed for the eight (8) drug substances used to treat ADHD during the period of observation (Table 2).

During the pre-exclusivity period (November 2003 to October 2004), 32.7 million prescriptions were dispensed by retail pharmacies in the U.S. for these eight (8) substances used to treat ADHD. During the post-exclusivity period (November 2004 to October 2005), over 36 million prescriptions were dispensed. This represented a 10.4% increase from the pre-exclusivity period to the post-exclusivity period. Methylphenidate products had the highest market share among these eight (8) substances (approximately 41%) by the end of October 2005.

The total number of prescriptions for combination amphetamine/dextroamphetamine (AMP/DEX) products (i.e., Adderall®, Adderall XR®, and others) increased from approximately 10.8 million prescriptions in the pre-exclusivity period (November 2003 to October 2004) to approximately 12.5 million prescriptions in the post-exclusivity period (November 2004 to October 2005). This

[1] Note that data concerning the total number of patients based on Verispan's Total Patient Tracker are only available at this time in the age groupings 0 – 12 years and 13 – 17 years. These numbers are not additive due to aging of patients during the study period.

represented a 15.1% increase from the pre-exclusivity period to the post-exclusivity period. The group of AMP/DEX products represented approximately 35% of the prescription volume for the eight (8) ADHD drugs during two (2) of the three (3) years of observation.

Table 2: Total Number of Prescriptions Dispensed (in Thousands) by Retail Pharmacies for Adderall XR® and Other Agents Used for ADHD during November 1, 2002 through October 31, 2005

	November 1, 2002 - October 31, 2003		November 1, 2003 - October 31, 2004		November 1, 2004 - October 31, 2005	
	TRxs (000)	%	TRxs (000)	%	TRxs (000)	%
TOTAL MARKET	**28,000**	***100.0%***	**32,696**	***100.0%***	**36,096**	***100.0%***
AMPHETAMINE and DEXTROAMPHETAMINE (COMBINATIONS)	**9,869**	***35.2%***	**10,848**	***33.2%***	**12,483**	***34.6%***
Adderall XR	6,144	*62.3%*	7,306	*67.3%*	8,598	*68.9%*
Amphetamine Salt Cmb	2,710	*27.5%*	2,966	*27.3%*	3,461	*27.7%*
Adderall	1,015	*10.3%*	576	*5.3%*	424	*3.4%*
ATOMOXETINE HCL	**2,469**	***8.8%***	**5,396**	***16.5%***	**5,215**	***14.4%***
Strattera	2,469	*100.0%*	5,396	*100.0%*	5,215	*100.0%*
DEXTROAMPHETAMINE	**1,246**	***4.4%***	**1,110**	***3.4%***	**1,081**	***3.0%***
Dextroamphetamine Sf	721	*57.9%*	765	*69.0%*	821	*75.9%*
Dexedrine Spansules	258	*20.7%*	163	*14.7%*	122	*11.3%*
Dexedrine	123	*9.8%*	94	*8.5%*	81	*7.5%*
Dextrostat	113	*9.1%*	84	*7.6%*	57	*5.2%*
Dextrostat 10mg	30	*2.4%*	4	*0.3%*	1	*0.1%*
DAS	0	*0.0%*	0	*0.0%*	0	*0.0%*
DEXMETHYLPHENIDATE	**260**	***0.9%***	**306**	***0.9%***	**567**	***1.6%***
Focalin	260	*100.0%*	306	*100.0%*	379	*66.8%*
Focalin XR	--	--	--	--	188	*33.2%*
METHAMPHETAMINE	**20**	***0.1%***	**21**	***0.1%***	**21**	***0.1%***
Desoxyn	20	*100.0%*	19	*87.0%*	16	*76.8%*
Methamphetamine HCl	--	--	3	*13.0%*	5	*23.2%*
METHYLPHENIDATE HCL	**12,757**	***45.6%***	**13,344**	***40.8%***	**14,715**	***40.8%***
Concerta	6,818	*53.4%*	7,434	*55.7%*	8,199	*55.7%*
Methylphenidate	2,040	*16.0%*	1,897	*14.2%*	1,967	*13.4%*
Ritalin-LA	649	*5.1%*	1,072	*8.0%*	1,414	*9.6%*
Methylin	1,086	*8.5%*	1,025	*7.7%*	1,141	*7.8%*
Metadate CD	662	*5.2%*	752	*5.6%*	940	*6.4%*
Methylin ER	357	*2.8%*	335	*2.5%*	355	*2.4%*
Methylphenidate SR	429	*3.4%*	336	*2.5%*	321	*2.2%*
Ritalin	468	*3.7%*	346	*2.6%*	283	*1.9%*
Metadate ER	150	*1.2%*	84	*0.6%*	49	*0.3%*
Ritalin-SR	99	*0.8%*	62	*0.5%*	45	*0.3%*
MODAFENIL	**1,211**	***4.3%***	**1,533**	***4.7%***	**1,893**	***5.2%***
Provigil	1,211	*100.0%*	1,533	*100.0%*	1,893	*100.0%*
PEMOLINE	**168**	***0.6%***	**138**	***0.4%***	**121**	***0.3%***
Pemoline	89	*53.0%*	76	*55.1%*	64	*52.6%*
Pemadd	37	*22.0%*	35	*25.7%*	38	*31.0%*
Cylert	42	*25.0%*	27	*19.2%*	20	*16.4%*

Source: Verispan, LLC, November 2002 to October 2005. Data extracted 12/21/2005.
(File D040761 ADDXR MOL PROD TRx.qry)

The number of Adderall XR® prescriptions increased from approximately 7.3 million prescriptions in the pre-exclusivity period to approximately 8.6 million prescriptions in the post-exclusivity period. This represented an increase of 18%. During the post-exclusivity period, Adderall XR® accounted for approximately 69% of the prescription volume for all AMP/DEX products.

The percent share of generic products for AMP/DEX drug combination was relatively stable at approximately 27% during the 3 years of observation. Generic equivalents of several strengths of the Adderall® regular-release tablet were first approved by FDA in February 2002 and were marketed soon after. Thus, Adderall® brand's share of the AMP/DEX prescription volume decreased from 10.3% in the first of the three observed periods (November 2002 to October 2003) to 3.4% in the post-exclusivity period (November 2004 to October 2005).

II. Prescriber Specialty

Psychiatrists were the most frequent prescribers of Adderall XR® in two (2) of the three (3) periods of observation (Table 3). In the post-exclusivity period (November 2004 to October 2005), psychiatrists prescribed over 2.7 million (31.8%) of the Adderall XR® prescriptions dispensed in the retail setting. Pediatricians were the second most frequent prescribers, with over 2.5 million dispensed prescriptions (29.7%) for the same period. General Practice/Family Medicine/ Osteopathic Medicine prescribed approximately 1.3 million dispensed prescriptions in the same period (14.9%). Together, these three (3) specialty groups accounted for 76.4% of the dispensed prescriptions for Adderall XR® in the post-exclusivity period.

Table 3: Total Number of Retail Prescriptions Dispensed (in thousands) for Adderall XR® by Prescriber Specialty, During November 2002 – October 2005, Verispan LLC: VONA.

Prescriber Specialty	November 1, 2002 – October 31, 2003		November 1, 2003 – October 31, 2004		November 1, 2004 – October 31, 2005	
	TRxs (000)	%	TRxs (000)	%	TRxs (000)	%
ALL PRESCRIBERS	**6,144**	***100.0%***	**7,306**	***100.0%***	**8,598**	***100.0%***
1. Psychiatry	2,105	*34.3%*	2,309	*31.6%*	2,731	*31.8%*
2. Pediatrics	2,109	*34.3%*	2,276	*31.2%*	2,552	*29.7%*
3. General Practice, Family Medicine, or Osteopathic Medicine	691	*11.3%*	915	*12.5%*	1,279	*14.9%*
4. Unspecified	531	*8.7%*	936	*12.8%*	946	*11.0%*
5. Nurse Practitioner	147	*2.4%*	206	*2.8%*	275	*3.2%*
6. Neurology	253	*4.1%*	256	*3.5%*	268	*3.1%*
7. Internal Medicine	110	*1.8%*	162	*2.2%*	244	*2.8%*
8. Other	55	*0.9%*	59	*0.8%*	64	*0.7%*
9. Hospital	33	*0.5%*	48	*0.7%*	55	*0.6%*
10. Physician Assistant	19	*0.3%*	34	*0.5%*	51	*0.6%*
All Others	89	*1.4%*	105	*1.4%*	133	*1.5%*

Source: Verispan, LLC, November 2002 to October 2005. Data extracted 12/21/2005.
(File: D040761 ADDXR PROD MD TRx.qry)

III. Patient Demographics

Retail prescriptions for Adderall XR® dispensed to the pediatric population (ages 0 – 16 years) increased by 8%, from approximately 5.1 million prescriptions dispensed during the pre-exclusivity

period (November 2003 to October 2004) to approximately 5.5 million prescriptions dispensed during the post-exclusivity period (November 2004 to October 2005) (Table 4). Adderall XR® prescriptions dispensed to the pediatric population aged 0-16 years old accounted for 63.8% of the total dispensed Adderall XR® prescriptions during the post-exclusivity period.

Table 4. Outpatient Prescriptions Dispensed for Adderall XR® by Age Groups*
During November 2002 to October 2005 (Source: Verispan, LLC: National (VONA)

	November 1, 2002 – October 31, 2003		November 1, 2003 – October 31, 2004		November 1, 2004 – October 31, 2005	
	TRxs (000)	***%***	**TRxs (000)**	***%***	**TRxs (000)**	***%***
Adderall XR® TOTAL	**6,144**	***100.0%***	**7,306**	***100.0%***	**8,598**	***100.0%***
Age 0-16 years	4,599	*74.9%*	5,080	*69.5%*	5,483	*63.8%*
Age 17+ years	1,522	*24.8%*	2,148	*29.4%*	2,988	*34.8%*
Age Unspecified	23	*0.4%*	78	*1.1%*	126	*1.5%*

***Subtotals may not sum exactly, due to rounding error.**
Source: Verispan, LLC, November 2002 to October 2005. Data extracted 1/12/2005.
(File: D040761 ADDXR MOL PROD DEMOS TRx.qry)

The projected number of patients of all ages per year who received a dispensed retail prescription for Adderall XR® during this three (3) year period increased from approximately 1.7 million patients in the pre-exclusivity period to 2 million patients in the post-exclusivity period (Table 5). This represented an increase of approximately 18%.

Table 5. Projected Number of Patients Receiving Dispensed Adderall XR® Prescriptions by Age Group*
During November 2002 through October 2005. (Source: Verispan, LLC: Total Patient Tracker)

Age Groups	November 1, 2002 – October 31, 2003		November 1, 2003 – October 31, 2004		November 1, 2004 – October 31, 2005	
	Projected Patient Count	**Total Patient Share**	**Projected Patient Count**	**Total Patient Share**	**Projected Patient Count**	**Total Patient Share**
Grand Total	**1,631,104**	***100.00%***	**1,732,514**	***100.00%***	**1,984,498**	***100.00%***
00 to 12 years	813,671	*49.88%*	786,869	*45.42%*	797,228	*40.17%*
13 to 17 years	496,324	*30.43%*	512,410	*29.58%*	571,023	*28.77%*
18 to 25 years	161,133	*9.88%*	207,326	*11.97%*	284,089	*14.32%*
26 to 30 years	29,601	*1.81%*	41,062	*2.37%*	62,458	*3.15%*
31 to 35 years	32,835	*2.01%*	42,362	*2.45%*	59,261	*2.99%*
36 to 40 years	36,278	*2.22%*	46,360	*2.68%*	63,232	*3.19%*
41 to 45 years	42,233	*2.59%*	51,083	*2.95%*	68,606	*3.46%*
46 to 50 years	39,601	*2.43%*	48,770	*2.81%*	64,922	*3.27%*
51 to 55 years	27,805	*1.70%*	34,411	*1.99%*	47,941	*2.42%*
56 to 60 years	14,527	*0.89%*	18,509	*1.07%*	25,630	*1.29%*
61 to 65 years	5,152	*0.32%*	7,123	*0.41%*	10,245	*0.52%*
66 to 70 years	2,065	*0.13%*	2,429	*0.14%*	3,375	*0.17%*
71 to 75 years	1,047	*0.06%*	1,144	*0.07%*	1,537	*0.08%*
76 to 80 years	735	*0.05%*	838	*0.05%*	779	*0.04%*
81+ years	842	*0.05%*	786	*0.05%*	911	*0.05%*

***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, LLC; Vector One®: Total Patient Tracker (TPT). November 2002 to October 2005. Data Extracted 1-6-2005.
(File: Adderall XR BPCA Age Group Report)

The projected number of pediatric patients aged 0 to 12 years who received a dispensed prescription for Adderall XR® remained relatively constant (fluctuating only 1 – 3%) over the three-year period, at about 800,000 patients annually. Patients aged 0 to 12 years decreased from 50% of all patients dispensed Adderall XR® to just over 40% during the three-year study period.

The projected number of pediatric patients aged 13 to 17 years who received a dispensed prescription for Adderall XR® increased by 11.4% between the pre- and post-exclusivity periods. This was preceded by a more modest 3% increase between the first two periods (November 2002 to October 2003 and November 2003 to October 2004). Patients aged 13 to 17 years remained about 30% of all patients dispensed Adderall XR® throughout the 3-year study period.

IV. Indication for Use

According to IMS Health, NDTI™, the diagnosis, or indication, most frequently linked to Adderall XR® use in the pediatric population (0-16 years) during November 2002 through October 2005 was Attention Deficit Disorder (ICD-9 code 314.0), accounting for over 97% of all Adderall XR® mentions during office-based physicians visits (Table 6).

During the post-exclusivity period (November 2004 through October 2005), nearly three-fourths of the mentions (73.3%) for adults aged 17 and older were for Unspecified Disturbance of Conduct (ICD-9 code 312.9). During the same period Attention Deficit Disorder (ICD-9 code 314.0) accounted for 20.1% of all mentions in this age group.

Over the three-year period, the percentage of visits for adults aged 17 years and older in which Adderall XR® was mentioned increased from 18% of all Adderall XR®-associated visits to 29% of such visits. Consequently, the percentage of visits among patients aged 0 to 16 years declined.

Table 6: Indications Associated with Mentions of Adderall XR® (in thousands) During Office-Based Physician Visits by Patient Age Groups During November 1, 2002 through October 31, 2005

	November 1, 2002-October 31, 2003 Drug Uses (000)	%	November 1, 2003-October 31, 2004 Drug Uses (000)	%	November 1, 2004-October 31, 2005 Drug Uses (000)	%
ADDERALL XR Total Uses	**4,380**	***100.0***	**4,682**	***100.0***	**5,666**	***100.0***
Patient Age 0 to 16 yrs	**3,380**	***77.2***	**3,392**	***72.5***	**3,844**	***67.8***
314.0 Attention deficit disorder	3,278	*97.0*	3,300	*97.3*	3,738	*97.3*
Total Others (17)	102	*3.0*	92	*2.7*	105	*2.7*
Patient Age 17 +	**808**	***18.4***	**1,103**	***23.6***	**1,634**	***28.8***
312.9 Unspecified disturbance of conduct	495	*61.4*	736	*66.7*	1,198	*73.3*
314.0 Attention deficit disorder	229	*28.3*	300	*27.2*	329	*20.1*
Total Others (23)	84	*10.4*	67	*6.1*	106	*6.5*
Patient Age Unspecified	**192**	***4.4***	**187**	***4.0***	**188**	***3.3***
314.0 Attention deficit disorder	184	*95.6*	177	*95.1*	178	*94.9*
Total Others (2)	8	*4.4*	9	*4.9*	10	*5.1*

Source: IMS Health, National Disease and Therapeutic Index™, Years 2002 – 2005. Extracted December 2005.
Original file: 0512AXR_Dx4.dvf

DISCUSSION

Based on the databases employed for this analysis, the use of most of these eight (8) drug substances to treat ADHD has been increasing throughout the three years of observation (November

2002 to October 2005). The two (2) most frequently dispensed drug substances were methylphenidate products and amphetamine/ dextroamphetamine combination products. During the one-year post-exclusivity period (November 2004 to October 2005), methylphenidate products made up approximately 41% and amphetamine/dextroamphetamine products made up approximately 35% of these dispensed prescriptions.

The volume of dispensed prescriptions for Adderall XR® (a combination of 4 amphetamine/dextroamphetamine salts) in both adult and pediatric populations has been increasing during this time period. The majority of the prescriptions were dispensed to children aged 0 to 16 years. In the post-exclusivity period, children received 63.8% of all dispensed prescriptions for Adderall XR® (i.e., 5.5 million of the 8.6 million total dispensed prescriptions, approximately).

The indication for use most frequently mentioned for Adderall XR® in children (ages 0-16 years) was Attention Deficit Disorder (ICD-9 code 314.0), accounting for over 97% of all Adderall XR® IMS Health, NDTI™ mentions during office-based physician visits. Among adults 17 years and older, nearly three-fourths of the mentions (73.3%) during the post-exclusivity period were for Unspecified Disturbance of Conduct (ICD-9 code 312.9).

The projected number of pediatric patients aged 0 to 12 years who received a dispensed prescription for Adderall XR® remained relatively constant (fluctuating only 1 – 3%) over the three-year period, at about 800,000 patients annually. The projected number of pediatric patients aged 13 to 17 years who received a dispensed prescription for Adderall XR® increased by 11.4% between the pre- and post-exclusivity periods.

Prescriber specialties were relatively similar for Adderall XR® prescriptions dispensed in retail pharmacy settings from November 2002 through October 2005. Psychiatrists were the most frequent prescribers of Adderall XR® in 2 of the 3 years observed, although the proportion of Pediatrician prescribers was very similar. Combined with a third group, General Practice/Family Medicine/Osteopathic Medicine, these specialties accounted for 76.4% of the prescriptions dispensed in the one-year post-exclusivity period (November 2004 to October 2005).

Findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated that the use of Adderall XR® was primarily in the outpatient settings based on the IMS Health, National Sales Perspectives™, Combined. These data 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, 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, use outside of the retail pharmacy settings was not captured in our analysis.

Throughout the analysis, we used the FDA's cut-off age definition of a pediatric patient (age 0-16 years), except when we used the Verispan Total Patient Tracker tool for providing estimates of the total number of unique patients receiving prescriptions for Adderall XR® through retail pharmacies and mass merchandisers. Age bands available through this data resource with an age break at age 17 years are fixed and cannot yet be customized to reflect the FDA's definition. In addition, using this

tool does not allow summary of age bands in each time period, due to patient aging in the course of the study period.

IMS Health's, National Disease and Therapeutic Index (NDTI)™ 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.

CONCLUSION

In summary, for most of the ADHD drugs in this analysis, the volume of bulk drug sales and the number of retail prescriptions dispensed increased over the three-year period of observation (November 2002 through October 2005). The number of patients receiving a dispensed prescription for at least one of these products also increased.

For Adderall XR®, the number of dispensed prescriptions increased from approximately 7.3 million prescriptions in the pre-exclusivity period (November 2003 to October 2004) to approximately 8.6 million prescriptions in the post-exclusivity period (November 2004 to October 2005). Adderall XR® prescriptions dispensed to children 0-16 years of age accounted for 63.8% of the total dispensed Adderall XR® prescriptions during the post-exclusivity period.

The projected number of unique pediatric patients aged 0 to 12 years who received a dispensed prescription for Adderall XR® remained relatively constant over the three-year period, at approximately 800,000 patients annually. The number of children between the ages of 13 and 17 years who received a dispensed Adderall XR® prescription increased by 11.4% between the pre- and post-exclusivity periods.

The indication for use most frequently linked to Adderall XR® in the children aged 0-16 years was Attention Deficit Disorder (ICD-9 code 314.0).

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APPENDIX

IMS HEALTH, IMS NATIONAL SALES PERSPECTIVES™

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

Data for this analysis include prescriptions dispensed for Adderall XR® and other agents used to treat ADHD from November 1, 2002 – October 31, 2005, inclusive.

VERISPAN, LLC

Vector One®: National (VONA)

Verispan's VONA is a nationally projected database which measures the 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, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 1.8 billion prescription claims, representing over 150 million unique patients.

The number of dispensed prescriptions is obtained from a sample of virtually all retail pharmacies throughout the U.S and represents approximately half of the 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. Mail order prescriptions are not included in the sample at this time.

Data for this analysis include prescriptions dispensed for Adderall XR® and other agents used to treat ADHD from November 1, 2002 – October 31, 2005, inclusive.

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.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers

and their data systems, physician offices and hospitals. Vector One® receives over 1.8 billion prescription claims per year, which represents over 150 million patients tracked across time.

Data for this analysis include prescriptions dispensed for Adderall XR® and other agents used to treat ADHD from November 1, 2002 – October 31, 2005, inclusive.

IMS HEALTH, NATIONAL DISEASE AND THERAPEUTIC INDEX™ (NDTI™)

The National Disease and Therapeutic Index™ (NDTI™) is an ongoing survey designed and conducted by IMS Health to provide descriptive information on the patterns and treatment of disease encountered in office-based practice in the continental U.S. The data are collected from a panel of roughly 2,000 – 3,000 office-based physicians who complete and submit a survey of their practice patterns to IMS Health for two consecutive days per quarter. These data may include profiles and trends of diagnoses, patients, drug products mentioned and treatment patterns. The data are projected nationally to reflect national prescribing patterns.

NDTI™ uses the term drug uses for 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.

For this analysis, we examined annual mentions of Adderall XR® during office-based physician visits during the time period November 1, 2002 – October 31, 2005, inclusive.

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