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Office of Surveillance and Epidemiology**

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Subject: Risperdal<sup>®</sup> (risperidone) tablets BPCA Drug Use Review

Drug Name(s): Risperdal<sup>®</sup> (risperidone)

Application Type/Number: NDA 20-272

Applicant/sponsor: Janssen Pharmaceuticals

OSE RCM #: 2007-508

**\*\*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 Risperdal<sup>®</sup> (risperidone), 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 February 28, 2007. Since around 67% of Risperdal<sup>®</sup> bottles and packets of pills were sold to U.S. retail settings and approximately 33% were sold to non-retail [mainly long-term care (~67%)] 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 Risperdal<sup>®</sup> during the three 12-month periods from March 1, 2005 through February 29, 2008.

For each of the three 12-month periods from March 1, 2005 - February 29, 2008:

- Oral Risperdal<sup>®</sup> represented approximately 26.5% of the total projected number of select oral atypical antipsychotic dispensed prescriptions.
- Oral Risperdal<sup>®</sup> prescriptions in the pediatric population (ages 0-17 years) accounted for approximately 25% of total dispensed oral Zyprexa<sup>®</sup> prescriptions.
- Around 25% of total projected patients who filled a prescription for oral Risperdal<sup>®</sup>, were aged 0 to 17 years.
- Psychiatry was the top prescribing specialty for risperidone oral dosage forms.
- The top diagnosis code associated with the use of oral Risperdal<sup>®</sup> for patients aged 0 to 12 years and 13 to 17 years were “Infantile Autism” (ICD-9 299.0) and “Attention Deficit Disorder” (ICD-9 314.0).

## 1 INTRODUCTION

Using the currently available proprietary drug use databases licensed by the Agency, this review describes outpatient drug use patterns for oral Risperdal<sup>®</sup> (risperidone) 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 February 29, 2007.

## 2 METHODS AND MATERIALS

IMS Health, IMS National Sales Perspectives<sup>TM</sup> data (*see Appendix 2*) were used to determine the setting in which oral Risperdal<sup>®</sup> 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 March 1, 2005 - February 29, 2008 (*data not provided*).<sup>1</sup> 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 Risperdal<sup>®</sup> sales (67%) and approximately 33% were sold to non-retail [mainly long-term care (~67%)] settings. Thus, the examination of oral Risperdal<sup>®</sup> 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 Risperdal<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 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 Risperdal<sup>®</sup>, and the number of drug mentions by office-based physicians, were obtained from March 1, 2005 - February 29, 2008, inclusive. For comparative purposes, other select atypical antipsychotics (oral, solid, liquid dosage forms only) were also examined; those included: quetiapine fumarate, olanzapine, aripiprazole, ziprasidone, clozapine, and paliperidone.

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<sup>1</sup> IMS Health, IMS Nationals Sales Perspectives<sup>TM</sup>, Data extracted 7-16-2008, Source file: 0805ris.DVR

### **3 RESULTS**

During the three 12-month periods from March 1, 2005 - February 29, 2008, dispensed prescriptions for oral Risperdal<sup>®</sup> represented approximately 26.5% of the projected number of select atypical antipsychotic prescriptions dispensed in the United States. The projected number of oral Risperdal<sup>®</sup> dispensed prescriptions increased by 2% from the pre-exclusivity period (March 1, 2006 - February 28, 2007) to the post-exclusivity period (March 1, 2007 - February 29, 2008) (*Table 1*).

During the three 12-month periods from March 1, 2005 - February 29, 2008, dispensed prescriptions for Risperdal<sup>®</sup> in the pediatric population (ages 0-17 years) accounted for approximately 25% of the total projected number of dispensed prescriptions for oral Risperdal<sup>®</sup>. Of the prescriptions dispensed to patients aged 0 to 17 years, around 60% were dispensed to patients aged 12 years or younger and 40% dispensed to patients ages 13 to 17 years (*Table 2*). Of the patients who filled a prescription for oral Risperdal<sup>®</sup> in the outpatient retail pharmacy setting, 25% 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 were similar to the proportion of dispensed prescriptions for the same age groups (*Table 3*).

During the three 12-month periods from March 1, 2005 - February 29, 2008, Psychiatry was the top prescribing specialty for risperidone oral dosage forms accounting for approximately 52% of all dispensed prescriptions for these products. Among the Psychiatry specialty, around 21.5% of oral Risperdal<sup>®</sup> prescriptions were prescribed by Child Psychiatry (*Table 4*).

According to office-based physician practices in the U.S., “Infantile Autism” (ICD-9 299.0) and “Attention Deficit Disorder” (ICD-9 314.0) were the top diagnosis codes associated with the use of oral solid and liquid dosage forms of risperidone for patients aged 0 to 12 years and 13 to 17 years. Adults aged 18 years and older accounted for the majority (86%) of office-based physician visits reportedly associated with the use of oral Risperdal<sup>®</sup> 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 Risperdal<sup>®</sup> is distributed primarily in outpatient retail settings based on the IMS Health, IMS National Sales Perspectives<sup>™</sup>. Within the non-retail distribution channels (32%), the long-term care 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 Risperdal<sup>®</sup> (risperidone) oral formulations in the pediatric and adult populations has been increasing over the three 12-month study periods examined.

### **CONCURRENCE**

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**APPENDICES**

**APPENDIX 1: Tables**

**Table 1. Projected Number of Select Atypical Antipsychotic Prescriptions (In Thousands) Dispensed from U.S Retail Pharmacies, MAT March 1, 2005 – February 29, 2008**

	MAT/FEB/2006		MAT/FEB/2007		MAT/FEB/2008	
	Retail TRxs (000)	Share %	Retail TRxs (000)	Share %	Retail TRxs (000)	Share %
<b>TOTAL MARKET</b>	<b>26,914</b>	<b>100.0%</b>	<b>28,629</b>	<b>100.0%</b>	<b>31,214</b>	<b>100.0%</b>
quetiapine fumarate	8,625	32.0%	9,790	34.2%	11,219	35.9%
<b>risperidone</b>	<b>7,464</b>	<b>27.7%</b>	<b>7,679</b>	<b>26.8%</b>	<b>7,838</b>	<b>25.1%</b>
aripiprazole	3,186	11.8%	3,771	13.2%	4,342	13.9%
olanzapine	4,615	17.1%	4,227	14.8%	4,033	12.9%
ziprasidone hcl	1,674	6.2%	2,021	7.1%	2,245	7.2%
clozapine	1,349	5.0%	1,133	4.0%	1,134	3.6%
paliperidone	--	--	7	0.0%	403	1.3%

Verispan, LLC: Vector One<sup>®</sup>: National (VONA) Data extracted 7-16-2008. Source File: 2007-508 VONA 7-16-08 risperidone comparators BPCA.qry  
 For Oral Solid, Liquid Dosage forms Only

**Table 2. Projected Number of Risperidone Prescriptions (In Thousands) Dispensed from U.S Retail Pharmacies stratified by age, MAT March 1, 2005 – February 29, 2008**

	MAT/FEB/2006		MAT/FEB/2007		MAT/FEB/2008	
	Retail TRxs (000)	Share %	Retail TRxs (000)	Share %	Retail TRxs (000)	Share %
<b>risperidone</b>	<b>7,464</b>	<b>100.0%</b>	<b>7,679</b>	<b>100.0%</b>	<b>7,838</b>	<b>100.0%</b>
<b>0-17</b>	<b>1,835</b>	<b>24.6%</b>	<b>1,812</b>	<b>23.6%</b>	<b>1,996</b>	<b>25.5%</b>
<b>0-12</b>	<b>1,090</b>	<b>59.4%</b>	<b>1,082</b>	<b>59.7%</b>	<b>1,215</b>	<b>60.9%</b>
<b>13-17</b>	<b>745</b>	<b>40.6%</b>	<b>730</b>	<b>40.3%</b>	<b>781</b>	<b>39.1%</b>
<b>18+</b>	<b>5,410</b>	<b>72.5%</b>	<b>5,773</b>	<b>75.2%</b>	<b>5,765</b>	<b>73.6%</b>
<b>UNSPEC.</b>	<b>219</b>	<b>2.9%</b>	<b>93</b>	<b>1.2%</b>	<b>77</b>	<b>1.0%</b>

Verispan, LLC: Vector One<sup>®</sup>: National (VONA) Data extracted 7-16-2008. Source File: 2007-508 VONA 7-16-08 risperidone age BPCA.qry  
 For Oral Solid, Liquid Dosage forms Only

**Table 3. Projected Number of Patients who filled a Risperidone<sup>™</sup> Prescription at a U.S. Retail Pharmacy, MAT March 1, 2005 – February 29, 2008**

	MAT Ending 02-06		MAT Ending 02-07		MAT Ending 02-08	
	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share
<b>Risperidone</b>	1,578,459	100.0%	1,523,704	100.0%	1,480,031	100.0%
<b>0-17</b>	382,157	24.2%	366,172	24.0%	389,048	26.3%
<b>0 - 12</b>	229,219	60.0%	220,906	60.3%	239,912	61.7%
<b>13 - 17</b>	167,529	43.8%	159,378	43.5%	163,910	42.1%
<b>18 - 85</b>	1,149,141	72.8%	1,142,300	75.0%	1,081,156	73.0%
<b>Unknown</b>	113,448	7.2%	62,085	4.1%	53,673	3.6%

*Verispan, Total Patient Tracker, data extracted 7-16-08. Source File: 2007-508 TPT 7-16-08 risperidone age BPCA.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 Risperidone Prescriptions Dispensed (*In Thousands*) from U.S. Retail Pharmacies by Prescriber Specialty (Top 10), MAT March 1, 2005 – February 29, 2008

	MAT/FEB/2006		MAT/FEB/2007		MAT/FEB/2008	
	Retail TRxs (000)	Share %	Retail TRxs (000)	Share %	Retail TRxs (000)	Share %
<b>Risperidone</b>	<b>7,464</b>	<b>100.0%</b>	<b>7,679</b>	<b>100.0%</b>	<b>7,838</b>	<b>100.0%</b>
<b>PSYCHIATRY</b>	<b>3,665</b>	<b>49.1%</b>	<b>4,145</b>	<b>54.0%</b>	<b>4,187</b>	<b>53.4%</b>
PSYCHIATRY	2,796	76.3%	3,225	77.8%	3,229	77.1%
CHILD PSYCHIATRY	821	22.4%	860	20.8%	892	21.3%
PSYCHIATRY, GERIATRIC	48	1.3%	59	1.4%	66	1.6%
<b>GP/FM/DO<sup>†</sup></b>	<b>770</b>	<b>10.3%</b>	<b>896</b>	<b>11.7%</b>	<b>886</b>	<b>11.3%</b>
<b>UNSPEC</b>	<b>1,385</b>	<b>18.6%</b>	<b>771</b>	<b>10.0%</b>	<b>787</b>	<b>10.0%</b>
<b>INTERNAL MEDICINE</b>	<b>519</b>	<b>7.0%</b>	<b>562</b>	<b>7.3%</b>	<b>552</b>	<b>7.0%</b>
<b>NURSE PRACTITIONER</b>	<b>332</b>	<b>4.4%</b>	<b>427</b>	<b>5.6%</b>	<b>491</b>	<b>6.3%</b>
<b>PEDIATRICS</b>	<b>211</b>	<b>2.8%</b>	<b>233</b>	<b>3.0%</b>	<b>279</b>	<b>3.6%</b>
PEDIATRICS	193	91.4%	212	91.1%	254	91.1%
PEDIATRICS, INTERNAL MEDICIN	12	5.7%	15	6.5%	17	6.2%
PEDIATRIC, OTHER	2	0.9%	1	0.5%	2	0.8%
PEDIATRIC HEMATOLOGY	1	0.7%	2	0.7%	2	0.7%
PEDIATRIC CARDIOLOGY	1	0.4%	1	0.4%	1	0.4%
PEDIATRIC ENDOCRINOLOGY	1	0.3%	1	0.2%	1	0.2%
PEDIATRIC NEPHROLOGY	0	0.2%	0	0.2%	1	0.2%
PEDIATRIC ALLERGY	0	0.2%	0	0.2%	0	0.2%
PEDIATRIC SURGERY	0	0.1%	0	0.1%	0	0.2%
PEDIATRIC PULMONOLOGY	0	0.1%	0	0.1%	0	0.1%
PEDIATRIC EMERGENCY MED.	0	0.1%	0	0.0%	0	0.0%
PEDIATRIC OTOLARYNGOLOGY	0	0.0%	0	0.0%	0	0.0%
PEDIATRIC RADIOLOGY	0	0.0%	0	0.0%	0	0.0%
<b>NEURO</b>	<b>167</b>	<b>2.2%</b>	<b>177</b>	<b>2.3%</b>	<b>184</b>	<b>2.3%</b>
NEUROLOGY	99	59.4%	106	59.7%	107	57.9%
CHILD NEUROLOGY	68	40.6%	71	40.3%	77	42.1%
<b>HOSPITAL</b>	<b>131</b>	<b>1.8%</b>	<b>148</b>	<b>1.9%</b>	<b>132</b>	<b>1.7%</b>
PA	45	0.6%	61	0.8%	77	1.0%
OTHER	48	0.6%	55	0.7%	65	0.8%
<b>All Others</b>	<b>190</b>	<b>2.4%</b>	<b>205</b>	<b>2.4%</b>	<b>195</b>	<b>2.2%</b>

Source: Verispan, LLC: Vector One®: National (VONA) Data extracted 7-16-2008. File: 2007-508 VONA 6-16-08 risperidone specialty BPCA.qry

<sup>†</sup>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 Risperidone, MAT March 1, 2005 – February 29, 2008**

	MAT/FEB/2006		MAT/FEB/2007		MAT/FEB/2008	
	Uses (000)	Share %	Uses (000)	Share %	Uses (000)	Share %
<b>Risperidone</b>	<b>4,847</b>	<b>100.0%</b>	<b>3,792</b>	<b>100.0%</b>	<b>3,638</b>	<b>100.0%</b>
<b>0-12</b>	<b>240</b>	<b>5.0%</b>	<b>266</b>	<b>7.0%</b>	<b>262</b>	<b>7.2%</b>
2990 INFANTILE AUTISM	7	2.7%	21	8.0%	54	20.5%
3140 ATTENTION DEFICIT DIS	32	13.4%	42	15.7%	44	16.8%
2967 BIPOLAR AFFECTIVE NOS	47	19.5%	48	17.9%	37	14.2%
2969 AFFECT PSYCHOSES NEC/NOS	37	15.5%	14	5.1%	22	8.4%
3138 OTH EMOTIONAL DIS CHILD	20	8.4%	29	11.1%	18	6.9%
All others	99	40.3%	111	42.3%	86	32.9%
<b>13-17</b>	<b>173</b>	<b>3.6%</b>	<b>116</b>	<b>3.1%</b>	<b>127</b>	<b>3.5%</b>
2990 INFANTILE AUTISM	--	--	6	5.0%	23	18.2%
3140 ATTENTION DEFICIT DIS	35	20.4%	16	13.6%	15	12.2%
2969 AFFECT PSYCHOSES NEC/NOS	34	19.6%	9	7.8%	13	10.1%
2967 BIPOLAR AFFECTIVE NOS	18	10.2%	17	15.0%	13	10.1%
2966 BIPOLAR AFFECTIVE, MIXED	--	--	--	--	9	7.0%
All others	87	49.9%	67	58.7%	57	42.5%
<b>18+</b>	<b>4,243</b>	<b>87.5%</b>	<b>3,280</b>	<b>86.5%</b>	<b>3,065</b>	<b>84.2%</b>
2953 PARANOID SCHIZOPHRENIA	589	13.9%	479	14.6%	548	17.9%
2967 BIPOLAR AFFECTIVE NOS	433	10.2%	334	10.2%	466	15.2%
2957 SCHIZOAFFECTIVE TYPE	498	11.7%	470	14.3%	343	11.2%
2959 SCHIZOPHRENIA NOS	324	7.6%	250	7.6%	332	10.8%
2989 PSYCHOSIS NOS	222	5.2%	218	6.6%	284	9.3%
All others	2,176	51.0%	1,525	46.4%	1,090	35.7%
<b>UNSPEC.</b>	<b>191</b>	<b>3.9%</b>	<b>129</b>	<b>3.4%</b>	<b>185</b>	<b>5.1%</b>
2959 SCHIZOPHRENIA NOS	51	26.8%	47	36.5%	123	66.8%
2967 BIPOLAR AFFECTIVE NOS	52	27.1%	30	23.2%	13	6.8%
3140 ATTENTION DEFICIT DIS	5	2.5%	5	3.7%	11	6.1%
2962 DEPR PSYCH, SINGL EPISOD	17	9.0%	7	5.3%	11	5.8%
3098 OTHER ADJUST REACTION	5	2.5%	--	--	6	3.3%
All others	61	32.3%	40	31.4%	21	11.3%

Verispan, LLC. Physician Drug and Diagnosis Audit, Extracted 7-16-08; File: 2007-508 PDDA 7-16-08 risperidone diagnosis BPCA.xls

-- 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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