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FINAL

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CONTENTS

EXECUTIVE SUMMARY	1
1 BACKGROUND	1
1.1 Introduction (Product Formulations and Indications)	3
1.2 Pediatric labeling.....	4
2 METHODS AND MATERIALS.....	6
2.1 Introduction.....	6
2.2 AERS Selection of Cases.....	6
3 AERS RESULTS for Risperidone.....	7
3.1 Count of Reports: All sources- US and Foreign from marketing approval (Table 1)....	7
3.2 Count of Reports: All Sources- US and Foreign from Pediatric Exclusivity (Table 2). 8	
3.3 Case Characteristics From One-Year Review (Table 3).....	8
4 DISCUSSION/Summary Of Cases.....	9
4.1 Total Reports with an Outcome of Death (n = 31).....	9
4.1.1 Nervous System (10):.....	9
4.1.2 Cardiac System (9):.....	10
4.1.3 Miscellaneous (8):.....	10
4.2 Non-Fatal Serious Adverse Event Reports (n=116).....	10
4.2.1 Metabolic Effects (15)	11
4.2.2 Gynecomastia/Hyperprolactinemia (6).....	11
4.2.3 Extrapyramidal Adverse Events Including Tardive Dyskinesia (14).....	12
5 CONCLUSION.....	12
6 RECOMMENDATIONS.....	12
APPENDICES.....	13
Appendix 1 Narrative summaries of the cases of death associated with risperidone from market approval December 29, 1993 until March 28, 2008.....	13
Appendix 2.....	17
Table 1- Count of Metabolic Syndrome, Weight Increased, Hyperglycemia, and Hyperlipidemia Reports: All Sources Combined- US and Foreign from marketing approval up until March 28, 2008	17
Table 3 -Count of Hyperprolactinemia Reports: All Sources- US and Foreign from marketing approval up until March 28, 2008	18
Table 4- Count of Extrapyramidal Disorder including Tardive Dyskinesia Reports: All Sources- US and Foreign from marketing approval up until March 28, 2008	18

EXECUTIVE SUMMARY

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of risperidone in pediatric patients. Up to the "data lock" date of March 28, 2008, AERS contained 20,352 reports for risperidone (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 7.5 % of the total (1535/20352).

DPV was asked to focus on the 1-year period following the approval of pediatric exclusivity, February 28, 2007. We used an AERS data lock date of March 28, 2008, to allow time for reports received up to February 28, 2008 to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 1791 reports (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review. Pediatric reports represent approximately 8% of the total number of cases (150/1791). The projected number of risperidone prescriptions dispensed from U.S. retail pharmacies in 2007 for the pediatric population (0-17 years) was 1,812,000 (23.6%) and the total patient share of risperidone was 366,172 (24%).¹ In addition, as requested, we will provide crude numbers² (see appendix 2) of reports submitted to the AERS database (marketing approval) of the adverse events of metabolic syndrome, weight gain, hyperglycemia, hyperlipidemia, hyperprolactinemia, and extrapyramidal effects including tardive dyskinesia in both the adult and pediatric populations.

A review of the 116 pediatric post-marketing cases submitted during the period of pediatric exclusivity, and a review of the 31 pediatric cases with an outcome of death submitted since the beginning of marketing did not reveal any new safety concerns. The review revealed adverse events that are qualitatively similar to those currently found in the product label and described in the adult population. Among the associated adverse events in these pediatric cases, expected (labeled) metabolic effects (hyperglycemia, weight gain, etc) were described in the majority of the pediatric cases followed closely by extrapyramidal effects including tardive dyskinesia, which are also labeled.

Based on the potential long-term consequences of weight gain, hyperglycemia and metabolic effects DPV recommends:

- The current risperidone label appears to address all of the issues discussed in this review. We recommend that no further labeling changes regarding the pediatric population are necessary at this time.
- Continue routine monitoring of the AERS database for adverse events with the use of risperidone in pediatric patients.

1 BACKGROUND

Risperidone, an atypical antipsychotic agent (marketed as Risperdal by Janssen) received FDA approval on December 29, 1993. Pediatric population specific approvals occurred on October 6, 2006 for use in irritability associated with autistic disorder in children and adolescents aged 5-16

¹ Borders-Hemphill V. Risperdal (risperidone) tablets BPCA Drug Use Review. FDA Postmarketing Review. July 29, 2008.

² Duplicated reports have not been reconciled and causality has not been assessed for crude number reports.

years; and on August 22, 2007 for the treatment of schizophrenia in adolescents aged 13-17 years, and for the treatment of bipolar mania in children and adolescents aged 10-17 years. Pediatric exclusivity was granted on February 28, 2007 based on three, randomized, double-blind, placebo-controlled, multi-center, efficacy studies in adolescents 10-17 years old. The first two studies³ evaluated the safety and efficacy of risperidone in patients with schizophrenia and the third study⁴ evaluated the safety and efficacy of risperidone in two dose ranges in patients with bipolar I disorder. The data from the studies demonstrated that risperidone is effective in treating pediatric schizophrenia and bipolar I disorder.

In reference to the safety evaluation for schizophrenia, the data was derived from three studies; two were the same efficacy studies mentioned above, in addition to a long-term, open-label extension study in 284 patients⁵. In bipolar disorder, the safety data was derived from the study mentioned above, as well as the same long-term, open-label extension study in schizophrenia patients in addition to a pharmacokinetic study⁶. Overall, the results of the short-term treatment of risperidone in pediatric patients appeared to be “reasonably safe” without the occurrence of unexpected adverse events. Based on this information, DPP determined that the sponsor submitted sufficient data to support the use of risperidone in pediatric patients to treat schizophrenia and bipolar I disorder, and therefore issued an approvable action pending the negotiation of labeling.⁷

Previous OSE Post-Marketing Reviews:

- August 20, 1999. An updated review on serious hematologic events associated with risperidone use. The review concluded that a potential increased risk might exist for the development of neutropenia and agranulocytosis in patients with a history of leukopenia or neutropenia and concomitant use with antipsychotics.⁸
- December 17, 1999. A review (all ages) of the atypical antipsychotics clozapine, olanzapine, risperidone, and quetiapine and the event of **new-onset diabetes mellitus**. Although not specifically focusing on children, the review mentioned cases of diabetes mellitus with hyperosmolality associated with olanzapine. Based on the review, the recommendation to increase the prominence of diabetes mellitus in the labeling for clozapine, risperidone, olanzapine, and quetiapine was made.⁹
- June 25, 2003. A literature review concerning the issue of **diabetes mellitus/hyperglycemia** associated with the atypical antipsychotic drugs. The findings of the review suggested that a risk management program be put in place for these drugs.¹⁰
- October 4, 2005. A class review of galactorrhea with atypical antipsychotic drugs in pediatric patients. The review supported further analysis of hyperprolactinemia and galactorrhea with atypical antipsychotics in order to update risperidone labeling to reflect the increased

³ RIS-SCH-302- n=160, 6 weeks, RIS-USA-231- n=279, 8 weeks

⁴ RIS-BIM-301- n=169, 3 weeks

⁵ RIS-USA-234- n=284, 6 months

⁶ RIS-USA-160

⁷ Mathis M. Recommendation of approvable action for risperidone (Risperdal) for the treatment of schizophrenia and bipolar I disorder in pediatric patients (response to PWR). June 18, 2007.

⁸ Bennett K. Update on Serious hematologic events. FDA Postmarketing Safety Review. August 20, 1999.

⁹ Wysowski D. New onset Diabetes Mellitus. FDA Postmarketing Safety Review. December 17, 1999.

¹⁰ Mosholder A. Literature review concerning the issue of diabetes mellitus/hyperglycemia associated with the atypical antipsychotic drugs. FDA Postmarketing Safety Review. June 25, 2003.

numbers of reports of hyperprolactinemia and galactorrhea associated with risperidone relative to other atypical antipsychotic drugs.¹¹

- October 4, 2005. A class review of pituitary tumors with atypical antipsychotic drugs. The review recommended further investigation, perhaps including reanalysis of the risperidone NDA, in order to update the risperidone label to include increased hyperprolactinemia compared to other atypical antipsychotic agents.¹²
- May 21, 2007. A post-marketing review of pediatric adverse events with an emphasis on brain edema, and death of cardiac etiology in association with risperidone. The reviewer recommended that a pediatric cardiologist be consulted to review the case series to determine if specific labeling was needed for the pediatric population.¹³
- January 25, 2008. A class review of selected antipsychotics and the occurrence of agranulocytosis. The review recommended the addition of agranulocytosis to the Precautions section of the olanzapine and risperidone label as well as elevating agranulocytosis to the Precautions section for chlorpromazine and haloperidol.¹⁴
- April 29, 2008. A class review of post-marketing cases coded with death in children 16 years old and younger. In general, for the cases reviewed, the causes of death were all cause death with the most cases reporting cardiac disorders/sudden death. The review recommended continued surveillance of the AERS database for deaths associated with pediatric patients treated with atypical antipsychotics with a particular focus on cardiac and diabetes related cases.¹⁵

1.1 INTRODUCTION (PRODUCT FORMULATIONS AND INDICATIONS)

Risperidone is available in four formulations.

- Orally disintegrating tablet- FDA approved April 2, 2003 and is available as 0.5, 1, 2, 3, and 4 mg tablets
- Intramuscular Injection- FDA approved October 29, 2003 and is available as 12.5, 25, 37.5, and 50 mg injections
- Oral tablet- FDA approved December 29, 1993 and is available as 0.25, 0.5, 1, 2, 3, and 4 mg tablets
- Oral solution- FDA approved June 10, 1996 and is available in a 1mg/mL concentration

Risperidone is indicated for:

- The treatment of schizophrenia in adults and adolescents aged 13-17 years

¹¹ Phelan K. A class review of pituitary tumors with atypical antipsychotic drugs. FDA Postmarketing Safety Review. October 4, 2005.

¹² Phelan K. A class review of pituitary tumors with atypical antipsychotic drugs. FDA Postmarketing Safety Review. October 4, 2005.

¹³ Elekwachi O. Pediatric adverse events with emphasis on brain edema and death of cardiac etiology. FDA Postmarketing Safety Review. May 21, 2007.

¹⁴ Diak I. A mixed class review of antipsychotics and the occurrence of agranulocytosis. FDA Postmarketing Safety Review. January 25, 2008.

¹⁵ Diak I. A class review of postmarketing cases coded with death in children 16 years old and younger. FDA Postmarketing Safety Review. April 29, 2008.

- The short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults and alone in children and adolescents aged 10-17 years as monotherapy or in combination with lithium or valproate
- The treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years

1.2 PEDIATRIC LABELING¹⁶

The labeling for pediatric use includes the following:

WARNINGS/PRECAUTIONS

Suicide

The possibility of a suicide attempt is inherent in patients with schizophrenia and bipolar mania, including children and adolescent patients, and close supervision of high-risk patients should accompany drug therapy.

Discontinuations due to Adverse Reactions

Schizophrenia - Pediatrics

Approximately 7% (7/106), of RISPERDAL®-treated patients discontinued treatment due to an adverse event in a double-blind, placebo-controlled trial, compared with 4% (2/54) placebo-treated patients. The adverse reactions associated with discontinuation for at least one RISPERDAL®-treated patient were somnolence (2%), dizziness (2%), anorexia (1%), anxiety (1%), ataxia (1%), hypotension (1%), and palpitation (1%).

Bipolar Mania - Pediatrics

In a double-blind, placebo-controlled trial 12% (13/111) of RISPERDAL®-treated patients discontinued due to an adverse event, compared with 7% (4/58) of placebo treated patients. The adverse reactions associated with discontinuation in more than one RISPERDAL®-treated pediatric patient were somnolence (5%), nausea (3%), abdominal pain (2%), and vomiting (2%).

Autistic Disorder - Pediatrics

In the two 8-week, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder (n = 156), one RISPERDAL®-treated patient discontinued due to an adverse reaction (Parkinsonism), and one placebo-treated patient discontinued due to an adverse event.

Use in Specific Populations- Pediatric Use

The efficacy and safety of RISPERDAL® in the treatment of schizophrenia were demonstrated in 417 adolescents, aged 13 – 17 years, in two short-term (6 and 8 weeks, respectively) double-blind controlled trials. Additional safety and efficacy information was also assessed in one long-term (6-month) open-label extension study in 284 of these adolescent patients with schizophrenia.

Safety and effectiveness of RISPERDAL® in children less than 13 years of age with schizophrenia have not been established.

The efficacy and safety of RISPERDAL® in the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in 169 children and adolescent patients, aged 10 – 17 years, were demonstrated in one double-blind, placebo-controlled, 3-week trial.

Safety and effectiveness of RISPERDAL® in children less than 10 years of age with bipolar disorder have not been established.

¹⁶ Risperdal Product Label, February 2008, Janssen Pharmaceuticals. USA; <http://www.risperdal.com/risperdal/prescribing.html>.

The efficacy and safety of RISPERDAL® in the treatment of irritability associated with autistic disorder were established in two 8-week, double-blind, placebo-controlled trials in 156 children and adolescent patients, aged 5 to 16 years. Additional safety information was also assessed in a long-term study in patients with autistic disorder, or in short- and long-term studies in more than 1200 pediatric patients with psychiatric disorders other than autistic disorder, schizophrenia, or bipolar mania who were of similar age and weight, and who received similar dosages of RISPERDAL® as patients treated for irritability associated with autistic disorder.

The safety and effectiveness of RISPERDAL® in pediatric patients less than 5 years of age with autistic disorder have not been established.

Tardive Dyskinesia

In clinical trials in 1885 children and adolescents treated with RISPERDAL®, 2 (0.1%) patients were reported to have tardive dyskinesia, which resolved on discontinuation of RISPERDAL® treatment.

Weight Gain

In a long-term, open-label extension study in adolescent patients with schizophrenia, weight increase was reported as a treatment-emergent adverse event in 14% of patients.

In 103 adolescent patients with schizophrenia, a mean increase of 9.0 kg was observed after 8 months of RISPERDAL® treatment. The majority of that increase was observed within the first 6 months. The average percentiles at baseline and 8 months, respectively, were 56 and 72 for weight, 55 and 58 for height, and 51 and 71 for body mass index.

In long-term, open-label trials (studies in patients with autistic disorder or other psychiatric disorders), a mean increase of 7.5 kg after 12 months of RISPERDAL® treatment was observed, which was higher than the expected normal weight gain (approximately 3 to 3.5 kg per year adjusted for age, based on Centers for Disease Control and Prevention normative data). The majority of that increase occurred within the first 6 months of exposure to RISPERDAL®. The average percentiles at baseline and 12 months, respectively, were 49 and 60 for weight, 48 and 53 for height, and 50 and 62 for body mass index.

In one 3-week, placebo-controlled trial in children and adolescent patients with acute manic or mixed episodes of bipolar I disorder, increases in body weight were higher in the RISPERDAL® groups than the placebo group, but not dose related (1.90 kg in the RISPERDAL® 0.5-2.5 mg group, 1.44 kg in the RISPERDAL® 3-6 mg group, and 0.65 kg in the placebo group). A similar trend was observed in the mean change from baseline in body mass index.

When treating pediatric patients with RISPERDAL® for any indication, weight gain should be assessed against that expected with normal growth.

Hyperprolactinemia, Growth, and Sexual Maturation

RISPERDAL® has been shown to elevate prolactin levels in children and adolescents as well as in adults [see Warnings and Precautions (5.6)]. In double-blind, placebo-controlled studies of up to 8 weeks duration in children and adolescents (aged 5 to 17 years) with autistic disorder or psychiatric disorders other than autistic disorder, schizophrenia, or bipolar mania, 49% of patients who received RISPERDAL® had elevated prolactin levels compared to 2% of patients who received placebo. Similarly, in placebo-controlled trials in children and adolescents (aged 10 to 17 years) with bipolar disorder, or adolescents (aged 13 to 17 years) with schizophrenia, 82–87% of patients who received RISPERDAL® had elevated levels of prolactin compared to 3–7% of patients on placebo. Increases were dose-dependent and generally greater in females than in males across indications.

In clinical trials in 1885 children and adolescents, galactorrhea was reported in 0.8% of RISPERDAL®-treated patients and gynecomastia was reported in 2.3% of RISPERDAL®-treated patients.

The long-term effects of RISPERDAL® on growth and sexual maturation have not been fully evaluated.

Pharmacokinetics

The pharmacokinetics of risperidone and 9-hydroxyrisperidone in children were similar to those in adults after correcting for the difference in body weight.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

This section describes the AERS searches performed as well as the case series selection.

2.2 AERS SELECTION OF CASES

We searched the AERS database on May 1, 2008 for all reports in the database of pediatrics (age 0-16 years) and adults (17 years and greater) associated with risperidone use from market approval until March 28, 2008 and from the pediatric exclusivity date of February 28, 2007 to March 28, 2008. We conducted separate searches as follows:

1. From Marketing to March 28, 2008 – Adults, 17 years old and older, (Section 3.1, Results, Table 1)
 - All adult cases
 - All adult cases coded serious
 - All adult cases coded ‘death’
2. From Marketing to March 28, 2008 – Pediatrics aged 0 to 16 years old, (Section 3.1, Results, Table 1)
 - All pediatric cases
 - All pediatric cases coded serious
 - All pediatric cases coded ‘death’
3. Pediatric Exclusivity Period – February 28, 2007 to March 28, 2008 – Adults, (Section 3.2, Results, Table 2)
 - All adult cases
 - All adult cases coded serious
 - All adult cases coded ‘death’
4. Pediatric Exclusivity Period — February 28, 2007 to March 28, 2008 - Pediatrics, (Section 3.2, Results, Table 2)
 - All pediatric cases
 - All pediatric cases coded serious
 - All pediatric cases coded ‘death’

The crude counts that resulted from the searches are included in section 3. However, for cases that will receive a hands-on review, the search retrieved 131 serious outcome reports and of these 131 reports, 116 cases met the inclusion criteria for our case series. Of the 15 cases not included in our case series, nine cases were duplicates and the remaining six did not meet our inclusion criteria. The search of all pediatric reports with an outcome of death from marketing approval to March 28, 2008 retrieved 48 reports. Of these 48 reports, 15 were duplicates and two were excluded for miscoding as a pediatric patient, therefore, 31 cases are included in our case series.

3 AERS RESULTS FOR RISPERIDONE

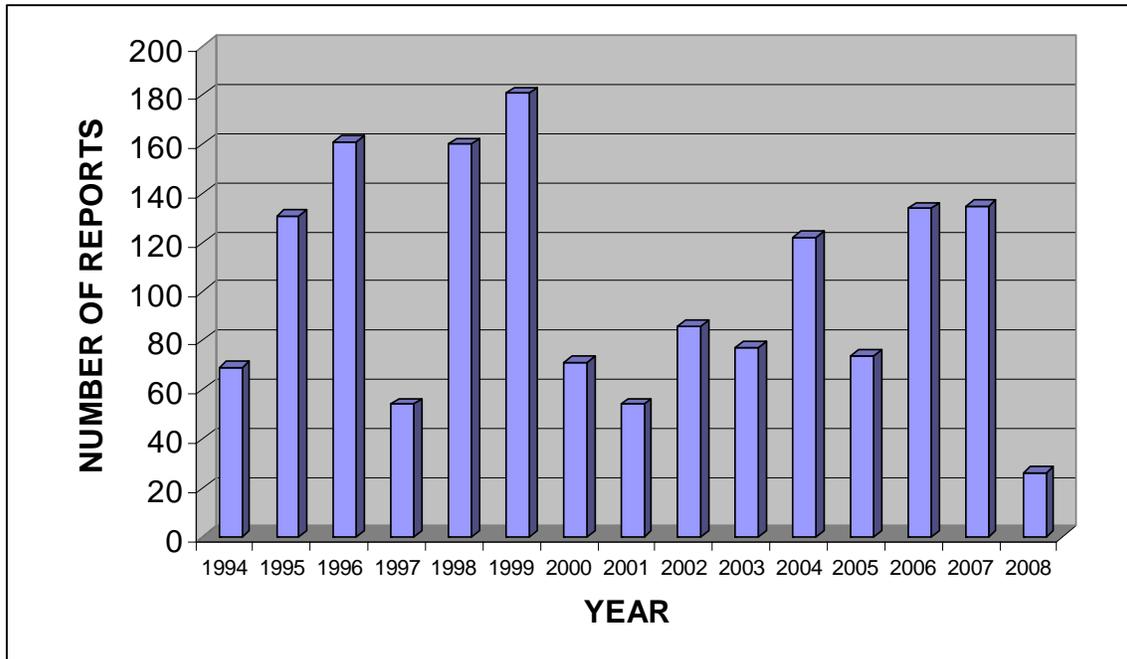
3.1 COUNT OF REPORTS: ALL SOURCES- US AND FOREIGN FROM MARKETING APPROVAL (TABLE 1)

Table 1: Crude counts¹ of AERS Reports for All Sources from December 29, 1993 up until March 28, 2008			
(US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	14910 (10845)	11029 (7077)	2035 (1272)
Pediatrics (0-16 yrs.)	1535 (1183)	1207 (860)	48 (33)
Age unknown (Null values)	3907	2867	530
Total	20352	15103	2613

¹ May include duplicates

² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, other serious.

Figure 1: Reporting trend for pediatric reports from approval (December 29, 1993) to March 28, 2008



3.2 COUNT OF REPORTS: ALL SOURCES- US AND FOREIGN FROM PEDIATRIC EXCLUSIVITY (TABLE 2)

Table 2: Crude counts¹ of AERS Reports for All Sources from date Pediatric Exclusivity was Granted¹⁷ until March 28, 2008			
(US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	1230 (488)	1155 (421)	189 (97)
Pediatrics (0-16 yrs)	150 (56)	131 (42)	8 (8)
Age unknown (Null Values)	411	378	47
Total	1791	1671	244

¹ May include duplicates

² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, congenital anomaly, and other serious.

3.3 CASE CHARACTERISTICS FROM ONE-YEAR REVIEW (TABLE 3)

Postmarketing Review of All Pediatric Adverse Event Reports received during the one-year period after risperidone received pediatric exclusivity.

Case Characteristics:

Table 3: Clinical and demographic characteristics of serious and non-serious pediatric cases reported during the pediatric exclusivity period (February 28, 2007 through March 28, 2008) n=150	
Gender [n=143]	Male: 92 Female: 51
Age [n=150]	0- <1 month (0) 1 month - <2 yrs (6) 2-5 yrs (16) 6-11 yrs (62) 12-16 yrs (66) Mean 11 years; Median 11 years; Range 6 months to 16 years
Origin [n=145]	US 56, Foreign 89
Event date [n=103]	1993 (1), 1997 (1), 2000 (2), 2001 (2), 2002 (2), 2003 (5), 2004 (2), 2005 (5), 2006 (16), 2007 (60), 2008 (7)
Daily dose [n=105]	Mean 1.8 mg , Median 1 mg , Range 0.25 to 10 mg
Intentional overdose situation [n=8]	Mean 21.75 mg, Median 15 mg, Range 10 to 60 mg
Long-acting injection [n=2]	37.5 mg and 50 mg doses were administered
Duration of therapy [n=44]	Mean 322 days , Median 90 days, Range 1 to 5156 days
Indications [n= 75] ¹⁸	Abnormal behavior (7), ADHD (7), Affective disorder (3), Aggression (3), Agitation (1), Anger issues (1), Anxiety (4), Asperger’s disorder (1), Autism (6), Bipolar disorder (9), Childhood psychosis (1), Conduct disorder (3), Depression (2), Epilepsy (3), Irritability (1), Learning disability/disorder (2), Lennox-Gastaut syndrome (1), Mania (1),

¹⁷ February 28, 2007

Table 3: Clinical and demographic characteristics of serious and non-serious pediatric cases reported during the pediatric exclusivity period (February 28, 2007 through March 28, 2008) n=150

	Manic depression (1), Mood disorder (1), Negativism (1), Oppositional defiant disorder (1), Pervasive developmental disorder (1), PTSD (2), Psychiatric disorder (7), Schizophrenia (1), Self-injurious behavior (1), Sleep disorder (1), Tic (1), Tourette's disorder (2)
Outcomes [n=138]	Death (8), Life-Threatening (2), Hospitalization (45), Required Intervention (3), and Other Serious (80)

4 DISCUSSION/SUMMARY OF CASES

4.1 TOTAL REPORTS WITH AN OUTCOME OF DEATH (N = 31)

In light of the fact that eight pediatric cases coded with death were reported during the pediatric exclusivity period, all pediatric cases coded with death submitted from marketing approval until March 28, 2008 were reviewed. Overall, there were 31 post-marketing pediatric cases with an outcome of death. Of these 31 cases there were 20 US and 11 foreign cases, which included 20 males and 10 females (one case did not provide a gender). The patients involved ranged in age from 1 to 16 years with a median of 12 years.

In general, for all 31 post-marketing death cases there was not a common theme underlying the outcome of death. A contributing factor or cause of death as determined by diagnosis or by autopsy could be identified in 27 of the 31 cases, leaving four cases with an indeterminate cause of death. The clinical categories linked with the most deaths associated with risperidone included the nervous (10) and cardiac systems (9). An overall assessment of these categories is provided in the following sections (4.1.1, 4.1.2). The adverse events that potentially contributed to the reported outcomes in the pediatric cases occurred in much the same manner as in adult patients. After reviewing the adult safety data in the labeling for risperidone, all known contributing factors or causes of death amongst the pediatric patients that took risperidone as prescribed were consistent with the current labeling. A narrative summary for each case with a coded outcome of death is located in Appendix 1.

4.1.1 NERVOUS SYSTEM (10):

Ten cases involved the nervous system, including five cases describing seizures; three cases describing neuroleptic malignant syndrome (NMS) or NMS-like symptoms (i.e. muscle rigidity, hyperthermia, elevated creatine phosphokinase, and rhabdomyolysis); and one case each of cavernous angioma and cerebral edema. Of the five seizure cases, the most severe case described status epilepticus leading to aspiration pneumonia and ultimately death. Two of the five patients had a history of epilepsy and in two additional cases concomitant medications played a confounding role.¹⁹ Of the three cases related to NMS, one case was confounded by the use of haloperidol, chlorpromazine, and lorazepam, which are all labeled for an association with NMS. Both seizures and neuroleptic malignant syndrome are labeled for an association with risperidone whereas cavernous angioma and cerebral edema are not labeled.

¹⁸ ADHD= Attention-Deficit Hyperactivity Disorder, PTSD = Post-Traumatic Stress Disorder.

¹⁹ Dexmethylphenidate and fluoxetine in one case and paroxetine in the second case are labeled for an association with seizures.

4.1.2 CARDIAC SYSTEM (9):

Nine cases were cardiac system related including two cases each describing left ventricular hypertrophy (LVH) and cardiac arrest; and the remaining five cases each describing a different adverse event (i.e. arrhythmia, congenital heart defect, myocarditis, myocardial infarction, suspected pulmonary embolism). In the cases of congenital heart defect and suspected pulmonary embolism, a family history of cardiac disease and Protein S Deficiency respectively, may have played a confounding role in the patients' deaths. Two additional cases were confounded by the use of concomitant medications.²⁰ Arrhythmia, myocarditis, myocardial infarction, and pulmonary embolism are labeled for an association with risperidone whereas LVH and cardiac arrest are not labeled.

4.1.3 MISCELLANEOUS (8):

Of the remaining eight cases, two cases each involved the respiratory system and suicide along with one case each of accidental exposure, hypoglycemic seizure, viral infection, and pneumonia + septicemia + acute respiratory distress + congestive heart failure + mixed acid/base disorder. In the two cases involving the respiratory system, the first described asphyxia due to the aspiration of vomit following drowning, and the second case described suffocation by the mother. In the case of hypoglycemic seizure, the patient had a past medical history of diabetes mellitus and was currently using insulin for diabetes mellitus, which is well known to cause hypoglycemia. Of these eight cases, suicide is the only event that is labeled for an association with risperidone.

4.2 NON-FATAL SERIOUS ADVERSE EVENT REPORTS (N=116)

DPV was asked to review adverse events associated with risperidone use during the exclusivity period with a focus on metabolic syndrome (including weight gain, hyperglycemia and hyperlipidemia), hyperprolactinemia, and extrapyramidal events (including tardive dyskinesia). These potential adverse events are reviewed in sections 4.2.1, 4.2.2 and 4.2.3. Additionally, we provide the following case counts of other potential adverse events reported in the pediatric population (during the period of exclusivity) below. Adverse events that are currently found in the product labeled are appended with an asterisk (*).

Adverse event case counts:

- **Biochemical laboratory tests and toxins (6):** increased alkaline phosphatase (2), increased bilirubin, increased creatine phosphokinase*, increased mercury level in hair, increased transaminases*
- **Cardiac (6):** arrhythmia* (2), bradycardia*, premature ventricular extrasystoles, tachycardia*, and supraventricular tachycardia
- **Drug exposure in utero (2)**
- **Gastrointestinal (3):** gastric ulcer, pancreatitis*, and vomiting*/dehydration
- **Hematologic (15):** leukopenia/thrombocytopenia (4), leukopenia* (3), thrombocytopenia* (3), neutropenia (3), decreased hemoglobin, and blood in stool
- **Off-label unintended use (20):** accidental exposure (9), intentional misuse/overdose (8), and poisoning food (3)
- **Miscellaneous (9):** drug interaction between risperidone and valproic acid* (2), angioedema*, edema*, hepatitis, hypothalamic tumor, increased intraocular pressure, night sweats, and precocious puberty*

²⁰ In two separate cases, sertraline was the concomitant medication and it is labeled for an association with cardiac arrhythmia as well as myocardial infarction.

- **Neurologic (11):** agitation during switch from risperidone to methylphenidate (4), neuroleptic malignant syndrome* (2), seizures* (2), transient ischemic attack*, tremors*, and anticholinergic syndrome
- **Psychiatric (9):** hallucinations (3), aggression (2), self-injurious behavior (2), depression, and anxiety*

4.2.1 METABOLIC EFFECTS (15)

Fifteen cases described metabolic effects associated with the use of risperidone, which included weight gain, hyperglycemia, hyperlipidemia, diabetes mellitus, and diabetic ketoacidosis. Among these 15 cases, 10 were of US origin and 5 were foreign, including 10 males and 5 females. The children ranged in age from 7 to 16 years, with a median of 12 years. Six cases reported a time to onset of events as short as 22 days after the initiation of therapy up to 304 days after initiation with a median of 101 days. Four cases reported a positive family history of diabetes mellitus with two of these also reporting a history of hypertension and heart disease. Two cases separately reported a past medical history of obesity and diabetes mellitus. Five cases were possibly confounded by the use of concomitant medications.²¹

Overall, eight of the 15 reported the diagnosis of diabetes mellitus, with three of these cases describing diabetes mellitus type 1. Of these eight cases, four described a simultaneous increase in weight and an additional two cases described the occurrence of diabetic ketoacidosis. Six cases reported weight gain alone without the diagnosis of diabetes mellitus with one of these cases also describing an increase in cholesterol. Five of these six cases reported a weight gain of 10 to 35 pounds with a median weight gain of 17 pounds. The final case described a patient that experienced glycosuria. A total of six cases, three each of diabetes mellitus and weight gain required hospitalization. Hyperglycemia and diabetes mellitus are labeled in the Warnings section and weight gain appears in the Adverse Events section of the risperidone label.

4.2.2 GYNECOMASTIA/HYPERPROLACTINEMIA (6)

Six cases described the occurrence of either gynecomastia (4) or hyperprolactinemia (2). These six cases included four cases of US origin and two foreign cases, with four males and two females. The children ranged in age from 8 to 16 years, with a median of 12.5 years. Of the four cases of gynecomastia, a 13-year old male described the gynecomastia as sufficient in size and magnitude to necessitate a bilateral mastectomy. The patient had received risperidone for three months, followed by the use of quetiapine and olanzapine (both labeled for gynecomastia). The patient received the bilateral mastectomy after changing therapy to quetiapine and/or olanzapine; however, the report did not say when the gynecomastia actually developed. The remaining three cases did not report any surgical intervention to correct the gynecomastia. Of the two cases of hyperprolactinemia, the first case described an MRI confirmed “pituitary adenoma filling up most of the pituitary sulcus” along with the development of galactorrhea due to an increased prolactin level. This case was possibly confounded by the concomitant use of quetiapine. The second case reported hyperprolactinemia with negative MRI results. Both gynecomastia and hyperprolactinemia are labeled in the Warnings and Adverse events sections of the risperidone label.

²¹ Case 1-Loxapine and periciazine, Case 2- paliperidone, dexamethylphenidate XR and guanfacine, Case 3 – valproic acid and cetirizine, Case 4 – drospirenone/ethinyl estradiol, are all labeled for an association with increased weight. Case 5 – quetiapine is labeled for an association with diabetes mellitus.

4.2.3 EXTRAPYRAMIDAL ADVERSE EVENTS INCLUDING TARDIVE DYSKINESIA (14)

Fourteen cases described extrapyramidal adverse events with three specifically describing tardive dyskinesia. These 14 cases included seven cases each of US and foreign origin, with eight males, four females, and two cases of unknown gender. The children ranged in age from 6 months to 16 years with a median of 11 years. Of note, the 6-month-old baby was accidentally exposed to risperidone and experienced dystonic movements in addition to a seizure and lethargy. Of the remaining 13 cases that described extrapyramidal events including tardive dyskinesia, the most serious outcome reported was hospitalization in five cases. Eight cases reported discontinuing risperidone completely and a recovery of extrapyramidal effects, however, two cases continued risperidone despite the development and continuation of extrapyramidal effects, and the remaining four cases did not report an action taken with risperidone therapy. In two of the discontinued cases, therapy was initiated with other medications without the recurrence of extrapyramidal effects. In a total of five cases, the use of concomitant medications possibly played a confounding role in the development of extrapyramidal events.²²Tardive dyskinesia is labeled in the Warnings section and extrapyramidal symptoms appear in the adverse events section of the risperidone label.

5 CONCLUSION

Among the 31 reviewed post-marketing cases with an outcome of death and the 116 post-marketing cases identified during the period of pediatric exclusivity, the post-marketing safety profile of the pediatric population is very similar compared to the adults, and the adverse events occurred in much the same manner as well. In 2007, the pediatric population (0-17 years) accounted for 23.6% [~14% (0-12 years) and ~10% (13-17 years)] of all risperidone prescriptions dispensed in US retail pharmacies as well as making up approximately 24% [~14.5% (0-12 years) and ~10% (13-17 years)] of the total patient share.²³ In addition, the adverse events reported amongst children and adolescents appear to occur in a similar frequency. Across all cases of death and non-fatal serious outcomes, metabolic effects were reported as a majority of the adverse events. Although metabolic effects such as weight gain, hyperglycemia, and dyslipidemia are well-known effects in the adult population, special attention should be focused on the impact they have among the pediatric population. No new safety signals emerged as part of this review; however, it has made us aware that the pediatric population is not spared from the adverse events caused by risperidone therapy. The potential risks of risperidone therapy should be weighed against the potential benefit when choosing to initiate therapy.

6 RECOMMENDATIONS

- The current risperidone label appears to address all of the issues discussed in this review. We recommend that no further labeling changes regarding the pediatric population are necessary at this time.
- Continue routine monitoring of the AERS database for adverse events with the use of risperidone in pediatric patients.

²² Case 1- bupropion and quetiapine, Case 2 – methylphenidate, Case 3- quetiapine and clozapine, Case 4- topiramate, Case 5- fluoxetine and methylphenidate, are all labeled for association with extrapyramidal events.

²³ Borders-Hemphill V. Risperdal (risperidone) tablets BPCA Drug Use Review. FDA Postmarketing Review. July 29, 2008.

APPENDICES

Appendix 1. Narrative summaries of the cases of death associated with risperidone from market approval December 29, 1993 until March 28, 2008.

Nervous System (10):

- **ISR# 4440782; Foreign, 2004.** This 14-year old male experienced an “epileptic fit and died” seven months after initiating therapy with risperidone 1mg daily for the treatment of agitation and anxiety. Concomitant medications included acetaminophen and diprobase cream. The autopsy reported a diagnosis of “sudden death in epilepsy.”
- **ISR# 3180753; Foreign, 1999.** This 14-year old male with a history of epilepsy died possibly due to “asphyxiation secondary to seizure.” His medication therapy included risperidone (dose and duration unknown) for the treatment of conduct disorder along with carbamazepine and valproate. The patient did not have any seizures in the two years prior to his death.
- **ISR# 4369054; US, 2004.** This 15-year old male experienced a “violent seizure, collapsed and died” an unspecified time after initiating therapy with risperidone 0.5 mg daily for the treatment of autism. His concomitant medications included lorazepam and paroxetine. Paroxetine has labeling describing an association with seizures. The toxicology results reported “normal blood.”
- **ISR# 3002276; US, 1997.** This 15-year old female died of aspiration pneumonia and possible adult respiratory distress syndrome after experiencing status epilepticus several weeks earlier. Her medication therapy included risperidone 1 mg daily (unknown duration and indication).
- **ISR# 4816962; Foreign, 2005.** This 16-year old male died “unexpectedly after a two minute seizure” at an unspecified time after initiating therapy with risperidone (dose and indication unknown). The patient had a history of epilepsy and his concomitant medications included carbamazepine, clobazam, and topiramate. The autopsy results confirmed the causes of death to be epilepsy and blepharophimosis.
- **ISR# 4572267; Foreign, 2005.** This 16-year old male died of neuroleptic malignant syndrome after receiving therapy with risperidone (dose and duration unknown) and anafranil for two years for the treatment of depression. An autopsy confirmed the diagnosis of neuroleptic malignant syndrome and included findings of brain edema.
- **ISR# 4261733; US, 2003.** This 16-year old male receiving therapy with risperidone 1mg daily (duration and indication unspecified) experienced hyperthermia; elevated creatine kinase, myoglobin, and troponin levels; decreased sodium levels, and an unstable blood pressure. He died after 30 minutes of advanced life support. His concomitant medications included topiramate and valproic acid. The urine toxicology screening reported negative findings.
- **ISR# 4495497; US, 2004.** This 8-year old female experienced muscle rigidity, elevated heart rate, hyperthermia, elevated creatine phosphokinase levels, and rhabdomyolysis after receiving treatment with risperidone, haloperidol, chlorpromazine, diphenhydramine, and lorazepam (doses unspecified) for unspecified duration during her hospitalization. She also developed multi-organ system failure and was declared “brain dead” on day 12 of her hospitalization. The autopsy reported bronchopneumonia as the immediate cause of death and revealed findings consistent with neuroleptic malignant syndrome. Haloperidol, chlorpromazine, and lorazepam all have labeling describing an association with NMS.

- **ISR# 4317567; Foreign, 2004.** This 7-year old male experienced “encephalitis, hypotension, arrhythmia, cyanosis, muscle rigidity and loss of consciousness” after two days of therapy with risperidone 2mg daily for the treatment of psychosis. The autopsy results revealed cerebral edema, but no exact cause of death could be determined.
- **ISR# 5449063; US, 2007.** This 9-year old female died 12 days after initiating therapy with risperidone (dose unclear) for the treatment of ADHD. Her concomitant medications included valproate and citalopram. The autopsy results revealed that the patient suffered from a condition of cerebral cavernous malformation of the brain and determined the cause of death to be from a cavernous angioma.

Cardiac System (9):

- **ISR#4770210; US, 2005.** This 6-year old male experienced cardiac arrest and died. He received therapy with risperidone for an unknown indication (dose and duration unknown). He did not receive treatment with any other concomitant medications.
- **ISR#5174266; Foreign, 2006.** This 12-year old male died because of damage from the cardiac arrest he experienced. The patient initiated treatment with risperidone at 0.5mg daily for unknown indication (duration unclear) and received no other concomitant medications. The autopsy results could not explain his death.
- **ISR#4828886; US, 2005.** This 12-year old female experienced a cardiac arrhythmia and died seven months after initiating therapy with risperidone 1 mg daily for bipolar disorder. Her concomitant medication included sertraline, which is labeled for an association with cardiac arrhythmias. The patient had a past medical history of tetralogy of fallot, which if repaired can put patients at an increased risk of developing cardiac arrhythmias.²⁴
- **ISR# 4333799; Foreign, 2004.** This 10-year old male suddenly died three months after initiating therapy with risperidone 0.5 mg daily for conduct disorder. The reporting physician related his death to a “congenital heart problem” or family history of cardiac disease. Autopsy results were pending at the time of the report.
- **ISR# 4414936; Foreign, 2004.** This 11-year old female died of myocarditis one month after initiating therapy with risperidone 2mg daily and oxcarbazepine 600mg daily for the treatment of mental disorder. Six days prior to her death, she also received intramuscular fluphenazine and intramuscular biperiden to prevent any psychomotor disorders. The autopsy findings were consistent with myocarditis.
- **ISR#5670801; US, 2008.** This 7-year old male experienced a heart attack and died at an unknown time after initiating therapy with risperidone 1 mg daily for an unknown indication. On an unknown date prior to his death and within four months of initiating risperidone therapy, he experienced QTc prolongation. His concomitant medication included sertraline, which is labeled for an association with myocardial infarction.
- **ISR# 5602030; US, 2008.** This 16-year old male experienced an upper respiratory infection and difficulty breathing ultimately leading to a massive blood clot and his death three months

²⁴ Spektor, M. “Tetralogy of Fallot.” *Emedicine*. 26 Mar. 2006. 27 Feb 2008. <http://www.emedicine.com/EMERG/topic575.htm>.

after initiating therapy with risperidone (dose and indication unspecified). The patient had a confounding family history of Protein S Deficiency. His concomitant medication included sertraline.

- **ISR# 1837168; US, 1997.** This 11-year old female died of “natural causes” one year after initiating therapy with risperidone 2 mg daily for the treatment of depression and hallucinations. Her concomitant medication included imipramine. The coroner’s office provided the causes of death as bronchial pneumonia and cardiomegaly with left ventricular hypertrophy. Autopsy results were pending at the time of reporting.
- **ISR# 3657916; Foreign, 2001.** This 16-year old male died while receiving therapy with risperidone 4 mg daily for three years for the treatment of “unspecified delay in development.” His concomitant medication included sertraline. The reporter had two hypotheses for his cause of death: left-ventricular hypertrophy or a drug interaction. The patient had a history of two syncopal episodes.

Miscellaneous (8):

- **ISR# 5081694; US, 2006.** This 6-year old male died after the accidental ingestion of his medications risperidone, lithium, mirtazapine, and clonidine (doses and duration unknown) for the treatment of bipolar disorder, post-traumatic disorder and attention-deficit hyperactivity disorder (ADHD). He also ingested ascorbic acid in addition to the other medications. His mother found him dead in bed and efforts to resuscitate him were unsuccessful.
- **ISR# 1828655; US, 1997.** This 5-year old male died because of “asphyxia due to aspiration of vomitus due to near drowning with other contributing factors being status-post ventricular peritoneal shunt placement and dysrhythmia effect of tricyclic antidepressant” within three months of initiating therapy with risperidone 2 mg daily for the treatment of ADHD. He also received treatment with imipramine. The autopsy results reported “no evidence of trauma accounting for/or contributing to death.”
- **ISR# 3326649; US, 1999.** This 1-year old female died from suffocation after the mother gave her 0.5 mg of risperidone from her own supply. The mother had done this in the past. The patient had a history of sleep apnea. The autopsy results confirmed the cause of death.
- **ISR# 1828659; US, 1996.** This 13-year old male experienced a seizure resulting in a hospitalization 1&1/2 years after initiating therapy with risperidone 3 mg daily for the treatment of Tourette’s syndrome. He went into cardiac arrest and never regained consciousness. The final diagnoses given included pneumonia, septicemia, acute respiratory distress, congestive heart failure, and mixed acid/base disorder. Autopsy results were consistent with the diagnoses as well as other findings.
- **ISR# 4080453; US, 2003.** This 8-year old male experienced a hypoglycemic seizure and died while on therapy with risperidone 0.25 mg as needed (duration unknown) for ADHD and unspecified behavioral disorder. He had a past medical history of diabetes. His concomitant medications included insulin, Obetrol²⁵, and clonidine. Hypoglycemia is a well-known adverse event associated with insulin therapy.
- **ISR# 4770680; US, 2005.** This 14-year old female ingested unspecified amounts of risperidone, fluoxetine, zolpidem, and unspecified benzodiazepines. After two days of continuous treatment measures to reverse her overdose condition, she died. The medical

²⁵ Also known as Adderall, consisting of four mixed dextro and levo amphetamine salts

examiner found massive hepatic necrosis and attributed the cause of death to suicide from the multi-drug overdose. The report did not state if the patient had a current prescription for these medications.

- **ISR# 5104374; US, 2006.** This 12-year old male hanged himself approximately four years after initiating therapy with risperidone for the treatment of hyperactive compulsive disorder and post-traumatic disorder. His concomitant medications included sertraline and methylphenidate. Sertraline has labeling describing an association with suicidal ideation. Incomplete autopsy results were available at the time of reporting that included blood results showing only sertraline present.
- **ISR# 4952850; US, 2006.** This 14-year old female experienced viral infection, myoglobin blood increased, and creatine phosphokinase increased and died at an unknown time after the initiation of risperidone (dose and duration unknown) for the treatment of unrest. According to the reporter, the patient may have experienced rhabdomyolysis. This possibly occurred prior to the initiation of risperidone therapy. Her concomitant medications included lorazepam, prednisolone, teprenone, dilazep, alfalcidol, and domperidone. Lorazepam and prednisolone have labeling describing an association with unspecified infections. The patient went into cardio-respiratory arrest prior to her death.

Indeterminate cause (4):

- **ISR# 5373324; US, 2007.** This 8-year old male was found dead “in a questionable seizure state” within two months of initiating therapy with risperidone 2.25 mg daily for the treatment of autism, ADHD, and anxiety. His concomitant medications included dexamethylphenidate and fluoxetine and both have labeling describing an association with seizures. The initial autopsy results were negative.
- **ISR# 4511880; US, 2004.** This 13-year old male died during a hospitalization for diarrhea and a urinary tract infection while receiving therapy with risperidone (dose and duration unknown) for the treatment of “behavioral disorder associated with hyperactivity.” Autopsy results were unavailable at the time of reporting.
- **ISR# 5352705; US, 2007.** This 16-year old male died while receiving therapy with risperidone 3 mg daily (duration and indication unknown). Autopsy results were unavailable at the time of reporting.
- **ISR# 3482525; US, 2000.** This is a case of a 15-year old. This is a hearsay case from the mother of a patient of this reporting psychiatrist. The patient died while on risperidone therapy. No other details were provided.

APPENDIX 2.

Table 1- Count of Metabolic Syndrome, Weight Increased, Hyperglycemia, and Hyperlipidemia Reports: All Sources Combined- US and Foreign from marketing approval up until March 28, 2008

AERS search criteria:

Time period: Marketing approval to March 28, 2008

Coded outcomes: all reports, all serious reports, all death reports

Ages: 17 years and older (adults) ‘AND’ 16 years and younger (pediatrics)

MedDRA Preferred Terms: Metabolic Syndrome, Weight Increased, Hyperglycaemia, and Hyperlipidaemia

Table 1: Crude counts¹ of AERS Reports from all sources from Marketing Approval up until 3/28/08						
Preferred Terms	All reports		Serious²		Death	
	> 17 yrs	0-16 yrs	> 17 yrs	0-16 yrs	>17 yrs	0-16 yrs
Metabolic Syndrome	2	0	2	0	0	0
Weight Increased	576	141	416	117	16	0
Hyperglycaemia	97	7	74	5	5	0
Hyperlipidaemia	24	1	20	1	0	0
¹ May include duplicates						
² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, and congenital anomaly.						

** Table 2 is derived from the 0-16 yrs all reports column in Table 1 above

Table 2** –Pediatric age stratification of crude count AERS reports from all sources from Marketing Approval until 3/28/08 for Metabolic Syndrome, Weight Increased, Hyperglycaemia, & Hyperlipidaemia				
MedDRA Preferred Term	All reports Total	0-6 years	7-11 years	12-16 years
Metabolic Syndrome	0	0	0	0
Weight Increased	141	11	48	82
Hyperglycaemia	7	0	3	4
Hyperlipidaemia	1	0	1	0

Table 3 -Count of Hyperprolactinemia Reports: All Sources- US and Foreign from marketing approval up until March 28, 2008

AERS search criteria:

Time period: Marketing approval to March 28, 2008

Coded outcomes: all reports, all serious reports, all death reports

Ages: 17 years and older (adults) ‘AND’ 16 years and younger (pediatrics)

MedDRA Preferred Term: Hyperprolactinemia

Table 3: Crude counts¹ of AERS Reports from all sources from Marketing Approval up until 3/28/08			
	All reports	Serious ²	Death
Adults (> 17 yrs)	184	177	3*
Pediatrics (0-16 yrs)	33	32	0
Age unknown (Null values)	62	61	0
Total	279	270	3
¹ May include duplicates ² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, and congenital anomaly. * Two cases of death occurred in 2004 and one case occurred in 2005			

Table 4- Count of Extrapyramidal Disorder including Tardive Dyskinesia Reports: All Sources- US and Foreign from marketing approval up until March 28, 2008

AERS search criteria:

Time period: Marketing approval to March 28, 2008

Coded outcomes: all reports, all serious reports, all death reports

Ages: 17 years and older AND 16 years and younger

MedDRA Preferred Terms: Extrapyramidal Disorder and Tardive Dyskinesia

Table 4: Crude counts¹ of AERS Reports from all sources from Marketing Approval up until 3/28/08			
	All reports	Serious ²	Death
Adults (> 17 yrs)	751	544	39
Pediatrics (0-16 yrs)	83	60	0
Age unknown (Null values)	166	112	2
Total	1000	716	41
¹ May include duplicates ² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, and congenital anomaly.			

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Mark, this is the final BPCA after meeting with
OPT and PMHS. No substantive changes have been
implemented. A correction to the numbers in the
case narratives in the appendix occurred.

Mark Avigan
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