Johnson & Johnson Pharmaceutical Research & Development, LLC
Benefit-Risk Management Medical Group

Use of Risperdal® (risperidone) in Children Aged 5 to 17 Years
A Response to FDA

I have read this report and confirm that, to the best of my knowledge, it accurately and completely describes the data available to date:

Deborah Arrindell MD Oct 20, 2004

Deborah Arrindell, MD — Date
Benefit Risk Physician, Central Nervous System
Benefit-Risk Management

I have read this report and, based on the data as presented, agree with the conclusions drawn:

20 Oct 04

Jürgen Schmider, MD, PhD — Date
Therapy Area Leader, Central Nervous System
Benefit-Risk Management

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PLAINTIFF'S EXHIBIT 44

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EXECUTIVE SUMMARY

This assessment was undertaken in response to an approvable letter received from the United States Food, And Drug Administration (FDA), dated 18 June 2004, regarding the Company's "supplemental new drug application for the use of Risperdal® in the treatment of irritability associated with autism." FDA requested that the Company provide "a summary of worldwide experience on the safety of this drug in the pediatric population. Include an updated estimate of the use for drug marketed in other countries."

A search was conducted of the Johnson and Johnson worldwide safety database to identify cases involving all formulations and dosage forms of the product. In addition, the search included all cases of spontaneous adverse events reported in children aged 5 to 17 years in association with the administration of risperidone from 31 May 1993 through 30 June 2004. A total of 3148 cases were retrieved, of which 1015 were female, 1912 were male, and sex was indeterminable in 221 cases. Over 68% of the cases were from the United States and, where the indication for therapy was reported, psychosis/psychoses; schizophrenia, various behavioral disorders; attention deficient disorder/hyperactivity disorder; autistic disorder; and bipolar disorder were the indications most frequently reported.

There were 22 deaths reported and, in most cases, autopsy results provided causes of death such as drowning; cerebral edema (although exact cause of death could not be clearly specified and the EEG was consistent with encephalitis); pulmonary embolism; broncho-pneumonia along with cardiomegaly and focal left ventricular hypertrophy; pneumonia (including acute respiratory distress syndrome [ARDS] and septicemia in a patient with Kostmann's neutropenia); aspiration pneumonia (and ARDS); severe pancreatitis (and cardiopulmonary arrest); neuroleptic malignant syndrome; and hypoglycemic seizure. In 2 cases pre-existing medical conditions may have contributed to the patients deaths. Seizures were also implicated as the cause of death in some of the cases. In 5 cases suicide was reported as the cause of death (ages 16, n=1 and 17, n=4). In the general US population, suicide is the third leading cause of death in 15 to 24 year olds. In 2000 the suicide rate (US) was 8.2 per 100,000 teenagers (ages 15-19). Pediatric exposure data were only available for the years 2001-2003. Therefore, reporting rates of spontaneous adverse events in children age 5-17 could only be calculated for these years. A calculation of the observed rate of suicide per 100,000 in patients aged 5-17 for the years 2001-2003 versus a derived

(from 2001 rates) suicide rate of 3.67 per 100,000 in patients aged 5-17 showed no increase in suicide in patients aged 5 to 17 years administered risperidone. Thus, there is no evidence of an increased risk of suicide in patients aged 5 to 17 years who are administered risperidone.

Two System Organ Classes (SOCs) were identified (Congenital, Genetic and Familial Disorder and Immune System Disorder) with a 2-fold difference between proportional reporting rates in the 5-to-17-years age group compared to proportional reporting rates in all other age groups. Most of the events in these SOCs are known to manifest during childhood and adolescence and can, therefore, be expected to be reported more frequently in the 5-to-17-years age group.

In an assessment of adverse events of interest, gynaecomastia had a proportional reporting rate in patients age 5 to 17 years that was greater than 2. In the United States Package Insert for risperidone, gynaecomastia is labeled as a rare event. For the years 2001, 2002, and 2003, the respective reporting rates of gynaecomastia were 12.3, 6.4, and 9.7 cases per 100,000 person years. These rates meet the CIOMS III definition of a rare event for the year 2001 and very rare event for the years 2002 and 2003.

Except for a relative greater rate of gynaecomastia in patients age 5-17, this assessment does not provide evidence that the administration of risperidone to patients aged 5 to 17 years results in a safety profile that is different from the reference safety data on file for risperidone. The current safety reference document for risperidone adequately reflects the safety of the administration of risperidone to children aged 5 to 17 years, including gynaecomastia.

1. BACKGROUND

This assessment is in response to a approvable letter received from the United States Food And Drug Administration (FDA) dated 18 June 2004 regarding the company's supplemental new drug applications for the use of Risperdal® (risperidone) in the treatment of irritability associated with autism. FDA requested that the Company provide "a summary of worldwide experience on the safety of this drug in the pediatric population. Include an updated estimate of use for drug marketed in other countries."

2. METHODS

2.1. Identification of Cases

In order to capture all medically confirmed (non-consumer) and consumer cases involving the use of risperidone in the pediatric population, a search was conducted of the Johnson & Johnson worldwide safety database (SCEPTRE) to identify cases involving all formulations and dosage forms of the product. The search included all cases of spontaneous adverse events reported in children aged 5 to 17 years in association with the administration of risperidone from 31 May 1993 (international birthdate) through 30 June 2004.[a]

The identified or retrieved cases were then sorted according to age, sex, indication for therapy, and county of origin. Cumulative frequency tabulations for both serious and nonserious cases in patients ages 5 through 17 were generated (Attachments 1-4), as well as a cumulative frequency tabulation of spontaneous cases of adverse events reported in association with risperidone in all other ages sorted by seriousness (tabulation not provided). In addition, 7 adverse events of interest (tardive dyskinesia, increased prolactin levels, gynaecomastia, pituitary tumors, impaired glucose/diabetes mellitus, completed suicide, and suicide ideation and/or attempt) were individually assessed, because of their relevance to the pediatric population and/or the product.

All searches included risperidone identified as either a suspect or concomitant medication and included all spontaneous, postmarketing studies, literature, registry, and health-authority reports; reports from clinical trials were excluded from the search. All cases were retrieved independent of the reporter's relationship attribution. All spontaneous reports are considered

a: Support desk ticket number HD0116549, September 16, 2004.

possibly related per Company policy and, therefore, individual assessments may not be in agreement with the causality assessment of the reporter.

2.2. Background Rate of Suicide

A suicide rate of 3.67 deaths per 100,000 in 5 to 17-year-olds was derived from a suicide rate of 0.7 per 100,000 in children ages 5 to 14 years for the year 2001 and 3/10 of a suicide rate of 9.9 per 100,000 in individuals aged 15 to 24 years for the year 2001.[a] An assumption was made that the rate would stay constant over the years 2001 through 2003.

2.3. Postmarketing Exposure

The Company was asked to provide an updated estimate of use of drug marketed in other countries. Provided below is the estimated exposure in person months worldwide for risperidone from 31 May 1993 thorough 30 June 2004, for both oral and intramuscular formulations.

Algorithm(s) Summary:

Oral formulations: 0.1342 g equals 1 person month for schizophrenia; 0.0732 g equals 1 person month for bipolar mania; 0.0305 g equals 1 person month for senile dementia; and 0.0732 g equals 1 person month for all other indications.

Intramuscular formulation: 0.975 g equals 1 person-year

When providing an estimate of patient exposure in a safety update containing postmarketing surveillance data, it is important to stress the limitations of reporting rates for evaluation of adverse events. Reporting rates do not reflect occurrence rates. Numerous factors may influence the reporting of spontaneous experiences and, therefore, limit the use of spontaneous reports for quantification or evaluation of events.

Patient exposure was estimated by calculation from sales and distribution data. In order to characterize exposure, estimates were made as to how much medication equals one person month of exposure.

Assumptions:

Oral formulations: The proportion of sales for each indication is based on previously supplied marketing data, and these are being used for purposes of consistency over reporting periods. An average daily dose

[a] Arias E, Anderson RN, Kung H, Murphy SL, Kochanek KD. Deaths: Final data for 2001. National Vital Statistics Reports 2003;52(3).

for each indication (Table 1) was converted to g/month by assuming that there are 30.5 days in a month.

Intramuscular formulations: The regimen is 25-50 mg once every 2 weeks. An average dose of 37.5 mg was used for exposure calculations; there are 26 doses administered in a year, therefore 0.975 g equals one person year exposure. Person months are calculated by multiplying person years by 12.

Based on 15,915,118.3 grams sold or distributed worldwide (from launch to June 2004), the estimated worldwide exposure is 233,328,876 person months (Table 1). Worldwide exposure estimates for the years 2001 through 2003 are provided in Table 2 and Table 3.

2.3.1. Postmarketing Pediatric Exposure

An estimate of worldwide pediatric exposure for the years 2001-2003 was obtained by multiplying the percentage of risperidone prescriptions (or market share) written for the 5-to-17-years age group during the years 2001, 2002, and 2003 (4.7%, 6.3%, 6.3%, respectively) by the total person years of exposure for each respective year.[a] The total pediatric exposure for 2001, 2002, and 2003 was 129890, 186991, and 204830 person years, respectively (See Table 2, Table 3 and Table 4).

3. RESULTS

A total of 3148 cases were identified. Of the 3148 cases identified, specific age could not be extracted from the narrative (ie, indeterminable) in 189, 1015 were female, 1912 were male, and sex was indeterminable in 221. In 189 of the cases in which the patient was reported as a child or adolescent, on manual review there was insufficient information to categorize the patient as being between the ages of 5 and 17. The distribution of cases by age is provided in Table 5 and distribution by indication is provided in Table 6. Distribution of cases by county of origin is provided in Table 7; over 68% of the cases were received from the US (n=2199).

a: Percentages of risperidone prescriptions written for the 5-to-17-years age group for the years 2001-2003 were obtained from the IMS Global Prescription Insights Database (worldwide total Risperdal by patient age only includes those IMS countries where patient age data are available), which was provided courtesy of Johnson & Johnson Pharmaceuticals Group Strategic Marketing US (PGSMUS).

3.1. Deaths

A total of 22 deaths were reported (2 deaths were reported for which the age was indeterminable).

Case US-JNJFOC-20030707355 - a 16-year-old boy with a history of mental retardation, behavioral disorder, and developmental delay was prescribed risperidone 0.5 mg twice daily, topiramate 100 mg twice daily, and valproic acid 125 mg ("7 or 8 times a day") and was found unconscious at home with a temperature of 110°F. On admission to the hospital the patient had a temperature of 107°F, elevated creatine kinase 1911 (units not provided/later values were noted to be 4747), myoglobin of 9954 (units not provided), troponin levels 33.8 (units not provided), and sodium of 123 (units not provided). The patient's vital signs remained unstable despite treatment with intravenous fluids and "pressors (dopamine, dobutamine, epinephrine, norepinephrine)". One day following admission, the patient expired after being unable to be resuscitated. A urine toxicology screen was reported as negative. Also reported was that the parents were mentally retarded and their home may have been without electricity for several days. On follow up the only information provided was the reporting of abnormal laboratory values. Duration of risperidone therapy was not assessable in this report.

Case US-JNJ-FOC-20030904721 (Literature report) - a 17-year-old boy was found seizing at home after an intentional ingestion of risperidone, bupropion, and sertraline. The patient was intubated and taken to the hospital for emergency treatment. On arrival at the hospital gastric contents were noted to be coming from the endotracheal tube. The endotracheal tube was repositioned and the patient "coded". The patient was noted to have severe acidosis (pH 6.9 and an arterial carbon dioxide of 80 mm Hg). The patient was unable to be resuscitated and was pronounced dead. According to the reporter, the official cause of death was acute intoxication due to effects of risperidone, bupropion, and sertraline. An autopsy revealed risperidone blood levels of 174 ng/mL, bupropion blood levels of 19,500 ng/mL, and sertraline blood levels of 100 ng/mL.

Case GT-JNJFOC-20040301623 - a 7-year-old boy with a history of acute psychosis was started on risperidone 1.0 mg daily on 23 February 2004. The dose of risperidone was increased to 2 mg daily on

25 February 2004. On an unspecified date the patient experienced an "incoherent state" described as an inability to recognize his parents as well as periods of hallucinations lasting 4-5 days. The patient was afebrile and a computed tomography and electroencephalogram of the brain were consistent with encephalitis. Two days after the dose of risperidone had been increased to 2 mg daily, the patient experienced hypotension, arrhythmia, cyanosis, muscle rigidity, and loss of consciousness. The patient was transferred to the hospital's intensive care unit and died 4 hours later. An autopsy revealed cerebral edema, but the exact cause of death "could not be clearly specified." Results of a lumbar puncture (performed on an unspecified date) were not provided. No follow up information was provided.

Case AU-JNJFOC-20040305038 - a 10-year-old boy was treated with risperidone (0.5 mg daily) for a "conduct disorder". The patient's medical history was unremarkable and no concomitant medications were reported. Three months following the initiation of risperidone therapy, the patient suddenly collapsed (14 hours after the last dose of risperidone), was unable to be resuscitated, and expired. According to the reporter, the child had been "doing extremely well on risperidone therapy" and an electrocardiogram done about 1 month prior to the child's death was "normal." Additionally, per the reporter the child's death was perhaps related to "congenital heart problems" or "family history of coronary artery disease" and the reporter "does not think the Risperdal was related to the death." An autopsy was performed but the results were not provided. Additional information provided stated that "electrophysiology of the brain (date unspecified) suggest affective disorder not disruptive disorder." No additional information was provided.

Case US-JNJFOC-20040505340 - a 15-year-old boy with a history of violent behavior was prescribed risperidone (0.25 mg twice daily) for autism. He experienced a "violent seizure", collapsed, and died. Concomitant medications included lorazepam, trazodone, and paroxetine hydrochloride. Toxicology reports obtained one day after the child's death revealed "normal blood" with no detectable medications noted. This report was received from a consumer.

Case EMADSS2001007063 - a 17-year-old boy received risperidone (dose unknown) for concentration problems (was having problems with

his studies) and was told by his physician to double his dose when it appeared that the initial dose was not helping. According to the reporter (consumer/mother), the "patient then started to feel bad which led to a deep depression and some days later he took his life." No further information was provided.

Case JACFRA2000000231 - a 17 year-old female who had recently emigrated from Africa to France was hospitalized secondary to "delirium of poisoning" and was treated with risperidone (up to 8 mg/ day) and cyamemazine. One week following hospitalization the patient experienced a pulmonary embolism and died. Autopsy results confirmed the diagnosis of pulmonary embolism. At the time of admission patient was noted to have iron deficiency anemia, a prothrombin time (PT) of 50%, and decreased factor V. No further information was provided.

Case JAKYO38627 - a 17-year-old girl who was on risperidone for schizophrenia committed suicide. On follow up it was revealed that the patient suffered from delusions of persecution/poisoning and auditory hallucinations. In addition, the patient, who was a second-year student in high school, experienced insomnia and decreased appetite. Risperidone, biperiden, and brotizolam were started for the treatment of schizophrenia on 12 February 1998. During a follow up psychiatric visit on 19 February 1998, the patient seemed to show signs of improvement and she could sleep without the brotizolam. According to the reporter, her condition improved to some extent and the medications were prescribed for 2 weeks. On 05 March 1998, the patient complained of difficulty in taking her medications and the dose of risperidone was changed from 3 times a day to 2 times a day. On 19 March 1998, the "patient complained, "I still have a little feeling that they are speaking ill of me. I feel my brains muddled and I don't want to go to school." Mother and attending physician dealt with the patient warmly, showing understanding. On 23 March 1998 the patient committed suicide by jumping from a high place. There was no history of previous suicide attempt. No further information was provided.

Case JAOCAN2000001168 - a 16-year-old boy who was on risperidone 4 mg daily (indication for use developmental delay) and sertraline 100 mg daily (indication anxiety) died. The patient's past medical history was significant for "2 syncopal episodes in the past." (Dates

were not clearly specified but one episode was about 18 months prior to his death and the other episode about 6-7 months prior to death.) The patient had been on methylphenidate prior to the initiation of risperidone therapy. Apparently sertraline had been discontinued on the same day that the patient died. According to the reporter, it was initially believed that the patient's death was due to left-ventricular hypertrophy, however, a possible drug-drug interaction was being investigated." No further information was provided.

Case JASAF42624 - a 14-year-old boy with a history of generalized tonic-clonic epilepsy and conduct disorder was treated with risperidone (3 mg daily). Diagnosis for use of risperidone was mental retardation. Concomitant medications included carbamazepine, thioridazine, methylphenidate, imipramine, and valproate. Although the patient had not had a seizure for 2 years at the last clinic visit (date unknown) sub-therapeutic levels of valproate (171 [units not provided]) and a therapeutic level of carbamazepine (35 [units not provided]) were noted. According to the reporter, the possible cause of death was asphyxiation secondary to a seizure. No autopsy was performed. According to the reporter, it was questioned whether the cause of death could have been secondary to "QT prolongation with torsades and also whether ECG monitoring during risperidone therapy would be recommended." On follow up, it was revealed that the "patient spoke of death, a few days before he died. He slept late. The patient was found deceased by his family, had urinated in his bed, in the prone position, head buried in a pillow, and some blood at the nose."

Case JAUSA24527 - a psychiatrist reported that an 11-year-old girl with a history of mental retardation and obesity was started on risperidone (2 mg daily) in August of 1995 for depression and hallucinations. Concomitant medications included imipramine for enuresis. On an unspecified date in August of 1996 the patient was found collapsed on her bedroom floor. The patient was transported to the hospital where she was pronounced dead. Family history was significant for a maternal second cousin who died suddenly as a teenager. One day prior to her own death, the patient attended the funeral of her father who died while undergoing a kidney transplant. On follow up the cause of death was reported as "broncho-pneumonia (acute and resolving), cardiomegaly (heart weight of 560 grams), focal left ventricular hypertrophy (wall

thickness of 1.7 cm), hepatosplenomegaly with chronic passive congestion and bridging necrosis of the liver (liver weight of 2,670b grams) and spleen (weight of 210 grams), and an accessory spleen. According to the forensic pathologist, the patient died of bronchopneumonia with cardiomegaly as a contributing cause of death.

Case JAUSA24817 - a consumer reported that her 13-year-old son who had a history of asthma (on cromoglicate and salbutamol) and Kostmann's neutropenia (on filgrastim) was on risperidone 3 mg daily for Tourette's syndrome. Reported co-suspect medications included guanfacine hydrochloride. Prior to the hospitalization, the patient had complained of cold symptoms (cough and low grade fever). In addition, the day before he was hospitalized, the patient had undergone a routine medical checkup for the Kostmann's neutropenia. The mother was unsure if her son's respiratory status was evaluated at this time (she was not present in the examination room). In addition, an antibiotic was not prescribed. The day before hospitalization the patient also complained of malaise, vomited twice, and was somnolent. The patient was admitted to the hospital with a history of mental status changes (had lost consciousness in the ambulance en route to the hospital), possible seizures, fever (102.4°F), tachycardia (heart rate of 144 bpm), and a blood pressure of 90/50 mm Hg. The patient was intubated secondary to tachypnea and decreased oxygen saturation despite administration of 100% oxygen. The patient was subsequently transferred to the intensive care unit where he experienced a cardiac arrest. The patient was successfully resuscitated although he never regained consciousness. The patient's clinical status continued to decline and he became oliguric, required increased ventilatory support, and cardiac pressors. The patient expired 2 days after being admitted to the hospital. Autopsy results reported left lower lobe consolidation and pleuritis, myeloid hypoplasia, congestive hepatosplenomegaly, two accessory spleens, single horseshoe kidney, atrophy of the right testicle, patchy acute anoxic ischemic neuronal necrosis of the cerebral cortex and subcortical gray matter. Final discharge summary diagnoses included pneumonia, septicemia, acute respiratory distress, congestive heart failure, and mixed acid/base disorder. The patient's past medical history was also significant for anoxia secondary to asthma and QT prolongation with pimozide.

Case JAUSA24864 - a 5-year-old boy who was on risperidone (2 mg daily) for attention deficit hyperactivity disorder and imipramine for depression died as a result of drowning in a backyard pool. The child's medical history was significant for physical and emotional abuse, premature delivery, a learning disability, and ventricular/peritoneal shunt (secondary to encephalitis). Autopsy results reported the cause of death as "due to asphyxia due to aspiration of vomitus due to near drowning." Other contributing factors stated in the autopsy results included "status post ventricular peritoneal shunt placement and dysrhythmia effect of tricyclic antidepressant." Toxicology results revealed an ante-mortem imipramine level of 0.14 (normal 10 to 110 ng/mL) and desipramine level of 0.35 (normal 0.1 to 0.28 units not provided). Postmortem levels of imipramine and desipramine were 0.25 and 0.69, respectively (units not provided). An ante-mortem combined serum level of risperidone and 9-hydroxyrisperidone was 23 ng/mL, which was reflective of an approximate dose of 2.5 mg daily. On follow up, the cause of death and contributing factors remained unchanged.

Case JAUSA30419 - a physician reported that a 15-year-old girl experienced status epilepticus while on risperidone (1 mg daily). The patient had a history of tuberous sclerosis and a history of epilepsy. The patient expired secondary to aspiration pneumonia and possible acute respiratory distress syndrome (ARDS). No concomitant medications were reported.

Case JAUSA31103 - a 17-year-old boy with a developmental disability was started on risperidone for the treatment of intermittent explosive episodes. Concomitant medications included lithium, valproate sodium, thioridazine, and diphenhydramine. The patient had been on risperidone for about 8 months. Twelve days prior to his death, the patient complained of lethargy, anorexia, ataxia and was subsequently diagnosed with otitis media. The patient was treated with Claritin-D and amoxicillin. One day prior to his death, the patient was hospitalized after becoming stuporous. At the time of hospitalization, the patient was noted to be hypothermic (91.2°F), tachycardic (100 bpm), tachypneic (respiratory rate of 20), hypotensive (99/80 mm Hg), and difficult to arouse. According to the reporter, the patient appeared to be in either septic or cardiogenic shock. In the emergency room, the patient's temperature was noted to decrease to 85°F (rectally).

Laboratory values were significant for a platelet count of 11,000 (units not provided), fibrinogen level of 323 (units not provided), lithium level of 3.3 mg/dL (in the toxic range), prothrombin time of 13.4 (units not provided), and a partial thromboplastin time of 49 (units not provided but double the normal value). The next day, the patient's condition deteriorated and he developed adult respiratory distress syndrome, pneumonia, shock, disseminated intravascular coagulation, and renal failure. The patient suffered a cardiopulmonary arrest and died. A pathology report stated that the patient experienced a "severe ongoing case" of pancreatitis. According to the reporter, no additional information would be provided because of "patient confidentiality."

Case JRFUSA2000002246 - a psychiatrist reported that he was informed (by the mother of one her patients) that an unidentified 15 year-old female (apparently not one of the psychiatrist's patients) died while on risperidone therapy. The psychiatrist was unable to confirm this death and could not provide any additional information.

Case NSADSS2001009791 - a 13-year-old boy with newly diagnosed schizophrenia was started on risperidone (2 mg daily) and 2 days later experienced neuroleptic malignant syndrome (NMS). Co-suspect medications included chlorpromazine and biperiden. The patient presented with fever, myoglobinuria, increased creatine phosphokinase, and disturbed consciousness. The parents were instructed to discontinue the medications and bring the child to the hospital for the treatment of those symptoms. The patient was hospitalized and treated with intravenous fluids and dantrolene sodium. A computerized tomogram was reported as showing no abnormalities, however, an electroencephalogram (EEG) was considered abnormal. (It is unclear whether the abnormal EEG results were pre-existing to the episode of NMS.) In addition, the patient was felt to have developed myoglobinuria and acute renal failure. The patient was transferred to the intensive care unit and despite supportive care, including dialysis, expired 7 days after initiating therapy with risperidone. The cause of death was listed as renal failure. The reporter assessed these events as probably related to risperidone, chlorpromazine, and biperiden. In addition, in follow-up information the reporter stated that the EEG abnormality was possibly related to risperidone.

Case NSADSS2002008721 - a 17-year-old girl who had been on risperidone for about 2 years for depression committed suicide about 5-6 months after discontinuing risperidone therapy. Concomitant medications included sertraline. The patient also had a history of posttraumatic stress disorder and cigarette smoking. No additional information was provided.

Case NSADSS2002015031 - a physician reported that an 8-year-old boy with a history of diabetes, attention deficit hyperactive disorder, and an unspecified behavioral disorder was found dead in bed. Risperidone (0.25 mg prn) had been prescribed for an unspecified indication and dates of therapy were reported as unknown. Concomitant medications included insulin (lispro and NPH), obetrol, and clonidine. According to the medical examiner, the cause of death was a hypoglycemic seizure.

Case NSADSS2002032601 (Literature report) - a 15-year-old patient (sex not specified) committed suicide by ingestion of up to 15 gm of risperidone and an unknown amount of desipramine. On follow up, it was reported that the patient was intubated, transported to the hospital, but was unable to be resuscitated and expired. No additional information was provided.

Deaths with Indeterminable Age

Case JAOCAN1999000130 - a nurse reported information regarding the deaths of 2 boys in a group home who had been on risperidone. The information regarding the 2 deaths was obtained from the mother of 1 of the nurse's patients. The source of the information (sister-in-law of the mother) called JOI pharmacovigilance on 18 June 1999 and stated that she was aware of 1 boy in a group home (in which her own son resided) who died while on risperidone and imipramine. According to the sister-in-law, the second boy who died was not risperidone but on Ritalin and imipramine. No additional information was provided.

Case NSADFSS2001027377- a physician reported that a child died while on risperidone therapy. On follow up, an attorney reported that "These events took place about 3 years ago, and the young mother is serving a sentence for second degree murder. I believe that she did administer Risperdal to the infant, her purpose being to calm and quiet the baby. I don't think she intended to kill the baby, and I don't believe the baby died as a result of ingesting Risperdal." Note: In the initial

report (which was medically confirmed from a physician) although the age was indeterminable the patient was reported to be a "child." In follow up information (which was medically unconfirmed and received from an attorney) the patient was reported to as a "baby/infant." Thus, the case was retained in the search based on initial medically confirmed information.

3.1.1. Summary of Deaths

Overall there were 22 deaths reported. Causes of death reported included intentional overdose/suicide (US-JNJFOC-20030904721, and NSADSS-2002032601), suicide (method unspecified) (EMADSS2001007063, JAKYO38627, and US-JNJFOC-20030707355), encephalitis (GT-JNJFOC-20040301623), pulmonary embolism (JACFRA2000000231), bronchopneumonia (JAUSA24527), drowning (JAUSA24864), acute respiratory distress syndrome (JAUSA24817, JAUSA30419 [aspiration pneumonia also reported], and JAUSA31103), hypoglycemic seizure (NSADSS2002015031), neuroleptic malignant syndrome (NSADSS-2001009791), and asphyxiation secondary to a seizure (JASAF42624). In Case JNJFOC-20040505340, the patient experienced a "violent seizure", collapsed and died. In another case (JNJFOC-20040305038), the patient suddenly collapsed and was unable to be resuscitated and expired. According to the reporter, the child's death may have been related to a "family history of coronary artery disease" or the child had "congenital heart problems" and risperidone administration was not related to the death. In an additional case (JAOCAN2000001168), a 16-year-old boy experienced 2 syncopal episodes prior to his death. In case (JRFUSA2000002246), a health-care practitioner reported a death in an unidentified 15-year-old girl; this death was not confirmed. In Case US-JNJFOC-20030707355, assessment of causality is confounded by the administration of concomitant medications including topiramate and valproic acid. However, the clinical picture (elevated temperature, elevated creatine kinase, and elevated myoglobin) is highly suggestive of NMS, although this was not explicitly stated as such in the report.

In 1 of the 2 cases in which death was reported and age was indeterminable, an unidentified patient (JAOCAN1999000130) in a group home, who was reported to be on risperidone and imipramine, died. No additional information was provided. In the other case (NSADFSS2001027377), a

child was administered risperidone by his mother and the child subsequently died.

3.2. Serious and Nonserious Reports

Eighteen percent (18.6%) of the spontaneous cases reported in the 5-to-17-years age group were reported as serious compared to 36.4% of the spontaneous cases reported in all other age groups (Table 8).

4. DISCUSSION

Sixteen percent (16.2%) of all spontaneous adverse events in patients administered risperidone from 31 May 1993 through 30 June 2004 were reported in children aged 5 to 17 years. There were more males than females. Mean age was 12.2 years and median age 13 years. The majority of the cases (70%) were from the United States.

4.1. Deaths

There were a total of 22 deaths identified (the age of the patient was indeterminable in 2 cases). Five of these cases were reported as suicide in adolescents ages 16 (n=1) and 17 (n=4). In two of the cases of suicide, indication for therapy was unknown and in the remaining cases the indication for therapy was depression, disturbance in attention, and schizophrenia. Suicide in children ages 5- 17 in the US is the third leading cause of death among persons aged 15 to 24 years.[a] Risk factors for suicide include psychiatric disorder, social factors, psychological factors, biological factors, genetic factors, and physical disorder.[b] In the year 2000 the suicide rate among 15 to 19 year olds was 8.2 deaths per 100,000 teenagers.[c] An observed-to-expected analysis for the years 2001 through 2003 in patients aged 5 to 17 years using 3.67 deaths per 100,000 as a reference, demonstrates no increase in the observed rate of suicide in children aged 5-17 for the years 2001-2003 administered risperidone (Table 9).

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a: Moscicki EK. Epidemiology of completed and attempted suicide: toward a framework for prevention. Clinical Neuroscience Research 2000; 1:310-323.

b: Roy A. Psychiatric Emergencies. Suicide. In Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 7th ed. Eds: BJ Sadock, MD and VA Sadock, MD. Vol 2, Chapter 29; pg 2031-2040. Lipponcott, Williams and Wilkins (2000), Philadelphia, Pennsylvania.

c: National Institute of Mental Health, In Harm's Way- Suicide in America: National Institute of Mental Health, Bethesda, National Institutes of Health, US Department of Health and Human Services; 2003[cited 5 October 2004]. (NIH Publication No. 03-4594) 3 pages. Available from: http://www.nimh.nih.gov/publicat/index.cfm.

4.2. Reporting Rates

Pediatric exposure data were available for the years 2001-2003. Therefore, reporting rates of spontaneous adverse events in children aged 5 to 17 years could only be calculated for these years. Reporting rates of spontaneous adverse events in children ages 5-17 remained constant, with 259, 243, and 236 cases per 100,000 person years for the years 2001, 2002, and 2003, respectively (Table 4).

4.3. Adverse Events by System Organ Class

An assessment of adverse events by System Organ Class (SOC) identified Congenital and Genetic and Familial Disorder and Immune System Disorder with a 2-fold or greater difference in proportional reporting rates of adverse events in those SOCs in the 5-to-17-years age group compared to the proportional reporting rate of adverse events in all other ages.[a] Most of the events in these SOCs are known to manifest during childhood and adolescence and can, therefore, be expected to be reported more frequently in the 5-to-17-years age group (Table 10).

4.4. Adverse Events of Interest

Reporting rates for 7 adverse events of interest were calculated for the years 2001-2003 (Table 11). Proportional reporting rates for those 7 adverse events of interest were also calculated for the years 2001-2003. Gynaecomastia was identified as an adverse event of interest with a proportional reporting rate in patients age 5-17 that was greater than 2 (Table 12). In addition, a slightly higher proportional reporting rate of hyperprolactinemia was observed in 2003 only. In the United States Package Insert (USPI), gynaecomastia is labeled as a rare event. For the years 2001, 2002, and 2003, the respective reporting rates of gynaecomastia were 12.3, 6.4, and 9.7 cases per 100,000 person years. These rates meet the CIOMSs definition of a rare event for the year 2001 and very rare for the years 2002 and 2003 (Table 11). The higher proportional reporting rates of gynaecomastia are likely due to the increased susceptibility of children to develop gynaecomastia.[b]

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a: A 2-fold difference was selected in order to increase the likelihood of detecting any possible differences between the rate of adverse events in children age 5-17 versus all other age groups

b: The Merck Manual of Diagnosis and Therapy. Section 18, Gynecology and Obstetrics. Chapter 242, Breast Disorders. Eds. MH Beers, MD and RR Berkow, MD. 17th ed. Available at http://www.Merck.com. Accessed 18 Oct 2004.

5. CONCLUSION

Except for a relative greater rate of gynaecomastia in patients aged 5-17 years, this assessment does not provide evidence that the administration of risperidone to patients aged 5 to 17 years results in a safety profile that is different from the reference safety data on file for risperidone. The current safety reference document for risperidone adequately reflects the safety of the administration of risperidone to children aged 5 to 17 years, including gynaecomastia.

6. TABLES

Table 1: Worldwide Exposure From Product Launch to June 2004

ORAL FORMULATIONS

Indication	% of Sales	g/indication	mg/day	g/month	Person Months
Schizophrenia	30	4,761,723.6	4.4	0.1342	35,482,292
Bipolar mania	12	1,904,689.4	2.4	0.0732	26,020,347
Senile dementia	15	2,380,861.8	1.0	0.0305	78,061,042
Other	43	6,825,137.1	2.4	0.0732	93,239,578
Total	100	15,872,411.9			232,803,259

INTRAMUSCULAR FORMULATION

Grams	mg/week	g/year	Person Months
42,706.4	37.5	0.975	525,617

TOTAL

	Grams	Person Years	Person Months
Oral formulations	15,872,411.9	19,400,271	232,803,259
Intramuscular formulations	42,706.4	43,801	525,617
Total	15,915,118.3	17,833,733	233,328,876

Table 2: Worldwide Exposure From 2001-2003 for Risperidone Intramuscular Formulation for Calculation of Reporting Rates

Year	Grams	mg/Week	g/Year	Person Years	Person Months
2001	10.0	37.5	0.975	10	123
2002	1,717.0	37.5	0.975	1,761	21,132
2003	17,483.3	37.5	0.975	17,932	215,178
Total	19,210.3	—	—	19,703	236,433

Table 3: Worldwide Exposure for Oral Risperidone for 2001-2003 for Calculation of Reporting Rates

Year	Indication	Grams/ Indication	Person Years	Person Months
2001	Schizophrenia	678,315.5	421,209	5,054,512
	Bipolar mania	271,326.2	308,887	3,706,642
	Senile dementia	339,157.7	926,661	11,119,926
	Other	972,252.2	1,106,844	13,282,133
	Sub-total	**2,261,051.6**	**2,763,601**	**33,163,213**
2002	Schizophrenia	728,078.4	452,110	5,425,323
	Bipolar mania	291,231.4	331,548	3,978,570
	Senile dementia	364,039.2	994,643	11,935,711
	Other	1,043,579.0	1,188,045	14,256,544
	Sub-total	**2,426,928.0**	**2,966,346**	**35,596,148**
2003	Schizophrenia	793,611.3	492,804	5,913,646
	Bipolar mania	317,444.5	361,390	4,336,674
	Senile dementia	396,805.6	1,084,168	13,010,021
	Other	1,137,509.5	1,294,979	15,539,747
	Sub-total	**2,645,370.9**	**3,233,341**	**38,800,088**

Table 4: Reporting Rates of Spontaneous Adverse Events With Risperidone Use in Patients Aged 5 to 17 Years From 2001 to 2003

Year	% Prescriptions in the 5-to-17-Years Age Group	Estimated Patient Exposure in the 5-to-17-Years Age Group (Person Years)	Number of Spontaneous Reports[a] in Patients Aged 5 to 17 Years Administered Risperidone	Estimated Reporting Rate (per 100, 000 Person Years)
2001	4.7%	129889	337	259[b]
2002	6.3%	186990	454	243[c]
2003	6.3%	204830	484	236[d]

a: Serious and nonserious

b: Calculations for year 2001: 2,763,611 person years x 4.7% = 129890 person years of pediatric exposure; 337/129889 = 259 cases per 100,000 person years.

c: Calculations for year 2002: 2,968,107 person years x 6.3% = 186991 person years of pediatric exposure; 454/186990 = 243 cases per 100,000 person years.

d: Calculations for year 2003: 3,251,272 person years x 6.3% = 204830 person years of pediatric exposure; 484/204830 = 236 cases per 100,000 person years.

Table 5: Distribution of Cases by Age

Age (yrs)	Number of Cases
5	96
6	128
7	137
8	193
9	198
10	215
11	174
12	209
13	243
14	259
15	345
16	323
17	343
"Child"	18
"Adolescent"	78
Indeterminable	189
Total	3148

Table 6: Distribution of Cases By Indication

Indication	Spontaneous Cases in Patients Aged 5 to 17 Years
Psychosis/Psychoses	399
Schizophrenic Disorder	329
Various Behavioral Disorders	231
Attention Deficient Disorder/Hyperactivity Disorder	218
Autistic Disorder	152
Bipolar Disorder	151
Other Diagnoses	1018
Indication Unknown	650

a: includes serious and nonserious cases received between May 31 1993 through 30 June 2004

Table 7: Distribution of Cases by Country of Origin

Country	Number of Cases	Country	Number of Cases
US	2199	Belgium	20
Canada	191	Spain	12
France	176	Ireland	12
UK	164	Denmark	11
Germany	138	Finland	11
Japan	55	New Zealand	11
The Netherlands	41	South Africa	10
Australia	40	Other[a]	57

a: Less than 10 reports each from Argentina, Austria, Brazil, Norway, Poland, Portugal, China, Czech Republic, Puerto Rico, Sweden, Guatemala, Israel, Switzerland, Turkey, Italy, Latvia, and Mexico.

Table 8: Number of Spontaneous Serious and Nonserious Cases in Patients Aged 5 to 17 Years and Number of Spontaneous Serious and Nonserious Cases in All Age Groups

	Serious Reports	Nonserious Reports	Total Reports	% of Reports That Are Serious
5 to 17 Years	587[a]	2561[b]	3148	18.6%
All Ages	6090	12157	18247	36.4%

a: Includes 20 cases in which the age is indeterminable
b: Includes 169 cases in which the age is indeterminable

Table 9: Observed Suicide Rate per 100,000 in Children Aged 5 to 17 Years Treated With Risperidone Compared to the Derived Rate of 3.67 Suicides per 100,000[a]

Year	Observed Number of Deaths Due to Suicide in Patients Aged 5 to 17 Administered Risperidone	Person Years of Exposure	Observed Rate of Suicides per 100,000
2001	2	129889	1.5
2002	0	186990	0
2003	1	204830	0.48

Note: Distribution of suicide reports by year was as follows: 1998, n=1; 2000, n=1; 2001, n=2; and 2003, n=1
a: Derived from 2001 suicide rates

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Table10: Distribution of Adverse Events by System Organ Class in Patients aged 5 to 17 Years and in Patients of all Other Ages

System Organ Class	Number of Spontaneous Serious Cases		% of Spontaneous Serious Cases		Proportional Ratio of Serious Cases[b]
	5 to 17 Years[a]	All Other Ages	5 to 17 Years	All Other Ages	
Blood & Lymphatic System Disorders	48	392	8.5	7.1	1.2
Cardiac Disorder	38	518	6.7	9.4	0.7
Congenital, Familial & Genetic Disorder	4	17	0.7	0.30	2.3 * 0.7/.30
Ear and Labyrinth Disorder	2	17	0.4	0.3	1.3
Endocrine Disorder	11	101	1.9	1.8	1.1
Eye Disorder	20	105	3.5	1.9	1.8
Gastrointestinal Disorder	64	399	11.3	7.2	1.6
General Disorders & Administration Site Conditions	148	1691	26.1	30.6	0.9
Hepatobiliary Disorders	12	142	2.1	2.5	0.8
Immune System Disorders	7	30	1.2	0.5	2.2 * 1.2/.05
Infections and Infestations	22	266	3.9	4.8	0.8
Injury, Poisoning & Procedural Complications	42	328	7.4	5.9	1.3
Investigations	103	712	18.2	12.9	1.4
Metabolism & Nutrition Disorders	41	406	7.2	7.3	<1.0
Musculoskeletal & Connective Tissue Disorders	22	252	3.9	4.6	0.8
Neoplasms Benign, Malignant & Unspecified (Incl Cysts & Polyps)	9	123	1.5	2.2	0.7
Nervous System Disorders	274	1974	48.3	35.7	1.4
Psychiatric Disorders	118	892	20.8	16.2	1.3
Renal & Urinary Disorders	31	218	5.5	3.9	1.4
Reproductive System & Breast	29	195	5.1	3.5	1.5
Respiratory, Thoracic & Mediastinal Disorders	47	343	8.2	6.2	1.3
Skin & Subcutaneous Tissue Disorder	29	205	5.1	3.7	1.4
Social Circumstances	1	37	0.2	0.7	0.3
Surgical and Medical Procedures	2	57	0.4	1.0	0.4
Vascular Disorders	25	285	4.4	5.2	0.8
Total Number of Cases	587	5503			

a: Excludes the 20 cases in which age was indeterminable

b: % of spontaneous serious cases in ages 5-17 years divided by the % of spontaneous serious cases in all other ages

Table 11: Reporting Rates by Age for Specific Adverse Events of Interest

Adverse Event of Interest	Reporting Rate: Ages 5 to 17 Years Per 100,000 PY[a]		
	2001	2002	2003
Tardive Dyskinesia	8.4	2.6	3.4
Hyperprolactinemia	18.4	12.3	15.1
Gynaecomastia	12.3	6.4	9.7
Pituitary Tumor	0.76	0.53	0.48
Impaired Glucose/Diabetes Mellitus[b]	2.3	1.06	2.9
Completed Suicide	0.76	1.06	0.48
Suicide Ideation and/or Attempt	2.3	1.6	2.9

a: PY=Person Years

b: Includes diabetes mellitus non-insulin dependent, diabetes mellitus insulin dependent, diabetes mellitus aggravated, diabetes mellitus NOS, diabetic ketoacidosis, glucose tolerance impaired, and hyperglycemia NOS

Table 12: Proportional Reporting Rates of Adverse Events of Interest

Adverse Event of Interest	Proportional Reporting Rates in Patients Aged 5 to 17 Years as Compared to All Other Ages[a]		
	2001	2002	2003
Tardive Dyskinesia	1.8 (11/337) / (39/2174)	0.64 (5/454) / (54/3087)	1.0 (7/484) / (53/3750)
Hyperprolactinemia	1.6 (24/337) / (96/2174)	0.96 (23/454) / (162/3087)	2.7 (31/484) / (88/3750)
Gynaecomastia	4.7 (16/337) / (22/2174)	4.3 (12/454) / (19/3087)	5.6 (20/484) / (27/3750)
Pituitary Tumor	0.90 (1/337) / (7/2174)	1.0 (1/454) / (7/3087)	0.4 (1/484) / (21/3750)
Impaired Glucose/Diabetes Mellitus[b]	0.88 (3/337) / (24/2174)	0.29 (2/454) / (47/3087)	0.9 (6/484) / (56/3750)
Completed Suicide	0.42 (1/337) / (15/2174)	1.0 (2/454) / (13/3087)	0.40 (1/484) / (19/3750)
Suicide ideation and/or attempt	0.92 (3/337) / (21/2174)	1.1 (3/454) / (18/3087)	1.0 (6/484) / (40/3750)
Total Number of Reports in Patients Aged 5 to 17 years (All Other Ages)	337 (2174)	454 (3087)	484 (3750)

a: calculations in each cell represent: (number of reports of specific AE in 5-17 year olds/total number of spontaneous reports in 5-17 year olds) / (number of reports of specific AE in all other age groups/total number of spontaneous reports in all other age groups)

b: Includes diabetes mellitus non-insulin dependent, diabetes mellitus insulin dependent, diabetes mellitus aggravated, diabetes mellitus NOS, diabetic ketoacidosis, glucose tolerance impaired, and hyperglycemia NOS

7. ATTACHMENTS

Frequency Report - Tabulation

Query Report Name: Frequency Tabulation
Total # of Cases: 2392

System Organ Class	Cases per SOC	Adverse Event(s)	Cases per Adverse Event
		DRY SKIN	2
		ECZEMA	2
		ERYTHEMA	1
		FACE OEDEMA	5
		HAIR GROWTH ABNORMAL	3
		HAIR TEXTURE ABNORMAL	1
		HYPERTRICHOSIS	3
		HYPOTRICHOSIS	2
		LICHEN PLANUS	1
		PHOTOSENSITIVITY REACTION NOS	5
		PIGMENTATION DISORDER NOS	2
		PRURITUS	15
		PURPURA NOS	3
		RASH ERYTHEMATOUS	2
		RASH GENERALISED	1
		RASH MACULAR	3
		RASH MACULO-PAPULAR	3
		RASH NOS	51
		RASH PAPULAR	1
		SEBORRHOEA	1
		SKIN DISCOLOURATION	2
		SKIN HYPERPIGMENTATION	3
		SKIN ODOUR ABNORMAL	2
		SKIN STRIAE	11
		SWEATING INCREASED	17
		SWELLING FACE	1
		SYSTEMIC LUPUS ERYTHEMATOSUS RASH	1
		URTICARIA ACUTE	1
		URTICARIA NOS	12
		VITILIGO	1

Frequency Report - Tabulation

Query Report Name: Frequency Tabulation
Total # of Cases: 2392

System Organ Class	Cases per SOC	Adverse Event(s)	Cases per Adverse Event
SOCIAL CIRCUMSTANCES (10041244)	2		
		DRUG ABUSER NOS	2
SURGICAL AND MEDICAL PROCEDURES (10042613)	1		
		ABORTION INDUCED NOS	1
VASCULAR DISORDERS (10047065)	44		
		FLUSHING	9
		HOT FLUSHES NOS	6
		HYPERTENSION	1
		AGGRAVATED HYPERTENSION NOS	7
		HYPOTENSION NOS	7
		ORTHOSTATIC HYPOTENSION	5
		PALLOR	2
		PERIPHERAL COLDNESS	2
		PETECHIAE	1
		RAYNAUD'S PHENOMENON	2
		VASOCONSTRICTION	1
		VASODILATATION	1

Attachment 3

Serious Adverse Events in Which Age Was Indeterminable With Risperidone as Suspect or Concomitant Medication - Frequency Tabulations From SCEPTRE Database From March 1993 Through June 2004

Frequency Report - Tabulation

Run Information

User Name:	Pereira, Ed (176388)
Run Date:	27-Sep-2004

Parameters

Report Query Name:	Frequency Tabulation
Results:	20 cases selected from 20 matching the following criteria
Status:	NOT = Deleted
Query Report:	= HD0117723 Risperidone #2 (Undeterminable Age) (Generic Drug Name RISPERIDONE, Case Criteria From Provided Spreadsheet)
Query Report Case Included in report:	= Yes
Last Distributed:	= Yes
First Case Version Initially Received:	BETWEEN (01-Mar-1993, 30-Jun-2004)
Serious:	= (Yes)

Frequency Report - Tabulation

Query Report Name: Frequency Tabulation
Total # of Cases: 20

System Organ Class	Cases per SOC	Adverse Event(s)	Cases per Adverse Event
BLOOD AND LYMPHATIC SYSTEM DISORDERS (10005329)	1		
		THROMBOCYTOPENIA	1
CARDIAC DISORDERS (10007541)	2		
		BRADYCARDIA NOS	1
		VENTRICULAR TACHYCARDIA	1
ENDOCRINE DISORDERS (10014698)	1		
		ACQUIRED HYPOTHYROIDISM	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS (10018065)	5		
		ADVERSE EVENT NOS	1
		CONDITION AGGRAVATED	1
		DEATH NOS	2
		NEUROLEPTIC MALIGNANT SYNDROME	1
IMMUNE SYSTEM DISORDERS (10021428)	2		
		ANAPHYLACTIC REACTION	1
		ANAPHYLACTOID REACTION	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS (10022117)	1		
		MEDICATION ERROR	1
INVESTIGATIONS (10022891)	2		
		BLOOD CREATINE PHOSPHOKINASE INCREASED	1
		LIVER FUNCTION TESTS NOS ABNORMAL	1
		WEIGHT INCREASED	1
NERVOUS SYSTEM DISORDERS (10029205)	8		
		COMA	1
		CONVULSIONS NOS	2
		EPILEPSY NOS	2
		TARDIVE DYSKINESIA	3

Frequency Report - Tabulation

Query Report Name: Frequency Tabulation
Total # of Cases: 20

System Organ Class	Cases per SOC	Adverse Event(s)	Cases per Adverse Event
PSYCHIATRIC DISORDERS (10037175)	1		
		SUICIDE ATTEMPT	1
RENAL AND URINARY DISORDERS (10038359)	1		
		RENAL IMPAIRMENT NOS	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS (10038738)	1		
		RESPIRATORY DISTRESS	1
VASCULAR DISORDERS (10047065)	1		
		HYPERTENSION NOS	1

Attachment 4

Nonserious Adverse Events in Which Age Was Indeterminable With Risperidone as Suspect or Concomitant Medication - Frequency Tabulations From SCEPTRE Database From March 1993 Through June 2004

Frequency Report - Tabulation

Run Information

User Name:	Pereira, Ed (176388)
Run Date:	27-Sep-2004

Parameters

Report Query Name:	Frequency Tabulation
Results:	169 cases selected from 169 matching the following criteria
Status:	NOT = Deleted
Query Report:	= HD0117723 Risperidone #2 (Undeterminable Age) (Generic Drug Name RISPERIDONE, Case Criteria From Provided Spreadsheet)
Query Report Case Included in report:	= Yes
Last Distributed:	= Yes
First Case Version Initially Received:	BETWEEN (01-Mar-1993, 30-Jun-2004)
Serious:	= (No)

Frequency Report - Tabulation

Query Report Name: Frequency Tabulation
Total # of Cases: 169

System Organ Class	Cases per SOC	Adverse Event(s)	Cases per Adverse Event
BLOOD AND LYMPHATIC SYSTEM DISORDERS (10005329)	2		
		NEUTROPENIA	1
		THROMBOCYTOPENIA	1
CARDIAC DISORDERS (10007541)	5		
		TACHYCARDIA NOS	5
CONGENITAL, FAMILIAL AND GENETIC DISORDERS (10010331)	1		
		FACIAL DYSMORPHISM	1
ENDOCRINE DISORDERS (10014698)	10		
		ANTIDIURETIC HORMONE ABNORMALITY	1
		HIRSUTISM	1
		HYPERPROLACTINAEMIA	8
GASTROINTESTINAL DISORDERS (10017947)	23		
		DYSPEPSIA	2
		DYSPHAGIA	4
		NAUSEA	1
		OESOPHAGEAL SPASM	1
		SALIVARY HYPERSECRETION	5
		STOMATITIS	1
		SWOLLEN TONGUE	6
		TONGUE OEDEMA	1
		TOOTH DISORDER NOS	1
		VOMITING NOS	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS (10018065)	13		
		CONDITION AGGRAVATED	4
		FATIGUE	1
		LETHARGY	2
		MASS NOS	1
		OEDEMA PERIPHERAL	1

Frequency Report - Tabulation

Query Report Name: Frequency Tabulation
Total # of Cases: 169

System Organ Class	Cases per SOC	Adverse Event(s)	Cases per Adverse Event
		THERAPEUTIC RESPONSE DECREASED	2
		THIRST	1
		UNEXPECTED THERAPEUTIC DRUG EFFECT	1
HEPATOBILIARY DISORDERS (10019805)	1		
		HEPATOTOXICITY NOS	1
INFECTIONS AND INFESTATIONS (10021881)	1		
		VIRAL INFECTION NOS	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS (10022117)	2		
		MEDICATION ERROR	2
INVESTIGATIONS (10022891)	44		
		BLOOD OESTROGEN INCREASED	1
		BLOOD PROLACTIN INCREASED	1
		LABORATORY TEST ABNORMAL NOS	2
		LIVER FUNCTION TESTS NOS ABNORMAL	3
		URINE VOLUME INCREASED	1
		WEIGHT INCREASED	36
		WHITE BLOOD CELL COUNT DECREASED	1
METABOLISM AND NUTRITION DISORDERS (10027433)	5		
		APPETITE INCREASED NOS	2
		ELECTROLYTE IMBALANCE	1
		FLUID RETENTION	1
		HYPERCHOLESTEROLAEMIA	1
		HYPERTRIGLYCERIDAEMIA	1
NERVOUS SYSTEM DISORDERS (10029205)	28		
		AKATHISIA	2
		COORDINATION ABNORMAL NOS	1
		DYSKINESIA	4
		DYSTONIA	2

Frequency Report - Tabulation

Query Report Name: Frequency Tabulation
Total # of Cases: 169

System Organ Class	Cases per SOC	Adverse Event(s)	Cases per Adverse Event
		EXTRAPYRAMIDAL DISORDER	4
		FACIAL PALSY	1
		LOSS OF CONSCIOUSNESS	1
		OCULOGYRIC CRISIS	1
		SEDATION	2
		SENSORY DISTURBANCE NOS	1
		SOMNOLENCE	3
		STUPOR	2
		TARDIVE DYSKINESIA	2
		TONGUE PARALYSIS	1
		TREMOR	4
PSYCHIATRIC DISORDERS (10037175)	11		
		AGGRESSION	3
		AGITATION	1
		ANXIETY	1
		CONFUSIONAL STATE	1
		INSOMNIA	1
		MANIA	2
		NEUROSIS NOS	1
		PARANOIA AGGRAVATED	1
RENAL AND URINARY DISORDERS (10038359)	22		
		ENURESIS	9
		HAEMATURIA	1
		MICTURITION URGENCY	1
		URINARY FREQUENCY	1
		URINARY INCONTINENCE	10
		URINARY RETENTION	1
REPRODUCTIVE SYSTEM AND BREAST DISORDERS (10038504)	14		
		BREAST MASS NOS	1

Frequency Report - Tabulation

Query Report Name: Frequency Tabulation
Total # of Cases: 169

System Organ Class	Cases per SOC	Adverse Event(s)	Cases per Adverse Event
		GALACTORRHOEA	8
		GYNAECOMASTIA	5
		PELVIC PAIN NOS	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS (10038738)	7		
		DYSPNOEA NOS	1
		EPISTAXIS	5
		HICCUPS	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS (10040785)	14		
		ALOPECIA	1
		DERMATITIS EXFOLIATIVE NOS	1
		PHOTOSENSITIVITY REACTION NOS	1
		PURPURA NOS	2
		RASH MACULAR	1
		RASH NOS	4
		SKIN STRIAE	2
		STEVENS JOHNSON SYNDROME	1
		URTICARIA NOS	1
VASCULAR DISORDERS (10047065)	2		
		HYPERTENSION NOS	1
		PETECHIAE	1