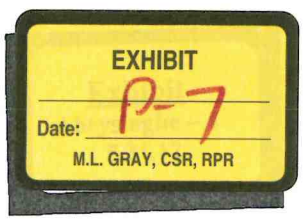
SAFETY OF RISPERIDONE IN NEONATES, INFANTS, CHILDREN, AND ADOLESCENTS

July 29, 1996

PLAINTIFF'S EXHIBIT 7



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LIST OF ABBREVIATIONS

ADHD	attention-deficit hyperactivity disorder
bpm	beats per minute
CT	computed tomography
DR	dose reduced
DI	dose increased
DS	drug stopped
D▲	dose changed; new dose not specified
EPS	extrapyramidal symptoms
H	hospitalization
MRI	magnetic resonance imaging
NMS	neuroleptic malignant syndrome
NR	not recovered at time of report
NMS	neuroleptic malignant syndrome
NS	not specified in report
OC	obsessive-compulsive disorder
R	resolved
R/D	resolved with reduction in dose
R/T	resolved with treatment
Rx	prescription or supportive therapy
TSH	thyroid-stimulating hormone
U	unknown
WHOART	world health organization adverse reaction terminology

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1. INTRODUCTION

Limited evidence regarding the effectiveness and safety of risperidone in the pediatric population (i.e., those less than 16 years of age) has been obtained. Risperidone, however, has been reported in the literature[6,7,8,20,21] to be effective and safe in children and adolescents in controlling the symptoms of a variety of psychiatric disorders, including schizophrenia, attention-deficit hyperactivity disorder, bi-polar disorder, depression, obsessive-compulsive disorder, and Tourette's syndrome.

The present summary is intended to review the reported safety of risperidone in four age categories:

- neonates birth up to 1 month,
- infants 1 month up to 2 years,
- children 2 years up to 12 years, and
- adolescents 12 years up to 16 years.

The safety information on the use of risperidone in these four age categories was derived from three sources: 1) clinical trials of risperidone conducted by Janssen; 2) spontaneous adverse events[1] reported during the period from January 1993 to March 31, 1996; and 3) medical literature. The medical literature was obtained through an in-house database that includes the following sources: 1) approximately 700 in-house journals; 2) literature searches from Medline and Embase; and 3) publications from Janssen affiliates worldwide. The database contained medical literature from 1986 (the beginning of drug development) through December, 1995. The literature search was conducted on January 15, 1996.

To facilitate review, all safety information in this summary has been presented by age category and then within each age category according to the source of the information. In addition, safety information for children and adolescents whose ages were not reported has been presented separately in Section 6.

In accordance with 21 CFR 310.305(b)(4), 312.32(a), 314.80(a) and 600.80(a), all serious adverse events included in this summary were defined as any event that was fatal or life threatening, permanently disabling, requiring in-patient hospitalization, or was a congenital anomaly, cancer, or overdose.

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2. SAFETY IN NEONATES (BIRTH UP TO 1 MONTH)

2.A. JANSSEN-SPONSORED CLINICAL STUDIES

No studies have been conducted in this age group by the sponsor.

2.B. PUBLISHED STUDIES AND CASE REPORTS

No studies have been conducted on the use of risperidone in neonates. No case reports have been published.

2.C. SPONTANEOUS ADVERSE DRUG EVENT REPORTS

Three spontaneous adverse events were reported for this age category during the period from January 1993 to March 31, 1996.

2.C.1. SERIOUS ADVERSE DRUG EVENTS

Of the 3 spontaneous adverse drug events reported for this age category, 2 were considered serious. A serious adverse event was defined as any event that was fatal or life threatening, permanently disabling, requiring in-patient hospitalization, or was a congenital anomaly, cancer, or overdose. Case narratives are provided below for all adverse events (serious and not serious) that were reported for this age category.

Case No. 40291: A one-week old neonate (gender not specified) born to a mother on long-term risperidone and Zoloft® (sertraline) therapy was normal at birth but within one week of birth experienced severe nervousness. A physical examination of the infant 19 hours after birth revealed increased muscle tone and jitteriness. The symptoms decreased 8 hours later and blood glucose was normal. No action was taken and the baby was discharged 38 hours after birth. Outcome: unknown.

Case No. 21733: A neonate (gender and age not specified) with congenital agenesia of the corpus callosum was born by caesarean section to a 34-year-old mother who had taken risperidone (dose not specified) and a number of concomitant medications during pregnancy. Risperidone was discontinued after 3½ days of therapy but many of the concomitant medications were continued throughout pregnancy. The concomitant medications included haloperidol, promethazine, zuclopenthixol, temazepam, thiamazol, perphenazine, biperiden, propylthiouracil, iron, and folic acid. Several of the concomitant medications

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were known to have teratogenic potential. The congenital anomaly was considered a serious adverse event. The action taken for the event was not specified. Outcome: alive sequelae.

Case No. 45026: A neonate (gender and age not specified) was born 10 weeks pre-term with a serious brain anomaly to a mother who had started taking risperidone during pregnancy. Other medications taken by the mother concomitantly during pregnancy included carbamazepine, paroxetine, flupentixol, and procyclidine. A brain scan of the neonate showed bleeding from a ventricular cyst, which was attributed by the reporting doctor to prematurity rather than drug effect. The neonate was under pediatric surveillance and was last seen to be developing normally, although the head circumference was above the 97 percentile. Outcome: congenital anomaly; developing normally.

2.C.2. Treatment Discontinuation

Information pertaining to the discontinuation of treatment for this age category was not specified in the spontaneous adverse event reports.

3. SAFETY IN INFANTS (1 MONTH UP TO 2 YEARS)

3.A. Janssen-Sponsored Clinical Studies

No studies have been conducted in this age group by the sponsor.

3.B. Published Studies and Case Reports

No studies have been conducted on the use of risperidone in infants. No case reports have been published.

3.C. Spontaneous Adverse Drug Event Reports

During the period from January 1993 to March 31, 1996, 4 cases of spontaneous adverse drug events in infants were reported.

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3.C.1. Serious Adverse Drug Events

Of the 4 spontaneous adverse drug events reported for this age category, 3 were considered serious. Table 1 and the following case narratives provide a summary of all adverse events (serious and not serious) that were reported for this age category.

Case No. 27705: A 20-month-old infant, whose gender was not specified, ingested an unknown amount of risperidone and experienced agitation and seizures, which were regarded as serious. The infant was admitted to the emergency room where vital signs were reported to be stable. Additional information was requested from the reporting physician. Outcome: unknown.

Case No. 42581: A 23-month-old boy accidentally ingested a 1-mg risperidone tablet and was found with a partially dissolved tablet in his mouth. The infant was evaluated by a pediatrician at an acute care medical facility. Although the infant remained clinically asymptomatic, diphenhydramine was administered as a prophylactic measure. Outcome: recovered.

Case No. 28254: A 20-month-old girl was suspected of ingesting ten 2-mg risperidone tablets. The event was reported as a serious adverse event. In the emergency room, the infant was given 2 separate doses of ipecac syrup, which induced vomiting both times. The infant was admitted to the pediatric intensive-care unit for observation. Cardiac monitoring indicated no arrhythmias or prolongation of the QT interval. Twenty-four hours later, the patient still had experienced no adverse events and the QT interval remained normal. Outcome: recovered.

Case No. 35521: An 18-month-old boy ingested one-half of a 3-mg risperidone tablet. He was seen in the emergency room within 2 hours, received charcoal and lavage, and experienced no adverse effects. Outcome: recovered.

3.C.2. Treatment Discontinuation

All spontaneous adverse events reported for this age category involved accidental ingestions of risperidone. In all cases, risperidone was discontinued.

Table 1. Summary of pharmacovigilance reports of adverse drug events in infants (1 month up to 2 years)

Case No.	Body System Adverse Event	Age (months) /Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
27705*	Central & peripheral nervous seizures	20/NS	U	NA	NA	Rx/DS	U
42581*	Psychiatric drug abuse	23/M	1	NA	NA	Rx/DS	R
28254*	Body as a whole therapeutic response increased	20/F	20	NA	NA	Rx/DS/H	R
35521	therapeutic response increased	18/M	1.5	NA	NA	Rx/DS	R
Total number of adverse events reported in infants: 4							

*Adverse events were regarded as serious. NA=not applicable; NS=not specified; R=recovered; U=unknown; H=hospitalization; DS=drug stopped; Rx=prescription or supportive therapy.

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4. SAFETY IN CHILDREN (2 YEARS UP TO 12 YEARS)

4.A. JANSSEN-SPONSORED CLINICAL STUDIES

The safety and tolerability of risperidone in children have been evaluated in 2 clinical studies. The safety information for the children who participated in these trials and who met the age criteria for inclusion in this safety review is summarized below and in Table 2.

Study No. RIS-BEL-21 (Part I and Part II): This open trial evaluated the pharmacokinetics and prolactin response (Part I)[2] and the tolerability and cardiovascular and laboratory safety (Part II)[3] of a single oral dose of risperidone in 6 healthy autistic children aged 3 through 7 years (mean: 4.7 years). A risperidone oral solution of 0.5 mg/mL (Lot No. 92H26/F45) was used in the trial. During the trial, each child received a single oral dose (0.03 mg/kg or 0.015 mg/kg) of risperidone with 30 mL of water. The dose was equivalent to 2 mg or 1 mg of risperidone administered to adult subjects with an average body weight of 70 kg. The drug intake was at least one hour before breakfast.

Following treatment, the patients were evaluated over a 3-day trial period. Patients 1, 2, and 3 received 0.03 mg/kg (range: 0.5-1.1 mg); Patients 4, 5, and 6 received 0.015 mg/kg (range: 0.3-0.4 mg). Except for a transient increase in heart rate in 2 patients (Patients 5 and 6) 1 to 2 hours after drug intake, no clinically important changes were observed in laboratory and cardiovascular safety measures. Somnolence was experienced by 5 children (Patients 1, 2, 3, 5, and 6), the degree of sedation being more pronounced after a dose of 0.03 mg/kg than after 0.015 mg/kg. One child (Patient 2) developed a fever on the third day of the trial and another child (Patient 5), who caught a cold before entering the trial, had diarrhea after treatment with risperidone. Overall, risperidone was well tolerated in the trial. Results did not show any clear differences between adults and children in tolerability and laboratory and cardiovascular safety. The safety information for all 6 patients is summarized below.

Patient 1 was a 3-year-old boy with autistic disorder, who weighed 17.5 kg and was 106.4 cm in height. The patient also had a history of eczema and asthmatiform bronchitis. The patient received a single risperidone dose of 0.03 mg/kg (0.5 mg); Varlane® was administered concomitantly for treatment of eczema. One to 2.5 hours after treatment, the patient became sedated. No clinically important changes were observed in any of the investigated laboratory and cardiovascular safety parameters and none of the adverse events resulted in discontinuation of treatment.

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Patient 2 was a 3-year-old boy with autistic disorder, who weighed 15.3 kg and was 100.5 cm in height. The patient received a single risperidone dose of 0.03 mg/kg (0.45 mg) with no concomitant medications. One to 2.5 hours after the administration of treatment, the patient developed moderate to severe sedation and then slept for 30 minutes to 2 hours. On Day 3 of the trial, the patient developed a fever. No clinically important changes were observed in any of the investigated laboratory and cardiovascular safety parameters. None of the adverse events resulted in discontinuation of treatment.

Patient 3 was a 7-year-old boy with autistic disorder, who weighed 37.0 kg and was 130.0 cm in height. The patient received a single risperidone dose of 0.03 mg/kg (1.1 mg) with no concomitant medications. One to 2.5 hours after drug intake, the patient developed moderate to severe sedation and then slept for 30 minutes to 2 hours. No clinically important changes were observed in any of the investigated laboratory and cardiovascular safety parameters. None of the adverse events resulted in discontinuation of treatment.

Patient 4 was a 5-year-old boy with autistic disorder, who weighed 18.8 kg and was 111.2 cm in height. The patient received a single risperidone dose of 0.015 mg/kg (0.275 mg) with no concomitant medications. No clinically important changes were observed in any of the investigated laboratory and cardiovascular safety parameters. The patient completed the trial with no adverse effects.

Patient 5 was a 4-year-old boy with autistic disorder (and a cold at the time of entry into the trial), who weighed 24.3 kg and was 115.1 cm in height. The patient received a single risperidone dose of 0.015 mg/kg (0.035 mg) with no concomitant medications. One to 2.5 hours after treatment, the patient developed somnolence. At 3.5 and 6.5 hours after receiving treatment, the patient had diarrhea. No clinically important changes were observed in any of the investigated laboratory and cardiovascular safety parameters except for a transient increase in heart rate 1 to 2 hours after drug intake. None of the adverse events resulted in discontinuation of treatment.

Patient 6 was a 6-year-old boy with autistic disorder, who weighed 19.5 kg and was 112.3 cm in height. The patient received a single risperidone dose of 0.015 mg/kg (0.30 mg) with no concomitant medication. Beginning 1 to 2.5 hours after drug intake, the patient developed somnolence. No clinically important changes were observed in any of the investigated laboratory and cardiovascular safety parameters except for a transient increase in heart rate 1 to 2 hours after drug intake. None of the adverse events resulted in discontinuation of treatment.

Study No. RIS-BEL-22: In this multicenter, dose-titration study,[4] risperidone was administered orally for 4 weeks to 7 patients with autistic disorder. Of these patients, 6 were children (3 through 9 years) and 1 was an adolescent (14 years).

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A risperidone oral solution containing 0.5 mg/mL (Lot No. 91A24/F2) was administered under open conditions twice daily. The daily dose of risperidone starting at 0.01 mg/kg on the first day was gradually increased for each patient in the course of the first week. On the seventh day of the study, the mean daily dose for all patients (including the adolescent) was 0.019 mg/kg (range: 0.01-0.041 mg/kg). Throughout the remainder of the study, there was a slow increase in the mean daily dose for all patients except for Patient 8 (and the adolescent, Patient 6), reaching 0.035 mg/kg on Day 28 (range: 0.014-0.072 mg/kg). The incidence of adverse events during the course of therapy with risperidone was low. The adverse events reported were fatigue, vomiting, weight increase, insomnia, increased alkaline phosphatase, rhinitis, "*absences*" (a term commonly used in French for a variety of minor epileptic seizures including those covered in English by the term *petit mal)*, and coma. All adverse events, except coma, were rated as mild to moderate in severity. None of the adverse events resulted in discontinuation of treatment. Safety information for the children (Patients 1, 2, 3, 4, 5, and 8) is summarized below; information for the adolescent (Patient 6) is summarized in Section 5.A.

Patient 1 was a 9-year-old boy with autism who weighed 33.5 kg and was 138 cm in height. The patient was treated with risperidone at a starting dose of 0.01 mg/kg/day for lack of eye contact. The daily dose was gradually increased during the course of the study to 0.04 mg/kg (1.34 mg). No concomitant medications were administered. At regular intervals on the first day of the study, the patient reported mild insomnia, which was considered by the investigator to be related to treatment. The risperidone dose was not reduced or discontinued as a result of the adverse event.

Patient 2 was a 5-year-old boy with autism and severe mental retardation, who weighed 18.5 kg and was 123 cm in height. The patient was treated with risperidone at a starting dose of 0.01 mg/kg/day for stereotypic movements. The daily dose was gradually increased during the course of the study to 0.08 mg/kg (1.48 mg). During the study, the patient was also administered an antitussive (Bronchosedal®). On the fifth day of the study, the patient reportedly took an overdose (25 mL) of the antitussive and became heavily sedated. The investigator recorded "subcomatose" on the patient's case report form for this event. The report of "subcomatose" was characterized according to World Health Organization Adverse Reaction Terminology (WHOART) as "coma." Although the event was regarded as serious, it did not entail a loss of consciousness. The event resolved without treatment and with no residual effects. In the opinion of the investigator, the event was not related to treatment with risperidone. Mild insomnia was also reported by this patient during the study. The event was attributed to the study drug but resolved without discontinuation of treatment or a reduction in the risperidone dose. No residual effects were reported.

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Patient 3 was a 3-year-old boy with autistic disorder and mild mental retardation, who weighed 17.6 kg and was 107 cm in height. The patient was treated with risperidone at a starting dose of 0.01 mg/kg/day (0.176 mg) for aggressive behavior. The daily dose was gradually increased to 0.06 mg/kg (1.056 mg) during the course of the study with no adverse effects. Levocarnitine was also administered as a concomitant dietary supplement to the patient during the study.

Patient 4 was a 6-year-old boy with autistic disorder and moderate mental retardation, who weighed 29.5 kg and was 127.5 cm in height. Risperidone at a starting dose of 0.01 mg/kg/day (0.295 mg) was administered to the patient for lack of eye contact and was gradually increased during the course of the study to 0.06 mg/kg/day (1.77 mg). No concomitant medications were administered. During the study, the patient reportedly experienced mild rhinitis (Day 4), a moderate increase in alkaline phosphatase (Day 30), and moderate weight gain (days in treatment not specified). In the opinion of the investigator, all events except the rhinitis were considered to be possibly related to treatment with risperidone. [The report of rhinitis was not considered to be related to treatment.] None of the events required an adjustment to the risperidone dose or led to discontinuation of treatment. At the time of reporting, the weight gain and increase in alkaline phosphatase were unresolved.

Patient 5 was a 7-year-old girl with autism and severe mental retardation, who weighed 19.5 kg and was 122 cm in height. Risperidone at a starting dose of 0.01 mg/kg/day (0.195 mg) was administered because of previous self-injury. The dose was gradually increased to 0.08 mg/kg/day until the third week (Day 21) of the study when the patient reportedly experienced moderate fatigue, vomiting, and weight gain. All events according to the investigator were considered to be possibly related to treatment. Because of the adverse events, the daily dose of risperidone was kept constant at 0.08 mg/kg (1.56 mg) for the remainder of the study. No concomitant medications were administered. At the time of reporting, the patient had recovered from the events with no residual effects.

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Patient 8 was a 9-year-old girl with autistic disorder, severe mental retardation, and epilepsy, who weighed 34.6 kg and was 140 cm in height. Risperidone at a starting dose of 0.01 mg/kg/day (0.346 mg) was administered to the patient for a behavioral disturbance. The dose was gradually increased in the course of the first week but was kept constant for the remainder of the study at 0.08 mg/kg/day (2.768 mg). Antiepileptic medication (carbamazepine) was administered concomitantly throughout the study. Beginning on Day 17 of the study, the patient reportedly experienced mild, intermittent *absences* (a term commonly used in French for a variety of minor epileptic seizures, including those covered in English by the term *petit mal*). In the opinion of the investigator, the events were considered to be possibly related to treatment. The event did not lead to discontinuation of the study drug.

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Table 2. Summary of adverse drug events elicited in clinical studies of risperidone in children (2 years up to 12 years)

Study No. Accession No. *Publication*	Patient	Age/ Sex	Body System Adverse Event	Dose (mg/day) at Onset	Time on Drug at Onset (days)	Diagnosis	Concomitant Drugs	Action Taken	Outcome
RIS-BEL-21/II N 102241/1 N/A	1	3/M	Psychiatric somnolence	0.5	1	autism, eczema, bronchitis	Variane®	none	R
RIS-BEL-21/II N 102241/1 N/A	2	3/M	Body as a whole fever Psychiatric somnolence	0.45 0.45	3 1	autism	none	none	R R
RIS-BEL-21/II N 102241/1 N/A	3	7/M	Psychiatric somnolence	1.1	1	autism	none	none	R
RIS-BEL-21/II N 102241/1 N/A	5	4/M	Gastrointestinal diarrhea Psychiatric somnolence	0.035 0.035	1 1	autism, cold	none	none	R R
RIS-BEL-21/II N 102241/1 N/A	6	6/M	Psychiatric somnolence	0.30	1	autism	none	none	R
RIS-BEL-22 N 121131 N/A	1	9/M	Psychiatric insomnia	1.34 *	1	autism	none	none	R
RIS-BEL-22 N 121131 N/A	2	5/M	Psychiatric insomnia Central & peripheral nervous coma†	1.48 ‡ 1.48	8 5	autism, mental retardation	Bronchosedal® overdose	NS	R R
RIS-BEL-22 N 121131 N/A	4	6/M	Metabolic & nutritional weight increase high alkaline phosphatase Respiratory rhinitis	1.77 § 1.77 1.77	NS 30 4	autism, mental retardation	none	none	NR R

*Dose was based on 0.04 mg/kg/day; †Coma=WHOART term for report recorded as "subcomatose" (the event did not entail loss of consciousness); ‡dose was based on 0.08 mg/kg/day; §dose was based on 0.06 mg/kg/day.
NR=not recovered at time of report; R=resolved; NS=not specified.

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Table 2. (Continued)...Summary of adverse drug events elicited in clinical studies of risperidone in children (2 years up to 12 years)

Study No. Accession No. *Publication*	Patient	Age/Sex	Body System Adverse Event	Dose (mg/day) at Onset	Time on Drug at Onset(days)	Diagnosis	Concomitant Drugs	Action Taken	Outcome
RIS-BEL-22 N 121131 N/A	5	7/F	Body as a whole fatigue Gastrointestinal vomiting Metabolic & nutritional weight increase	1.56* 1.56 1.56	21 21 21	autism, mental retardation	none	dose reduced	R R R
RIS-BEL-22 N 121131 N/A	8	9/F	Central & peripheral nervous absences †	2.8 ‡	17	epilepsy, autism, mental retardation	carbamazepine	none	NR

N/A=not applicable; NS=not specified in study; NR=not recovered at time of report; R=resolved.
*Dose was based on 0.08 mg/kg/day; †Absences=a term commonly used in French for a variety of minor epileptic seizures, including those covered in English by the term *petit mal*;
‡Dose was based on 0.08 mg/kg/day.

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4.B. Published Studies and Case Reports

The safety of risperidone in children as reported in publications of clinical studies and case histories is summarized below and in Tables 3 and 4.

Lombroso et al reported safety information from an 11-week, open-label trial,[5] which included 7 patients (5 boys and 2 girls) with a mean age of 12.9 ± 1.9 years. Of these patients, 1 was a child (age: 11 years) and 5 were adolescents (ages: 12-13 years). One patient (Patient 7), who was 16 years old, did not meet the age criteria for inclusion in this review. The objective of the trial was to evaluate the short-term efficacy and safety of risperidone in the treatment of chronic tic disorders in children and adolescents. The patients were seen at baseline and for two follow-up visits over an 11-week period. Risperidone appeared to be effective in reducing tic frequency and intensity in these patients. The most frequent side effect was weight gain, which ranged from 8 to 14 pounds. Safety information for the child (Patient 1) is provided below; safety information for the 5 adolescents (Patients 2, 3, 4, 5, and 6) is provided in Section 5.B. General safety information for patients for whom the age and sex were not specified in the report is provided in Section 6.

Patient 1 was an 11-year-old boy diagnosed with Tourette's syndrome. Risperidone was initiated at a starting dose of 0.5 mg on the first day and then increased by 0.5 mg every 5 days up to 1 mg/day. (A maximum dose of 5 mg/day was permitted under the protocol for the study.) An antihypertensive (clonidine 0.15 mg/day) was administered concomitantly. By the end of the study (11 weeks), the patient had gained weight. The amount of weight gained was not specified, however, weight gain for all patients ranged from 8 to 14 pounds.

Mandoki reported safety information from open clinical trials[6] in which 10 patients participated. Of these patients, 7 were children (7 to 11 years of age) and 1 an adolescent (12 years of age) refractory to previous treatment with other psychotropic drugs; 2 patients aged 17 years did not meet the age criteria for inclusion in this safety review. A variety of disorders were represented by the 7 children -- schizophrenia, bipolar disorder, major depression with psychotic features, Tourette's syndrome, obsessive-compulsive disorder, and post-traumatic stress disorder. Five of the 7 patients experienced at least one adverse event after risperidone treatment in doses ranging from 2 to 6 mg/day for 6-16 weeks. The adverse events were depression, weight gain, and extrapyramidal symptoms. Safety information for the 7 children (Patients 1, 2, 3, 4, 5, 6, and 7) is discussed below; information for the adolescent (Patient 8) is discussed in Section 5.B.

Patient 1 (Case No. 39325) was a 7-year-old boy with suicidal ideation who was treated with risperidone at an initial dosage of 0.5 mg twice daily. Over 4

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days, the dosage was increased to 4 mg/day. At 4 mg/day, the patient became dysphoric and developed a mild tremor, neither of which required treatment. After 3 months of risperidone 4 mg/day, the patient's dosage was increased to 6 mg/day because of the reemergence of prior psychotic symptoms including inappropriate sexual behavior; these symptoms responded to the addition of paroxetine 20 mg daily and an increase in risperidone to 8 mg daily in divided doses. At the time of reporting, the patient had been on this therapeutic regimen for 3 months but his prior psychotic symptoms were reemerging. His mild tremors had remained unchanged over this time period. Safety information for this patient was also included as a spontaneous adverse event report, which was regarded as serious. See Case No. 39325 in Tables 5 and 6 of Section 4.C.

Patient 2 (Case No. 39326) was an 8-year-old girl presenting with suicidal ideation and aggression was started on a risperidone dose of 0.5 mg twice daily. The dose was increased on the second day to 2 mg/day. On the third day of treatment, she developed extrapyramidal symptoms characterized by tongue protrusion and muscle rigidity. These symptoms were eliminated with benztropine at a dosage of 1 mg four times a day. Risperidone was then increased to 4 mg/day. At the time of reporting, the patient had received risperidone 4 mg/day for 6 weeks with no adverse effects. Safety information for this patient was also included as a spontaneous adverse event report. See Case No. 39329 in Table 5 of Section 4.C.

Patient 3 was a 9-year-old boy diagnosed with a DSM-IV major depressive disorder with psychotic features was treated with risperidone because he presented with a prior history of sedation with thioridazine and a history of neurological problems (current signs included tremors, tics, and poor coordination). The starting dose of risperidone, 0.5 mg twice daily, was increased over a period of 6 days to 3 mg daily. He continued on this regimen for 10 weeks with no adverse effects. Please refer to Table 4 for a tabular presentation of patients who demonstrated therapeutic effects with risperidone without experiencing adverse events.

Patient 4 (Case No. 39327) was a 10-year-old boy who presented with psychotic symptoms, suicidal ideation, and self-destructive behavior. Because of his lack of response to multiple medication trials, his paranoid ideation, and history of noncompliance, the patient was treated with risperidone at an initial dosage of 0.5 mg twice daily. The dose was increased by 1 mg/day to 5 mg daily. He became dysphoric upon initiation of risperidone therapy but no antidepressant was required and the dosage of risperidone was not adjusted because his psychotic symptoms were responding to therapy. The patient continued this regimen for 2 years but at age 12 he was sexually abused and rehospitalized for the reemergence of psychotic symptoms and suicidal ideation. The symptoms subsided after increasing the dose of risperidone to 8 mg/day.

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The patient had continued on risperidone 8 mg/day for an additional 11 months without recurrence of the psychosis. Since the start of risperidone, the patient had gained 30 pounds. Safety information for this patient was also included as a spontaneous adverse event report, which was regarded as serious. See Case No. 39327 in Tables 5 and 6 of Section 4.C.

Patient 5 (Case No. 39328) was a 10-year-old boy who presented with a 1-year history of bizarre behavior, withdrawal, apathy, thought blocking, poverty of thought, and auditory and visual hallucinations that remained unabated despite treatment. Risperidone was started at 2 mg/day, then increased to 4 mg/day, and then 6 mg/day on the third day. After reaching this dose, the patient became drowsy and lethargic. These symptoms resolved with a reduction in risperidone dosage to 4 mg/day. Ten days after initiating risperidone, the patient developed akinesia and dyskinetic movements, which were resolved with the addition of benztropine 2 mg/day. At the time of reporting, the patient had continued this combined regimen for 2 weeks with no adverse effect and was asymptomatic. Safety information for this patient was also included as a spontaneous adverse event report. See Case No. 39328 in Table 5 of Section 4.C.

Patient 6 was an 11-year-old boy presenting with severe aggression, visual and auditory hallucinations, motor and vocal tics, and continuing symptoms of Tourette's disorder and obsessive-compulsive disorder. The child had a family history of schizophrenia and bipolar disorder. Because he had failed to respond to antimanic agents and three neuroleptics, the child was treated with risperidone at an initial dosage of 2 mg/day. The dosage was increased to 4 mg on the second day and to 6 mg on the third day. After one week of therapy, the psychotic symptoms and tics improved with no adverse effects. Over a period of 8 months, the risperidone dose was increased to 8 mg/day. After 12 months of risperidone therapy, the patient had not developed any adverse effects. Please refer to Table 4 for a tabular presentation of patients who demonstrated therapeutic effects with risperidone without experiencing adverse events.

Patient 7 (Case No. 39329) was an 11-year-old girl with cerebral palsy who was hospitalized for treatment of sexual aggression and psychotic symptoms. Because of prior neurologic symptoms and a lack of response to classic neuroleptics, treatment with risperidone at a starting dose of 1 mg/day was initiated. The dose was increased by 0.5 mg twice daily up to 5 mg daily. At this dose, she presented with a possible tongue protrusion, which was difficult to assess because of her speech impediment. The child recovered without medical intervention. No anticholinergic medication was required and the risperidone dose was not adjusted. After 9 weeks, the child remained asymptomatic. Safety information for this patient was also included as a

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spontaneous adverse event report. See Case No. 39329 in Table 5 of Section 4.C.

Simeon et al[7] reported safety information for 7 patients with a variety of chronic psychiatric disorders who participated in open trials of risperidone. Of these patients, 1 was a child (age: 11 years) and 4 were adolescents (ranging in age from 13 to 15 years); all patients had previously received long-term therapy with antipsychotic medications. Two patients (Patients A and G), who were 17 and 18 years old, did not meet the age criteria for inclusion in this safety review. Safety information for the child (Patient B) is described below. Please refer to Section 5.B. for safety information pertaining to the adolescents (Patients C, D, E, and F).

Patient B was an 11-year-old boy diagnosed with schizophrenia (paranoid type) who was referred to a mental health clinic for an assessment of escalating behavioral problems. Risperidone treatment was initiated because of the chronic and severe nature of the patient's disorder and because the patient had not responded to prior psychotropic medications. The daily risperidone dose was rapidly increased to 6 mg but then reduced to 3 mg when the patient complained of dizziness, weakness, and "marked tiredness." Four months after the reporting of the adverse events, the patient was receiving an optimal daily dose of 2.5 mg with no major side effects.

Sternlicht and Wells[8] described a case of a child who had no adverse effects following treatment with risperidone. The risperidone treatment regimen for this child is described below and summarized in Table 4.

Patient 1 was a 6-year-old boy with a diagnosis of probable childhood schizophrenia and attention-deficit hyperactivity disorder who had not responded to high doses of desipramine, clonidine, and methylphenidate. Desipramine and clonidine were discontinued and risperidone (1 mg twice daily) was started in combination with methylphenidate. At the time of reporting, the patient had continued the risperidone regimen for 3 months with no side effects. Please refer to Table 4 for a tabular presentation of patients who demonstrated therapeutic effects with risperidone without experiencing adverse effects.

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Table 3. Summary of published safety information on the use of risperidone in children (2 years up to 12 years)

Author(s) Accession No. Study No.	Patient	Age/ Sex	Body System Adverse Event	Dose (mg/day) at Onset	Time on Drug at Onset	Diagnosis	Concomitant Drugs	Action Taken	Outcome
Lombroso et al N 118174 N/A	1	11/M	Metabolic & nutritional weight increase	1	11-week period	Tourette's	clonidine 0.15 mg/day	NS	NS
Mandoki N 112364/1 N/A	1 *	7/M	Psychiatric depression, psychotic symptoms Central & peripheral nervous tremors	4 4	4 days 4 days	bipolar disorder, psychosis, suicide ideation	paroxetine 20 mg/day	risperidone dose increased to 8 mg/day	NR
Mandoki N 112364/1 N/A	2 †	8/F	Central & peripheral nervous tongue protrusion, muscle rigidity	2	3 days	suicide ideation, psychosis	none	benztropine, dose increased	R/T
Mandoki N 112364/1 N/A	4 ‡	10/M	Metabolic & nutritional weight increase Psychiatric dysphoria	8 1-5	11 months 2 weeks	bipolar disorder, psychosis	none	none	NR R
Mandoki N 112364/1 N/A	5 §	10/M	Central & peripheral nervous akinesia dyskinesia Psychiatric lethargy	 4 4 6	 10 days 10 days 3 days	schizophrenia	none	dose reduced for lethargy; benztropine for akinesia, dyskinesia	R R
Mandoki N 112364/1 N/A	7 ‖	11/F	Central & peripheral nervous tongue protrusion	5	NS	psychosis, cerebral palsy sexual aggression	none	none	R
Simeon et al N 112430/1 N/A	8	11/M	Central & peripheral nervous dizziness Body as a whole weakness, tiredness	6	NS	schizophrenia	none	dose reduced	R/D

*Safety information also included as spontaneous adverse event report for Case No. 39325; †Safety information also included as spontaneous adverse event report for Case No. 39326; ‡Safety information also included as spontaneous adverse event report for Case No. 39327; §Safety information also included as a spontaneous adverse event report for Case No. 39328; ‖Safety information also included as a spontaneous adverse event report for Case No. 39329. N/A=not applicable; NS=not specified in report; NR=not recovered at time of report; R=recovered; R/D=resolved with an adjustment in dose; R/T=resolved with treatment.

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Table 4. Summary of published therapeutic effects of risperidone in children (2 years up to 12 years)

Author(s) Accession No. Study No.	Patient	Age/ Sex	Dose (mg/day)	Duration of Treatment	Diagnosis	Concomitant Drugs	Therapeutic Effects
Sternlicht & Wells N 112362/1 N/A	1	6/M	2	3 months	schizophrenia, ADHD	methylphenidate	stable
Mandoki N 112364/1 N/A	3	9/M	3	10 weeks	depression	none	stable
Mandoki N 112364/1 N/A	6	11/M	6-8	8-12 months	Tourette's, aggression, hallucinations, tics, obsessive-compulsive disorder	none	aggression controlled

N/A=not applicable. ADHD=attention-deficit hyperactivity disorder.

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4.C. Spontaneous Adverse Drug Event Reports

During the period from January 1993 to March 31, 1996, 64 spontaneous adverse drug events were experienced by children receiving risperidone. Table 5 provides a summary of the adverse events, the dose(s) at which the events occurred, and the outcomes of the events where information on the outcomes was available.

4.C.1. Serious Adverse Drug Events

Of the 64 spontaneous adverse drug events experienced by children, 18 were considered serious. Table 6 and the case narratives below provide a summary of the serious adverse events, the dose at which the events occurred, and the outcome of each event where information on the outcome was available.

Case No. 33068: An 11-year-old boy with bipolar disorder had exhibited mouth movements during thioridazine therapy. Thioridazine was discontinued and risperidone (4 mg/day) was started the following day. lithium and valproate sodium (Depakote®) were given concomitantly. After 21 weeks, mouth movements were noted and risperidone was discontinued. No recurrence of mouth movements was observed 20 days later.

Case No. 37367: A 7-year-old boy developed tardive dyskinesia after 3 months of risperidone (4 mg/day) therapy for hyperactivity. At the time of reporting, the symptoms had not abated and risperidone was not discontinued. The patient was lost to follow-up.

Case No. 38757: A 9-year-old boy developed tongue movements while being treated with haloperidol. Haloperidol was discontinued and the movements resolved. Risperidone (1 mg/day) was started and, although the patient's psychosis improved, the tardive dyskinesia recurred after 10 days of treatment. There was no improvement with a lower dose (0.5 mg/day); risperidone was discontinued. At the time of reporting, the patient was receiving valproate sodium (Depakote®), dexamphetamine, and vitamin E, which resulted in improvement of the tardive dyskinesia.

Case No. 36663: A 6-year-old mentally retarded girl who had participated in a short-term trial with good results was continued on risperidone (0.75 mg/day). Valproate sodium (Depakote®) was administered concomitantly for epilepsy. After 7 months of therapy with risperidone, the patient was hospitalized because of increasingly involuntary movements over a 3-week period. Upon admission, the patient exhibited frequent dystonic reactions in the right arm associated with a grumbling noise, increased eye blinking, and intermittent torticollis to the right. Orphenadrine was prescribed when tremor and myoclonus of shoulders and right hemifacies were observed. Because drug-

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induced dystonia was suspected, treatment with risperidone and orphenadrine were discontinued. Therapy with phenobarbitol and carbamazepine was then started. The involuntary movements were reduced, but the patient became more aggressive and unmanageable and was transferred to a psychologic clinic. The general outcome of the patient was unknown at the time of reporting.

Case No. 39042: A 7-year-old autistic boy with no previous history of seizures was hospitalized with a generalized seizure 4 months after starting risperidone (1 mg/day). Although febrile, there was no autonomic instability or muscle rigidity present. Results of a computed tomography (CT) scan, lumbar puncture, and laboratory safety tests (including electrolytes) were normal. Risperidone was discontinued and no further seizures occurred.

Case No. 36389: An 8-year-old boy with a history of seizures experienced a seizure when risperidone was added to an existing therapy of carbamazepine (Tegretol®), valproic acid (Depakene®), and phenytoin (Dilantin®). No information on the risperidone dose or on the doses of the concomitant medications was available. The general outcome of this patient was unknown at the time of reporting.

Case No. 44344: A 5-year-old boy with autism was treated with risperidone 2.5 mg/day, clonidine (Catapres®), and phenytoin (Dilantin®). After 2 months of therapy, the child experienced a grand mal seizure. The child was evaluated in an emergency room and was treated with phenytoin. The child had a history of one prior seizure for which phenytoin had been prescribed. The plasma level of the phenytoin was determined to be subtherapeutic (5.0 mg) and were corrected. Risperidone was discontinued and the seizures did not recur.

Case No. 40314: A 7-year-old girl experienced a head-face-neck dystonia after 2 days of risperidone therapy (0.5 mg three times daily or 1.5 mg/day) and excessive sedation, tremors, and hypersalivation after 6 days of risperidone therapy (0.5 mg three times daily or 1.5 mg/day). Concomitant medications included methylphenidate (Ritalin®), clonidine (Catapres®), and imipramine (Tofranil®) for hyperactivity. The child required hospitalization for 48 hours and received treatment with intramuscular diphenhydramine. Risperidone was discontinued. At the time of discharge, all events had resolved and risperidone was restarted at a lower dose.

Case No. 44911: A 6-year-old boy who was being treated with risperidone, and pemoline (Cylert®) developed an upper respiratory infection after 26 days of treatment. The risperidone dosage was 1 mg/day. Erythromycin was added to the patient's therapy but shortly after starting the drug, the patient was hospitalized for an acute dystonic reaction. Erythromycin and risperidone were discontinued and diphenhydramine was initiated. The reaction was attributed

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by the reporting physician to the combination of risperidone and erythromycin. The patient recovered.

Case No. 41120: A boy whose age was not specified experienced petit mal seizures while on risperidone therapy. The dose of risperidone, the date of initiation, concomitant medications, patient history, treatment required for the seizures, and the overall outcome of the patient were not reported. It was not known whether the event was an aggravation of an existing seizure disorder.

Case No. 27159: A 2-year-old girl was reported as emotionally withdrawn (apathetic) for 18 hours after accidentally ingesting a 3-mg tablet of risperidone. In the emergency room, the child was given 0.5 g/kg of activated charcoal with sorbitol and magnesium citrate. All vital signs reportedly remained normal and there were no laboratory abnormalities. The child was discharged from the hospital, fully recovered, within 36 hours.

Case No. 30384: Risperidone (1 mg/day) was given to a 6-year-old boy 1 day after tapered discontinuation of methylphenidate. The child exhibited severe sedation, tachycardia (heart rate: 170 bpm), and occasional irregular pulse; no electrocardiographic rhythm abnormalities were noted. After discontinuation of risperidone treatment, gastric lavage and activated charcoal were administered. After an overnight stay in the hospital, he was fully recovered and discharged.

Case No. 39325 (Patient 1): A 7-year-old boy refractory to previous treatment with other psychotropic drugs received treatment with risperidone at 4 mg/day. After 3 months, prior psychotic symptoms reemerged and the patient experienced depression. Safety information for this child was documented as a spontaneous adverse event report and in a publication: Mandoki M. Risperidone treatment of children and adolescents: increased risk of extrapyramidal side effects? *Journal of Child and Adolescent Psychopharmacology* 1995; 5(1):49-67. See Section 4.B. for detailed safety information reported by Mandoki for this child (Patient 1).

Case No. 43687: A 9-year-old mentally retarded girl with cerebral palsy was treated with risperidone 1 mg three times daily (3 mg) for self-destructive behaviour. After an unspecified period of therapy, the child was hospitalized with gastroparesis. A medical examination showed that the child was not diabetic. Cisapride therapy was started but at the time of the report, the child had not yet recovered from the event.

Case No. 40745: A 7-year-old boy experienced abdominal pain, nausea, vomiting, and constipation after 6 weeks of treatment with risperidone 2 mg/day, ranitidine (Zantac®), venlafexine (Effexor®), and benztropine

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(Cogentin®). The patient was hospitalized with diagnosis and outcome pending at the time of the report.

Case No. 39327 (Patient 4): A 10-year-old boy refractory to previous treatment with psychotropic drugs was treated with risperidone 5 mg/day. The condition of the patient reportedly worsened after 11 months of treatment. Safety information for this child was documented as a spontaneous adverse event report and in a publication: Mandoki M. Risperidone treatment of children and adolescents: increased risk of extrapyramidal side effects? *Journal of Child and Adolescent Psychopharmacology* 1995; 5(1):49-67. See Section 4.B. for detailed safety information reported by Mandoki for this child (Patient 4).

Case No. 41041: An 11-year-old girl developed moderate shortness of breath after two days of risperidone therapy at 1 mg/day. Concomitant medications included clonidine (Catapres®) for hyperactivity. The child required overnight hospitalization for observation. The event resolved spontaneously without treatment during the night of hospitalization. According to the mother of the child, all breathing and blood tests were normal. Risperidone was permanently discontinued.

Case No. 29632: An 11-year-old boy who received a titrated dose of risperidone (1-4 mg/day) over a 3-week period had an elevated prolactin level of 68.8 ng/mL (normal range: 2-15 ng/mL) and a pea-size breast mass. Risperidone was discontinued over a 2-day period with thiothixene initiated over the same two days. A pediatric endocrinologist was to make an evaluation and biopsy. Physician follow-up was denied.

4.C.2. TREATMENT DISCONTINUATION

Risperidone was discontinued in 23 of the 64 children who experienced adverse events, including 11 of the 18 children with serious adverse events. Details of the events leading to discontinuation of treatment for the children with serious adverse events are summarized in Table 7 and in the case narratives previously described in Section 4.C.1. A summary of all treatment discontinuations is provided in Table 8.

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Table 5. Summary of pharmacovigilance reports of adverse drug events in children (2 years up to 12 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
	Central & peripheral nervous						
33068	tardive dyskinesia	11/M	4	21 weeks	lithium/Depakote®	DS	R
37367	tardive dyskinesia	7/M	1-4	3 months	Ritalin®/Catapres®	none	NR
38757	tardive dyskinesia	9/M	0.5-1	10 days	Depakote®/Dexedrine®/vitamin E	Rx/DS	NR
36751	dyskinesia	9/M	4	8 weeks	NS	DR	NR
36842	dyskinesia	10/M	1	6 months	Catapres®	none	NR
39542	dyskinesia	10/M	1	28 days	Dexatrim®/Depakote®	DS	NR
39576	dyskinesia	10/M	4	NS	Catapres®/Benadryl®	DR	NR
26514	dystonia	10/M	4	2 days	Prozac®	Rx	R
29184	dystonia	8/NS	1	1 day	none	DS	R
36663	dystonia	6/F	0.75	7 months	Depakote®	DS/H/Rx	U
36389	convulsion aggravated	8/M	NS	NS	Tegretol®/Dilantin®/Depakene®	NS	U
39042	convulsions	7/M	1	17 weeks	NS	DS/H	R
37483	extrapyramidal symptoms	7/F	3	12 days	NS	none	NR
26569	tongue paralysis	10/M	2	1 day	NS	Rx	R
27685	stupor	11/F	3	2-4 weeks	lithium	DS	R
27956	dizziness	7/M	U	3 days	Haldol®/Depakote®/Tegretol®/Inderal®	none	NR
32281	oculogyric crisis	8/M	0.5-2	20 days	Tofranil®	DS	R
44911	dystonia	6/M	1	26 days	Cylert®/erythromycin	DS/H/Rx	R
44344	grand mal convulsions	5/M	2.5	2 months	Catapres®/Dilantin®	DS/Rx	R
42518	abnormal gait	6/M	NS	3 days	NS	DS	R
40314	dyskinesia	7/F	1.5	2 days	Ritalin®/Catapres®/Tofranil®	DS/H/Rx	R
39329*	tongue protrusion	11/F	5	NS	NS	none	R
39328*	dyskinesia	10/M	6	10 days	none	DR/Rx	R
39326*	extrapyramidal symptoms	8/F	1	3 days	NS	Rx	R
41120	petit mal seizures	NS/M	U	U	NS	NS	U

*Safety information also included in a publication: *Journal of Child and Adolescent Psychopharmacology* 1995; 5(1):49-67.
NS=not specified; NR=not recovered at time of report; R=resolved; U=unknown; DS=drug stopped; Rx=prescription or supportive therapy; H=hospitalization; DR=dose reduced.

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Table 5. (Continued)...Summary of pharmacovigilance reports of adverse drug events in children (2 years up to 12 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
	Psychiatric						
27159	apathy (accidental ingestion)	2/F	3	1 day	NS	H/DS/Rx	R
30384	somnolence	6/M	1	1 day	Ritalin®	H/DS/Rx	R
32613	somnolence	8/M	2	NS	NS	none	R
34639	somnolence	11/M	2	2 days	Depakote®/Dexedrine®	none	NR
37090	somnolence	8/M	4	1 year	Depakote®	DS	NR
36539	libido increase	5/M	6-8	10 months	NS	none	NR
39325*	depression	7/M	4	3 months	NS	H/DI/Rx	NR
41550	agoraphobia	7/M	0.75	26 days	Anafranil®	none	NR
39800	aggressive reaction	9/M	5	8 months	NS	none	NR
	Gastrointestinal						
29831	excessive appetite	10/M	3	9 days	NS	none	NR
32277	hypersalivation	11/M	NS	6 days	Paxil®/Depakene®	none	NR
40183	gastric ulcer	9/M	NS	NS	Effexor®/Cogentin®	Rx	NR
40745	abdominal pain	7/M	2	6 weeks	Zantac®/Effexor®/Cogentin®	H	NR
40875	fecal incontinence	7/M	1.5	NS	Ritalin®/Klonopin®	none	NR
40916	hypersalivation	6/NS	NS	NS	lithium/acetaminophen	DR/Rx	R
43431	nausea	8/M	0.5	4 days	NS	DR	NR
43687	gastric atony	9/F	3	NS	NS	H/Rx	NR
	Bleeding & clotting						
31242	epistaxis	NS	NS	NS	NS	DS	NR
33211	epistaxis	11/F	2-3	6 days	NS	Rx	NR
33212	epistaxis	10/M	7	4 days	NS	DS/Rx	R
33106	thrombocytopenia	8/M	2.5	7 weeks	Benadryl®/Catapres®	DS	R
42525	epistaxis	NS	U	U	NS	none	NR

*Safety information also included in a publication: *Journal of Child and Adolescent Psychopharmacology* 1995; 5(1):49-67.
NS=not specified; NR=not recovered at time of report; R=resolved; DS=drug stopped; Rx=prescription or supportive therapy; H=hospitalization; DR=dose reduced; DI=dose increased.

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Table 5. (Continued)...Summary of pharmacovigilance reports of adverse drug events in children (2 years up to 12 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
	Metabolic/nutritional						
33084	weight increase	10/M	2	2 months	Klonopin®	Rx	NR
42121	weight increase	5/M	NS	NS	Prozac®	DR	R
44347	weight increase	8/M	2.5	12 months	NS	none	NR
	Skin & appendages						
25739	urticaria	11/M	2	1 day	NS	DS	R
32322	rash	8/M	2	1 week	Dilantin®	DR/Rx	NR
40751	pruritus, genital	8/F	4	NS	NS	none	NR
	Urinary						
34672	urinary retention	7/M	6	10 days	Synthroid®/Tegretol®	none	NR
38523	urinary retention	9/M	2.5	NS	NS	none	NR
43954	urinary incontinence	10/M	2	7 days	NS	none	NR
	Body as a whole						
29172	therapeutic response decreased	9/M	4	NS	NS	none	NR
39327*	condition aggravated	10/M	5	11 months	NS	H/Rx	NR
	Vision						
27945	blurred vision	2/M	6	10 days	none	DS	NR
38756	blepharospasm	10/M	3-5	NS	Ritalin®	DR	NR
	Respiratory						
38676	cough	7/M	1	1-2 hours	NS	none	NR
41041	dyspnea	11/F	1	2 days	Catapres®	DS/H	R

*Safety information also included in a publication: *Journal of Child and Adolescent Psychopharmacology* 1995; 5(1):49-67.
NS=not specified; NR=not recovered at time of report; R=resolved; DS=drug stopped; Rx=prescription or supportive therapy; H=hospitalization; DR=dose reduced; DI=dose increased.

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Table 5. (Continued)...Summary of pharmacovigilance reports of adverse drug events in children (2 years up to 12 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
29632	Neoplasms breast neoplasm	11/M	4	3 weeks	NS	DS	NR
27677	Cardiovascular hypertension	8/F	1	2 days	Ritalin®	DS	R
Total number of adverse events reported in children: 64							

NS=not specified; NR=not recovered at time of report; R=resolved; DS=drug stopped; Rx=prescription or supportive therapy; H=hospitalization; DR=dose reduced; DI=dose increased.

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Table 6. Summary of pharmacovigilance reports of serious adverse events in children (2 years up to 12 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
	Central & peripheral nervous						
33068	tardive dyskinesia	11/M	4	21 weeks	lithium/Depakote®	DS	R
37367	tardive dyskinesia	7/M	1-4	3 months	Ritalin®/Catapres®	none	NR
38757	tardive dyskinesia	9/M	0.5-1	10 days	Depakote®/Dexedrine®/vitamin E	Rx/DS	NR
36663	dystonia	6/F	0.75	7 months	Depakote®	H/DS/Rx	U
39042	convulsions	7/M	1	17 weeks	NS	H/DS	R
36389	convulsion aggravated	8/M	NS	NS	Tegretol®/Dilantin®/Depakene®	NS	U
44344	grand mal convulsions	5/M	2.5	2 months	Catapres®/Dilantin®	DS/Rx	R
40314	dyskinesia	7/F	1.5	2 days	Ritalin®/Catapres®/Tofranil®	H/DS/Rx	R
44911	dystonia	6/M	1	26 days	Cylert®/erythromycin	H/DS/Rx	R
41120	petit mal convulsions	NS/M	NS	NS	NS	NS	U
	Psychiatric						
27159	apathy (accidental ingestion)	2/F	3	1 day	NS	H/DS/Rx	R
30384	somnolence/sedation	6/M	1	1 day	Ritalin®	H/DS/Rx	R
39325*	depression	7/M	4	3 months	NS	H/DI/Rx	NR
	Gastrointestinal						
43687	gastric atony	9/M	3	NS	NS	H/Rx	NR
40745	abdominal pain	7/M	2	6 weeks	Zantac®/Effexor®/Cogentin®	NS	NR
	Respiratory						
41041	dyspnea	11/F	1	2 days	Catapres®	DS/H	R
	Body as a whole						
39327*	condition aggravated	10/M	5	11 months	NS	H/Rx	NR

*Safety information was also included in a publication: *Journal of Child and Adolescent Psychopharmacology* 1995; 5(1):49-67.
NS=not specified; NR=not recovered at time of report; R=recovered; U=unknown; H=hospitalization; DS=drug stopped; DI=dose increased; Rx=prescription or supportive therapy.

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Table 6. (Continued)...Summary of pharmacovigilance reports of serious adverse events in children (2 years up to 12 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
29632	Neoplasms breast neoplasm	11/M	4	3 weeks	NS	DS	NR
Total number of serious adverse events reported in children: 18							

*Safety information was also included in a publication: *Journal of Child and Adolescent Psychopharmacology* 1995; 5(1):49-67.
NS=not specified; NR=not recovered at time of report; R=recovered; U=unknown; H=hospitalization; DS=drug stopped; DI=dose increased; Rx=prescription or supportive therapy.

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Table 7. Summary of pharmacovigilance reports of serious adverse drug events leading to discontinuation of treatment in children (2 years up to 12 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
	Central & peripheral nervous						
33068	tardive dyskinesia	11/M	4	21 weeks	lithium/Depakote®	DS	R
38757	tardive dyskinesia	9/M	0.5-1	10 days	Depakote®/Dexedrine®/vitamin E	DS/Rx	NR
36663	dystonia	6/F	0.75	7 months	Depakote®	DS/H/Rx	U
39042	convulsions	7/M	1	17 weeks	NS	DS/H/Rx	R
44344	grand mal convulsions	5/M	2.5	2 months	Catapres®/Dilantin®	Ds/Rx	R
40314	dyskinesia	7/F	1.5	2-6 days	Ritalin®/Catapres®/Tofranil®	DS/H/Rx	R
44911	dystonia	6/M	1	26 days	Cylert®/erythromycin	DS/H/Rx	R
	Psychiatric						
27159	apathy (accidental ingestion)	2/F	3	1 day	NS	DS/H/Rx	R
30384	somnolence	6/M	1	1 day	Ritalin®	DS/H/Rx	R
	Respiratory						
41041	dyspnea	11/F	1	2 days	Catapres®	DS/H	R
	Neoplasm						
29632	breast neoplasm	11/M	4	3 weeks	NS	DS	NR
Total number of serious adverse events leading to discontinuation of treatment in children: 11							

R=recovered; NS=not specified; U=unknown; DS=drug stopped; H=hospitalization; Rx=prescription or supportive therapy.

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Table 8. Summary of pharmacovigilance reports of treatment discontinuations due to adverse drug events in children (2 years up to 12 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
	Central & peripheral nervous						
33068	tardive dyskinesia	11/M	4	21 weeks	lithium/Depakote®	DS	R
38757	tardive dyskinesia	9/M	0.5-1	10 days	Depakote®/Dexedrine®/vitamine E	DS/Rx	NR
39542	dyskinesia	10/M	1	28 days	Dexatrim®/Depakote®	DS	NR
29184	dystonia	8/NS	1	1 day	none	DS	R
36663	dystonia	6/F	0.75	7 months	Depakote®	DS/H/Rx	U
39042	convulsions	7/M	1	17 weeks	NS	DS/H	R
27685	stupor	11/F	3	2-4 weeks	lithium	DS	R
32281	oculogyric crisis	8/M	0.5-2	20 days	Tofranil®	DS	R
44911	dystonia	6/M	1	26 days	Cylert®/erythromycin	DS/H/Rx	R
44344	grand mal convulsions	5/M	2.5	2 months	Catapres®/Dilantin®	DS/Rx	R
42518	abnormal gait	6/M	NS	3 days	NS	DS	R
40314	dyskinesia	7/F	1.5	2 days	Ritalin®/Catapres®/Tofranil®	DS/H/Rx	R
	Psychiatric						
27159	apathy (accidental ingestion)	2/F	3	1 day	NS	DS/H/Rx	R
30384	somnolence	6/M	1	1 day	Ritalin®	DS/H/Rx	R
37090	somnolence	8/M	4	1 year	Depakote®	DS	NR
	Bleeding & clotting						
31242	epistaxis	NS	NS	NS	NS	DS	NR
33212	epistaxis	10/M	7	4 days	NS	DS/Rx	R
33106	thrombocytopenia	8/M	2.5	7 weeks	Benadryl®/Catapres®	DS	R
	Respiratory						
41041	dyspnea	11/F	1	2 days	Catapres®	DS/H	R

NS=not specified; NR=not recovered at time of report; R=resolved; U=unknown; DS=drug stopped; Rx=prescription or supportive therapy; H=hospitalization.

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Table 8. (Continued)...Summary of pharmacovigilance reports of treatment discontinuations due to adverse drug events in children (2 years up to 12 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
25739	Skin & appendages urticaria	11/M	2	1 day	NS	DS	R
27945	Vision blurred vision	2/M	6	10 days	none	DS	NR
29632	Neoplasms breast neoplasm	11/M	4	3 weeks	NS	DS	NR
27677	Cardiovascular hypertension	8/F	1	2 days	Ritalin®	DS	R
Total number of adverse events leading to discontinuation of treatment in children: 23							

NS=not specified; NR=not recovered at time of report; R=resolved; DS=drug stopped.

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5. SAFETY IN ADOLESCENTS (12 YEARS UP TO 16 YEARS)

5.A. JANSSEN-SPONSORED CLINICAL STUDIES

The safety and tolerability of risperidone in adolescents have been evaluated in 3 clinical studies: RIS-BEL-11, RIS-BEL-22, and RIS-INT-005. Safety information for the adolescents who participated in RIS-BEL-22 and RIS-INT-005 and who met the age criteria for inclusion in this safety review is summarized below and in Table 9. Safety information for the adolescents who participated in RIS-BEL-11 is provided in Section 6.A.

Study No. RIS-BEL-22: In this multicenter, dose-titration study, risperidone was administered orally for 4 weeks to 7 patients with autistic disorder. Of these patients, 6 were children (3 through 9 years) and 1 was an adolescent (14 years). A risperidone solution containing 0.5 mg/mL (Lot No. 91A24/F2) was administered under open conditions twice daily, in the morning and the evening. The daily dose of risperidone starting at 0.01 mg/kg on the first day was gradually increased for each patient during the first week. On the seventh day of the study, the mean daily dose for all patients (including the adolescent) was 0.019 mg/kg (range: 0.01 mg/kg -0.041 mg/kg). Throughout the remainder of the study, there was a slow increase in the mean daily dose for all patients except for Patient 8 (and the adolescent, Patient 6), reaching 0.035 mg/kg on Day 28 (range: 0.014 mg/kg to 0.072 mg/kg). The incidence of adverse events during the course of therapy with risperidone was low and one patient (Patient 3) reported no adverse event. None of the adverse events resulted in the discontinuation of treatment for any of the patients. Safety information for the adolescent patient (Patient 6) is summarized below. Please refer to Section 4.A. for safety information pertaining to the children (Patients 1, 2, 3, 4, 5, and 8).

Patient 6 was a 14-year-old girl with autistic disorder, severe mental retardation, and epilepsy, who weighed 36 kg and was 145 cm in height. Risperidone at a starting dose of 0.01 mg/kg/day was administered for aggressive behavior. The dose was gradually increased during the first week to 0.02 mg/kg/day (0.72 mg) and remained constant at this dose for the remainder of the study. Antiepileptic medication (carbamazepine and clonazepam) and a neuroleptic (pipamperone) were administered before and concomitantly during the course of the study. During the study, the patient reportedly experienced mild hypersalivation and mild intermittent *absences*, which were considered by the investigator to be possibly related to treatment. *Absences* was a term commonly used in French for a variety of minor epileptic seizures, including those covered in English by the term *petit mal*. The events resolved with no residual effects and did not lead to discontinuation of treatment.

Study No. RIS-INT-005: This was an international, multicenter, double-blind, parallel-group trial[9] comparing risperidone (1-8 mg twice daily) with haloperidol (1-8 mg) twice daily when administered for 6 weeks to randomized groups of first-admission psychotic patients. An oral risperidone 2-mg tablet formulation (Lot Nos. 89J17/F13-91C11/F13) supplied in blister packs of 20 were used in the study. Patients received one to eight tablets per day given as a divided dose in the morning and evening for 6 weeks. The maximum permitted dosage of risperidone was 8 mg twice daily; the minimum allowed dosage was 2 mg once daily. The trial was conducted primarily with adults but included one adolescent patient (Patient 404) who was 15 years old. Safety information for this patient is described below:

Patient 404 was a 15-year-old adolescent girl who experienced 4 adverse events during the trial. On Day 2, oculogyric crisis was experienced by the patient at a daily risperidone dose of 4 mg. No action was taken and the event resolved with no residual effect. On Day 3, intermittent extrapyramidal disorder was experienced following a daily risperidone dose of 6 mg. No action was taken and the event resolved with no residual effect. The reports of oculogyric crisis and extrapyramidal disorder were considered by the investigator to be mild in severity and related to treatment. On Day 27, intermittent dizziness and palpitation were experienced by the patient at a daily risperidone dose of 10 mg. No action was taken for either event, both of which were considered by the investigator to be mild in severity and possibly related to treatment. None of the adverse events resulted in discontinuation of risperidone therapy.

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Table 9. Summary of adverse drug events elicited in clinical studies of risperidone in adolescents (12 years up to 16 years)

Study No. Accession No. *Publication*	Patient	Age/ Sex	Body System Adverse Event	Dose (mg/day) at Onset	Time on Drug at Onset (days)	Diagnosis	Concomitant Drugs	Action Taken	Outcome
RIS-BEL-22 N 121131 N/A	6	14/F	Gastrointestinal hypersalivation	0.72*	8	autism, mental retardation, epilepsy	carbamazepine clonazepam pipamperone	none	R
			Central & peripheral nervous absences†	0.72	NS				NR
RIS-INT-005 N 108011/1 N/A	404	15/F	Central & peripheral nervous extrapyramidal disorder	6	3	psychosis	none	none	R
			dizziness	10	27				NR
			oculogyric crisis	4	2				R
			Heart rate & rhythm palpitation	10	27				NR

N/A=not applicable; NR=not recovered at time of report; R=resolved.

*Dose was based on 0.02 mg/kg/day; †Absences=a term commonly used in French for a variety of minor epileptic seizures, including those covered in English by the term *petit mal*.

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5.B. Published Studies and Case Reports

The safety of risperidone in adolescents as reported in publications of clinical studies and case histories is summarized below and in Tables 10 and 11.

Cosgrove[10] reported 2 cases of adolescent patients who developed extrapyramidal symptoms following treatment with risperidone. The symptoms were controlled with an antispasmodic agent in one case and with a reduction in the risperidone dose in the other. Safety information for these patients is provided in the following case descriptions:

Case 1 was a 15-year-old boy diagnosed with schizophrenia. Prior to the start of risperidone, the patient had been treated with sertraline (Zoloft®) without benefit. Sertraline was discontinued and risperidone was started at 0.5 mg daily for 2 days. The dose was increased to 6 mg/day over the next 14 days and then over the next month to 4.5 mg in the morning and 4 mg in the evening. [At a risperidone dose of 2 mg twice daily, the patient experienced hand and leg tremors, which were controlled with concomitant procyclidine hydrochloride (5 mg 3 times daily).]

Case 2 was a 14-year-old girl who was experiencing acute symptoms of schizophrenia. The patient experienced hand and leg tremors with risperidone doses that were titrated up to 4 mg twice daily over a 19-day period. The tremors resolved with a gradual reduction in the risperidone dosage. At the time of reporting, the dosage had been reduced to 2.5 mg in the morning and 3 mg in the evening with no adverse effect.

Cozza and Edison[11] reported 2 cases of adolescent patients with treatment-emergent extrapyramidal symptoms, which were controlled with reductions in the risperidone dose. Safety information for these patients is provided in the following case descriptions:

Case 1 was a 15-year-old boy who had demonstrated positive and negative psychotic symptoms for 3 years before the start of risperidone therapy. The patient received a risperidone starting dose of 1 mg/day, which was rapidly titrated to 6 mg/day. At the higher dose, the patient developed extrapyramidal symptoms. A reduction in the risperidone dose to 1 mg twice daily resulted in an attenuation of the adverse symptoms. The patient demonstrated improvement of psychotic symptoms within 1 week of the initiation of risperidone.

Case 2 was a 15-year-old girl who exhibited symptoms consistent with a major psychotic illness. The patient received risperidone at a starting dose of 1

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mg/day, which was rapidly titrated to 6 mg/day. Within 1 week, the patient demonstrated improvement in psychotic symptoms, but the development of extrapyramidal symptoms at the higher dose necessitated a reduction in the dose to 1 mg twice daily. The reduction in dose resulted in an attenuation of the extrapyramidal symptoms. The patient reported an "awareness of feelings" of which she had been unaware before the start of risperidone. Because of discomfort over the feelings, the patient became noncompliant and later discontinued treatment.

Fras and Major[12] reported preliminary observations of 6 patients ranging in age from 8 to 14 years, who were treated with risperidone for aggressive behaviors. Therapeutic responses of these patients to risperidone ranged from effective control of aggressiveness to moderate effectiveness. The side effects were similar in all patients, with the most consistently reported being sedation and a "spacey" look, which appeared to be dose-related. With daily doses of less than 3 mg in adolescents and less than 2 mg in children, extrapyramidal side effects were avoided. At the time of the report, all patients were continuing active treatment. A case report of one of these patients was described by the authors and is summarized below. General safety information for the other patients whose age and sex were not specified in the report is presented in Section 6.

A 13-year-old boy with typical adolescent hypomania and a strong family history of bipolar disorder was described by the authors. The patient had initially responded to lithium but risperidone was started because the aggressive behavior had reemerged. An initial risperidone dose of 2 mg daily was increased on the second day to 4 mg/day. The increase in dose resulted in sedation and dizziness as well as subjective reports of numbness in the patient's legs and a "hot dry feeling in his throat." A "spacey" look was reported by the patient's mother. Risperidone was decreased to 0.5 mg twice a day and then to 0.25 mg in the morning and 0.5 mg in the evening. On the lower dosage, the patient had no sedation and at the time of reporting had remained free of aggressive symptoms.

Lombroso et al[5] reported safety information from an 11-week, open-label trial of risperidone, which included 7 patients (5 boys and 2 girls) with a mean age of 12.9 ± 1.9 years. Of these patients, 1 was a child (age 11 years) and 5 were adolescents (ages 12-13 years). One patient (Patient 7), who was 16 years old, did not meet the age criteria for inclusion in this review. The objective of the trial was to evaluate the short-term efficacy and safety of risperidone in the treatment of chronic tic disorders in children and adolescents. The patients were seen at baseline and for two follow-up visits over an 11-week period. Three of the 5 adolescent patients (Patients 4, 5, and 6) were diagnosed with Tourette's

syndrome and 2 (Patients 2 and 3) with chronic motor tic disorder. Additional diagnoses for these patients were attention-deficit hyperactivity disorder in 2 patients (Patients 4 and 5), obsessive-compulsive disorder in 2 patients (Patients 3 and 6), and major depression-single episode in 1 patient (Patient 5). One patient (Patient 2) had no concurrent diagnosis. In 4 patients (Patients 2, 4, 5, and 6), risperidone was titrated slowly over a course of several weeks: 0.5 mg/day with increases of 0.5 mg every 5 days as tolerated up to a maximum of 2.5 mg/day in divided doses twice daily. In 1 patient (Patient 3), a more rapid dose increase was prescribed because of severe obsessive-compulsive disorder in addition to a motor tic disorder. The maintenance dose of risperidone was generally achieved by all patients within 3 weeks. Risperidone appeared to be effective in reducing tic frequency and intensity in these patients. The most frequent side effect was weight gain, which ranged from 8 to 14 pounds. Safety information for the adolescent patients (Patients 2, 3, 4, 5, and 6) is provided below; information for the child (Patient 1) is provided in Section 4.B. General safety information for patients whose age and sex were not specified in the report is presented in Section 6.

Patient 2 was a 12-year-old boy diagnosed with a moderate to severe chronic motor tic disorder. Risperidone 0.5 mg/day was initiated because a course of clonidine (Catapres®) showed no improvement of symptoms. The initial dosage of risperidone was gradually increased to 1 mg/day over a 2-week period. No concomitant medication was administered. During the course of the 11-week study, the patient reported an increase in appetite with a modest increase in weight (8 pounds) in 8 weeks. Weight gain did not lead to discontinuation of treatment.

Patient 3 was a 12-year-old girl diagnosed with an obsessive-compulsive disorder and a chronic motor tic disorder. Because of this patient's severe obsessive-compulsive symptoms, the initial risperidone dose of 0.5 mg/day was increased more rapidly to a daily maintenance dose of 2.5 mg. Paroxetine 60 mg/day was administered concomitantly. Reported side effects following treatment were muscle stiffness and weight gain. The patient was treated with oral benztropine for the muscle stiffness. None of the adverse events resulted in discontinuation of treatment.

Patient 4 was a 12-year-old boy diagnosed with attention deficit hyperactivity disorder and moderate Tourette's syndrome. Risperidone was initiated at a starting dose of 0.5 mg on the first day and then increased gradually to a maintenance dose of 1 mg/day. No concomitant medication was administered. Risperidone was selected as treatment because of the emergence of sedation and headaches following previous treatment with clonidine (Catapres®). Therapeutic gains with risperidone were maintained over 4 months of follow-up

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at a daily dose of 1 mg. Reported side effects were an increase in appetite and weight gain of approximately 14 pounds over 3 months. None of the adverse events resulted in discontinuation of treatment.

Patient 5 was a 12-year-old boy diagnosed with Tourette's syndrome, attention-deficit hyperactivity disorder, and major depression (single episode). Prior to the start of risperidone therapy, this patient had received haloperidol for tics but it was discontinued because of sedation and psychomotor slowing. Risperidone was initiated at a starting dose of 0.5 mg on the first day of the study and then increased gradually to a maintenance dose of 1 mg/day. Fluoxetine 10 mg/day was administered concomitantly for depression, which remitted after several weeks of therapy. Weight gain was reported as a side effect following treatment, but the patient did not elect to discontinue treatment as a result of the weight gain. No other adverse effects were specified in the publication.

Patient 6 was a 13-year-old girl diagnosed with an obsessive-compulsive disorder and Tourette's syndrome. Risperidone was initiated at a starting dose of 0.5 mg on the first day of the study and then increased gradually by 0.5 mg every 5 days up to a maintenance dose of 2.5 mg/day. Sertraline (Zoloft®) 100 mg/day was administered concomitantly. Other than weight gain no adverse effects were reported following treatment with risperidone. The weight gain did not lead to discontinuation of treatment.

Mandoki[6] reported safety information from open clinical trials in which 10 patients participated. Of these patients, 7 were children (7-11 years of age) and 1 an adolescent (12 years of age) refractory to previous treatment with other psychotropic drugs. (Two patients, who were both 17 years old, did not meet the age criteria for inclusion in this safety review.) Safety information for the adolescent (Patient 8) is discussed below. Please refer to Section 4.B. for safety information pertaining to the 7 children (Patients 1, 2, 3, 4, 5, 6, and 7).

Patient 8 (Case No. 39330) was a 12-year-old girl diagnosed with Tourette's syndrome, schizophreniform disorder, obsessive-compulsive symptoms, and depression, who had a family history of schizophrenia and bipolar disorder. After a month of treatment with risperidone (6 mg/day), the patient became depressed. Risperidone was decreased to 2 mg twice daily for one month with no improvement. The depression responded to the addition of fluoxetine 10 mg daily. At the time of reporting, the patient had been on the combination of risperidone 2 mg daily and fluoxetine 10 mg daily for 12 months. Her weight had increased by 12 pounds over the year. An exacerbation of tics, which had also occurred during this period, responded to an increase in risperidone dose of 0.5 mg daily to a total dose of 2.5 mg/day. Safety information for this

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patient was also included as a spontaneous adverse event report. See Section 5.C., Table 12, which summarizes safety information for Case No. 39330.

Simeon et al[7] reported safety information for 7 patients with a variety of chronic psychiatric disorders who participated in open trials of risperidone. Of these patients, 1 was a child (age: 11 years) and 4 were adolescents (ranging in age from 13 to 15 years); all patients had previously received long-term therapy with antipsychotic medications. Two patients (Patients A and G), who were 17 and 18 years old, did not meet the age criteria for inclusion in this safety review. Safety information pertaining to the child (Patient B) is described in Section 4.B. Safety information for the 4 adolescents (Patients C, D, E, and F) is described below. Three of the 4 adolescent patients (Patients C, D, and E) reported no adverse effects with risperidone treatment. Please refer to Table 11 for a tabular presentation of patients who demonstrated therapeutic effects with risperidone without experiencing adverse events.

Patient C was a 15-year-old boy who was referred to a mental health clinic for aggression. Treatment with risperidone was initiated because of the patient's poor response to prior psychotropic medications and because of the chronic nature of his disorder, which was given a provisional diagnosis of schizophrenia. At the time of reporting, the patient had maintained the starting dose of 2 mg daily for 6 months with no adverse effects.

Patient D was a 13-year-old boy diagnosed with attention-deficit hyperactivity disorder and a pervasive developmental disorder. Risperidone treatment at 0.5 mg twice daily was initiated and titrated gradually to 3 mg/day. Prior treatment with psychotropic medications had been ineffective in controlling the patient's symptoms. At the time of reporting, the patient had been treated with risperidone 3 mg/day for 3 months with no adverse effects.

Patient E was a 14-year-old boy diagnosed with attention-deficit hyperactivity disorder. Risperidone 0.5 mg twice daily was administered for 3 months with no clinically significant side effects.

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Patient F was a 13-year-old girl with a provisional diagnosis of delusional disorder, somatic type. Risperidone treatment at 1 mg/day was initiated and titrated gradually to 6 mg/day combined with imipramine for enuresis. At 6 mg/day, the patient was "oversedated and felt very tired." These effects resolved with a reduction in dose to 3 mg/day. After 4 months, risperidone was tapered to 2 mg/day, imipramine was discontinued, and *d* -amphetamine 5 mg twice daily was added to assist her concentration. At the time of reporting, the patient had been treated with this regimen for 10 months with no adverse effects.

Quintana and Keshavan[13] presented case studies of three schizophrenic adolescents; Patient 1 (boy, 12 years), Patient 2 (boy, 14 years), and Patient 3 (girl, 15 years). Risperidone (4 mg/day) was given concomitantly with chlorpromazine (50-100 mg/day) to Patients 1 and 2, while Patient 3 received risperidone (4 mg/day) only. The patients were followed for 6 months. In that time, no adverse events were reported. Please refer to Table 11 for a tabular presentation of patients who demonstrated therapeutic effects with risperidone without experiencing adverse events.

Ribeiro and Correia[14] presented a case report of a 15-year-old girl with haloperidol-related neuroleptic malignant syndrome (NMS). Drug therapy (haloperidol 7.5 mg/day, lorazepam 7.5 mg/day, and benztropine 5 mg/day) was begun in treatment of insomnia, negativism, and auditory hallucinations, and levomepromazine (50 mg) was administered intramuscularly for an episode of psychomotor agitation. Within the first 11 days of treatment, NMS symptoms (cogwheel rigidity, hyperthermia, altered consciousness, leukocytosis, and elevated creatine phosphokinase) were observed. Neuroleptics were discontinued. On Day 30 of hospitalization, the introduction of bromocriptine (5 mg/day) coincided with the last day of hyperthermia. One month later, risperidone 0.5 mg/day was introduced and later increased to 1 mg/day: the patient remained without productive symptoms and exhibited no side effects of the drug. Please refer to Table 11 for a tabular presentation of patients who demonstrated therapeutic effects with risperidone without experiencing adverse events.

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Table 10. Summary of published safety information on the use of risperidone in adolescents (12 years up to 16 years)

Author(s) Accession No. Study No.	Patient	Age/ Sex	Body System Adverse Event	Dose (mg/day) at Onset	Time on Drug at Onset	Diagnosis	Concomitant Drugs	Action Taken	Outcome
Cosgrove N 104588/1 N/A	1	15/M	Central & peripheral nervous tremors (hands & legs)	4	1-2 weeks	schizophrenia	NS	procyclidine hydrochloride	R
Cosgrove N 104588/1 N/A	2	14/F	Central & peripheral nervous tremors (hands & legs)	8	19 days	schizophrenia	NS	dose reduced	R
Cozza & Edison N 104710/1 N/A	1	15/M	Central & peripheral nervous extrapyramidal symptoms	6	NS	psychosis	NS	dose reduced	R
Cozza & Edison N 104710/1 N/A	2	15/F	Central & peripheral nervous extrapyramidal symptoms	6	NS	psychosis	NS	dose reduced	R
Frns & Major N 114957 N/A	N/A	13/M	Psychiatric sedation Central & peripheral nervous dizziness, leg numbness	4	2 days	hypomania	NS	dose reduced	R
Lombroso et al N 118174 N/A	2	12/M	Metabolic & nutritional weight increase	1	11-week period	motor tic disorder	NS	none	NS
Lombroso et al N 118174 N/A	3	12/F	Metabolic & nutritional weight increase Central & peripheral nervous muscle rigidity	2.5	11-week period	OC, motor tic disorder	NS	paroxetine for muscle stiffness	NS
Lombroso et al N 118174 N/A	4	12/M	Metabolic & nutritional weight increase	1	3-month period	ADHD, Tourette's	NS	none	NS

OC=obsessive-compulsive disorder; ADHD=attention-deficit hyperactivity disorder; N/A=not applicable; NS=not specified in report; R=recovered.

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Table 10. (Continued)...Summary of published safety information on the use of risperidone in adolescents (12 years up to 16 years)

Author(s) Accession No. Study No.	Patient	Age/ Sex	Body System Adverse Event	Dose (mg/day) at Onset	Time on Drug at Onset	Diagnosis	Concomitant Drugs	Action taken	Outcome
Lombroso et al N 118174 N/A	5	12/M	Metabolic & nutritional weight increase	1	11-week period	ADHD, depression, Tourette's	fluoxetine 10 mg/day	none	NS
Lombroso et al N 118174 N/A	6	13/F	Metabolic & nutritional weight increase	2.5	11-week period	OC, Tourette's	sertraline 100 mg/day	none	NS
Mandoki N 112364/1 N/A	8*	12/F	Metabolic & nutritional weight increase Central & peripheral nervous exacerbation of tics Psychiatric depression	6	1 month	Tourette's, OC, depression schizo-phreniform disorder	fluoxetine 10 mg/day	dose reduced initially then increased to treat tics	NS R R
Simeon et al N 112430/1 N/A	F	13/F	Psychiatric sedation	6	NS	delusional disorder, enuresis	imipramine, amphetamine 10 mg/day	dose reduced	R

*Safety information also included as a spontaneous adverse event report for Case No. 39330;
ADHD=attention-deficit hyperactivity disorder; OC=obsessive-compulsive disorder; NS=not specified in report; R=recovered.

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Table 11. Summary of published therapeutic effects of risperidone in adolescents (12 years up to 16 years)

Author(s) Accession No. Study No.	Patient	Age/ Sex	Dose (mg/day)	Duration of Treatment	Diagnosis	Concomitant Drugs	Therapeutic Effects
Simeon et al N 112430/1 N/A	C	15/M	2	6 months	schizophrenia, aggression	none	aggression controlled
Simeon et al N 112430/1 N/A	D	13/M	3	3 months	attention-deficit hyper-activity disorder	none	stable
Simeon et al N 112430/1 N/A	E	14/M	1	3 months	attention-deficit hyper-activity disorder	none	stable
Quintana, Keshavan N 116761 N/A	1	12/M	4	6 months	schizophrenia	chlorpromazine 50-100 mg/day	stable
Quintana, Keshavan N 116761 N/A	2	14/M	4	6 months	schizophrenia	chlorpromazine 50-100 mg/day	stable
Quintana, Keshavan N 116761 N/A	3	15/F	4	6 months	schizophrenia	none	stable
Ribeiro, Correia N 112260 N/A	N/A	15/F	1	NS	haloperidol-related neuroleptic malignant syndrome	bromocriptine 5 mg/day	symptoms resolved, stable

N/A=not applicable; NS=not specified in report.

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5.C. Spontaneous Adverse Drug Event Reports

A total of 115 spontaneous adverse drug events in adolescents receiving risperidone was reported during the period from January 1993 to March 31, 1996. Table 12 provides a summary of the adverse events, the dose at which the events occurred, and the outcome of each event where information of outcome was available.

5.C.1. Serious Adverse Drug Events

Of the 115 spontaneous adverse drug events reported in adolescents, 20 were considered serious. Table 13 and the following case narratives provide a summary of the serious adverse events, the dose at which the events occurred, and the outcome of each event where information of outcome was available.

Case No. 31979: Risperidone (3 mg/day) was started in a 15-year-old behaviorally disturbed boy after amitriptyline (Elavil®) was discontinued. After 13 days of risperidone, he developed neuroleptic malignant syndrome (muscle rigidity, tachypnea, and an increase in creatine phosphokinase). Immediate improvement in muscle rigidity was noted with administration of intravenous diphenhydramine (Benadryl®) and benztropine (Cogentin®). He received intravenous fluids and was placed on 10 liters of oxygen (via nasal cannula). Risperidone was discontinued. The patient showed considerable improvement in 15 days. There was no history of recent trauma, intramuscular injections, or prior history of neuroleptic malignant syndrome.

Case No. 35872: A 15-year-old boy with schizoaffective psychosis and bipolar disorder who was receiving risperidone (2 mg/day) concomitantly with lithium (Eskalith®) and paroxetine (Paxil®), developed neuroleptic malignant syndrome (dystonia, agitation, cogwheel rigidity, tachycardia, elevated creatine phosphokinase and leukocytosis and fever) after 2 weeks of treatment. All medications were discontinued, and intravenous fluids were started. The patient showed cleared mentation, decreased muscle rigidity and decreased creatine phosphokinase within 24 hours. The patient had no prior history of neuroleptic malignant syndrome.

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Case No. 39352: A 15-year-old boy was hospitalized and treated with haloperidol (Haldol®), lithium (Eskalith®), and benztropine (Cogentin®) for acute mania with psychotic features. The patient remained refractory to treatment and subsequently developed extrapyramidal symptoms, drooling, dystonia, and bradykinesia. Valproic acid (Depakene®) was added to the patient's regimen and treatment with haloperidol was discontinued. The patient was then started on amantadine (200 mg/day). The extrapyramidal symptoms abated promptly and treatment with benztropine and lithium was discontinued. Risperidone was then started at 2 mg/day and titrated up to 4 mg/day. All affective and psychotic symptoms resolved with risperidone but the patient developed extrapyramidal symptoms with bradykinesia, muscle rigidity, and drooling despite the concomitant administration of amantadine. The symptoms abated with the discontinuation of risperidone but the psychotic symptoms reemerged. After administering a single 1 mg dose of risperidone, the patient developed fever, tachycardia, tachypnea, and unstable blood pressure. He was diaphoretic, tremulous, and incontinent and exhibited muscular rigidity, severe dystonia, bradykinesia, and clouding of consciousness evolving into stupor. The patient was diagnosed with neuroleptic malignant syndrome and transferred to the intensive care unit. Risperidone and valproic acid were discontinued, bromocriptine 15 mg/day was started and amantadine 200 mg/day was continued. Over the next 10 days, the patient's rigidity, akinesia, and dystonia resolved but the patient remained confused for another 2 weeks before recovering completely.

Case No. 22369: A 14-year-old girl diagnosed with bipolar disorder and schizoaffective psychosis exhibited neuroleptic malignant syndrome (extreme fatigue, anorexia, increased sweating, fever, hyperkinesia, hypertonia, tachycardia, hypotension, and an increase in creatine phosphokinase) 8 days after beginning therapy with risperidone. Risperidone (1 mg/day), lithium (Eskalith®), and chlorpromazine (Thorazine®) were discontinued. Administration of intravenous fluids (orally), acetaminophen, and cool baths resulted in clinical recovery and a decrease in creatine phosphokinase.

Case No. 24529: A 12-year-old boy experienced a dystonic reaction after 5 days of therapy with risperidone (6 mg/day) for depression. The dystonia resolved after 3 successive doses of 50 mg of intravenous diphenhydramine. Previous therapy with chlorpromazine (Thorazine®) had been discontinued immediately before risperidone was started. After risperidone was discontinued and the dystonia resolved, chlorpromazine was restarted.

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Case No. 25286: A 14-year-old girl developed tremors after 6 days of risperidone therapy at 14 mg/day. The patient had been taking valproate sodium (Depakote®) and was switched to risperidone after developing tremors. The tremors that developed with risperidone improved when the dose was decreased to 8 mg daily.

Case No. 27441: A 15-year-old schizophrenic girl experienced 2 seizures after 25 days of treatment with risperidone (6 mg daily). The first episode was described as "shaking" of extremities with a brief period of unconsciousness and unresponsiveness and recovery in about 5 minutes. The patient was diagnosed with possible onset of diabetes mellitus type II and placed on a diabetic control diet. Risperidone was continued. A second episode involved brief loss of consciousness with flaccidity and periods of apnea mixed with tachypnea. The patient regained consciousness and recovered completely after suctioning of large amounts of phlegm and clearing of the airway. Risperidone was discontinued. At the time of reporting, an evaluation of an underlying nasal obstruction, present prior to risperidone therapy, was planned.

Case No. 30197: A 15-year-old psychotic boy experienced tardive dyskinesia with haloperidol (Haldol®) and molindone. These medications were discontinued and risperidone (3 mg/day) was started. Twenty weeks after starting risperidone, the boy experienced tardive dyskinesia again. The tardive dyskinesia totally abated for 5 months with a reduction in dose and then reappeared. Risperidone was discontinued. At the time of reporting, the patient was receiving clozapine. The tardive dyskinesia was continuing. Further follow-up was not possible.

Case No. 37805: A 14-year-old girl with a history of tardive dyskinesia (jaw movements) on chlorpromazine (Thorazine®) was switched to risperidone. After 6 weeks of treatment with risperidone at 3 mg/day, the patient experienced sedation, bed wetting, continued jaw movements, and eye blinking. The sedation and bed wetting improved by altering the administration of the risperidone dose to 1 mg in the morning and 2 mg in the evening. The dosing was then changed to 1 mg three times daily and benztropine (Cogentin®) and vitamin E were added to the therapy. Despite these changes, the tardive dyskinesia had not improved at the time of reporting.

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Case No. 39577: A 14-year-old schizoaffective girl titrated to a risperidone dose of 6 mg/day became non-compliant with her medication, which resulted in a rapid re-emergence of her psychosis requiring hospitalization. While off risperidone, the patient developed dyskinesia (spastic tongue protrusion). Risperidone was restarted while the patient was hospitalized and the abnormal tongue movements abated. At the time of reporting, risperidone therapy was continuing.

Case No. 33067: A 15-year-old girl was hospitalized after attempting suicide with 20 to 30 1-mg risperidone tablets. In the emergency room, she exhibited confusion and dystonia of the head and neck. She received charcoal and recovered.

Case No 45411: A 15-year-old girl with depression experienced a return of her symptoms within 24 hours of missing two doses (1 day) of risperidone. The girl had been treated with risperidone 0.5 mg twice daily (1 mg/day) for 2 weeks. She was hospitalized and risperidone was restarted. The patient responded to the treatment, recovered, and was released within 48 hours. The risperidone dose was titrated up to 2 mg twice daily (4 mg/day). Concomitant medications were not specified.

Case No. 40198: A 15-year-old girl hospitalized for psychosis experienced a catatonic reaction, urinary incontinence, inability to perform activities of daily living, and auditory hallucinations while on risperidone 0.5 mg/day. The patient had been admitted 3 weeks prior to the events for an acute onset of confusion and thought disorder. Risperidone was initiated during the third week of hospitalization after resolution of the acute episode. All organic causes of the admitting condition had been ruled out. At the time of reporting, the patient had not yet recovered and hospitalization had been prolonged.

Case No. 32581: A 14-year-old girl with cerebral palsy, chronic pulmonary problems, and a history of tachycardia experienced tachycardia after inadvertently being administered 8.5 mg of risperidone at a long-term care facility. Concomitant medications included cisapride (Propulsid®), salbutamol, phenobarbital, ranitidine (Zantac®), and Augmentin®. The patient was transferred to a medical facility, placed on antibiotics and IV fluids, and observed. The patient recovered and was readmitted to the long-term care facility where she stabilized quickly.

Case No. 41884: A 14-year-old girl on risperidone 4 mg/day for 20 weeks and amfebutamone 400 mg/day (duration not specified) experienced right bundle branch block during a routine electrocardiogram. The patient had had a heart murmur during a previous hospitalization. An electrocardiogram and echocardiogram done at that time revealed only short P-R intervals, an

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equivocal intermittent trace mitral regurgitation, and normal biventricular size and function; no intervention was required. The bundle branch block was a new finding on the routine electrocardiogram performed after risperidone was started. The patient was asymptomatic and was discharged from the hospital. Risperidone therapy was continued.

Case No. 35161: A 13-year-old girl diagnosed with depression and anxiety exhibited edema of the pharynx and tongue, orthostatic hypotension, tachycardia, dyspnea, dysarthria, hypertonia, disorientation, and pallor. Risperidone (2 mg/day) therapy had been started 1.5 days earlier. Diphenhydramine was administered intravenously and the symptoms resolved within 10 minutes. A toxicology screen for drugs of abuse, acetylsalicylic acid, and paracetamol was negative. Risperidone was discontinued. Additional information has been requested.

Case No. 26087: A 15-year-old schizophrenic boy began vomiting, and was hospitalized after a 1-mg dose of risperidone. Risperidone was discontinued and an antiemetic was added. Nausea and vomiting resolved 3 days later. There was no prior history of neuroleptic therapy.

Case No. 43508: A 15-year-old girl developed increased prolactin levels, galactorrhea, and decreased thyroid stimulating hormone (TSH) levels while taking risperidone 8 mg daily, haloperidol, salbutamol, and diphenhydramine. Risperidone therapy was initiated 1-2 months prior to the report; dates of concomitant drug therapies were not specified. The prolactin level was 204 ng/mL and the TSH level was 0.3 (0.5 is the lower limit of normal); T4 and free T4 were within normal limits. Magnetic resonance imaging (MRI) revealed a pituitary microadenoma but no baseline MRI was available. At the time of reporting, the same dose of risperidone was continued and the general outcome of the patient was still pending.

Case No. 37020: A 13-year-old boy developed priapism 11 months after starting risperidone therapy (1 mg/3 times daily) for attention deficit disorder. Risperidone was discontinued, a surgical procedure was performed, and the priapism resolved. Treatment with amitriptyline (Elavil®) had been discontinued 2 weeks prior to the adverse event.

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Case No. 28503: A 15-year-old boy with Tourette's syndrome experienced recurrent episodes of respiratory distress after approximately 6 months of therapy with risperidone at 2 mg/day. The patient was also being treated with benztropine (Cogentin®) and diazepam. Diphenhydramine (Benadryl®) was added with no change. Treatment with risperidone was not discontinued. At the time of reporting, the adverse event had not resolved.

5.C.2. TREATMENT DISCONTINUATION

Risperidone was discontinued in 43 of the 115 adolescents who experienced adverse events, including 11 of the 20 adolescents with serious adverse events. Details of the events leading to discontinuation of treatment for the adolescents with serious adverse events are summarized in Table 14 and in the case narratives previously described in Section 5.C.1. A summary of all treatment discontinuations is provided in Table 15.

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Table 12. Summary of pharmacovigilance reports of adverse drug events in adolescents (12 years up to 16 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
	Central & peripheral nervous						
31979	neuroleptic malignant syndrome	15/M	3	13 days	Elavil®	DS/H/Rx	NR
35872	neuroleptic malignant syndrome	15/M	2	2 weeks	lithium/Paxil®	DS/H/Rx	R
39352	neuroleptic malignant syndrome	15/M	1	1 day	Depakene®/amantadine	DS/H/Rx	R
22369	neuroleptic malignant syndrome	14/F	1	8 days	lithium/Cogentin®/Thorazine®	DS/H/Rx	R
30197	tardive dyskinesia	15/M	3	20 weeks	NS	DS	NR
37805	tardive dyskinesia	14/F	3	6 weeks	Thorazine®	Rx	NR
29089	dystonia	15/F	1-3	2 days	none	DS/Rx	R
24529	dystonia	12/M	6	5 days	doxepin/acetazolamide	DS/H/Rx	R
39577	dyskinesia	14/F	6	NS	NS	H	R
25286	tremor	14/F	14	6 days	Benadryl®	DR/H	NR
27441	convulsions	15/F	6	25 days	isoniazid/beclomethasone	DS/H	R
33221	neuritis (sensory)	14/F	4	23 days	NS	none	NR
38172	dizziness	13/M	4	NS	NS	none	R
27684	dizziness	13/F	3	NS	lithium	DS	NR
25117	confusion	12/M	3	10 days	multiple*	DS	NR
44620	dizziness	14/F	2	14 months	Blaxin®/Claritin®	none	NR
41903	dizziness	15/F	2	NS	Ritalin®/Tofranil®	NS	NR
44232	extrapyramidal disorder	NS	NS	NS	NS	none	NR
	Reproductive female						
33102	lactation, nonpuerperal	14/F	2	NS	NS	none	NR
38488	lactation, nonpuerperal	15/F	NS	NS	NS	none	NR
33238	lactation, nonpuerperal	15/F	4	5 weeks	Paxil®/Haldol®	DS	R
33243	lactation, nonpuerperal	15/F	4	NS	Prozac®	none	NR
30926	lactation, nonpuerperal	15/F	NS	7 months	lithium	DS	R
35922	amenorrhea	13/F	6	17 days	lithium/Tegretol®/Cogentin®	Rx	NR
38335	lactation, nonpuerperal	15/F	6	13 weeks	Zoloft®	DS	NR
33234	lactation, nonpuerperal	15/F	2	7 days	Zoloft®/lithium	DS	NR
33242	lactation, nonpuerperal	15/F	2	6 weeks	Prozac®	DS	R

*Norpramin® (desipramine), Thorazine®, Stelazine®, lithium, Synthroid®, Desyrel®, Cogentin®, Depakote®. NS=not specified; NR=not recovered at time of report; R=resolved; DS=drug stopped; Rx=prescription or supportive therapy; H=hospitalization; DR=dose reduced.

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Table 12. (Continued)...Summary of pharmacovigilance reports of adverse drug events in adolescents (12 years up to 16 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
	Reproductive female (cont'd)						
41909	lactation, nonpuerpal	14/F	6	13 days	Tegretol®/Prozac®	DR	NR
43424	lactation, nonpuerpal	15/F	NS	NS	NS	DS	NR
39956	amenorrhea	15/F	4	NS	NS	none	NR
	Urinary						
27954	urinary incontinence	12/M	NS	NS	NS	NS	NR
27952	urinary incontinence	12/M	NS	NS	NS	NS	NR
24653	urinary incontinence	13/F	6	2 days	Depakote®/Zoloft®	none	U
27953	urinary incontinence	13/M	NS	NS	NS	NS	NR
26850	urinary incontinence	13/M	1	1 day	Prozac®	DS	R
30126	urinary incontinence	14/M	NS	NS	lithium	D▲	U
38712	urinary retention	12/F	6	NS	Luvox®	DR	NR
41598	urinary incontinence	12/M	2	NS	Paxil®/Depakote®	DR/Rx	NR
43234	urinary retention	12/F	6	8 days	Luvox®/Benadryl®/Ativan®	DR	R
42120	urinary incontinence	12/M	1.5	7 days	NS	none	U
44904	urinary incontinence	14/M	0.25	3 days	lithium	DS	R
	Psychiatric						
32309	somnolence	14/M	6	5 days	lithium	DR	NR
29181	somnolence	15/M	2	NS	Anafranil®	none	NR
27908	agitation	15/M	6	3 days	NS	DI/Rx	NR
27904	insomnia	13/F	5	21 days	NS	DR/Rx	R
30940	nervousness	15/F	3	NS	Ortho-Novum®	none	NR
39579	hallucinations	12/M	2	2 days	Cogentin®	DI	R
33067	suicide attempt	15/F	25	NS	NS	DS/Rx/H	R
41171	aggressive reaction	14/M	5	13 weeks	NS	NS	NR
40198	catatonic reaction	15/F	0.5	1 week	NS	H	NR
39330*	depression	12/F	6	1 month	Prozac®	DR/Rx	U
45411	depression aggravated	15/F	NA †	NA †	NS	DI/H	R

*Safety information was also included in a publication: *Journal of Child and Adolescent Psychopharmacology* 1995; 5(1):49-67.NS=not specified; NR=not recovered at time of report; R=resolved; U=unknown; DS=drug stopped; Rx=prescription or supportive therapy; H=hospitalization; DI=dose increased; DR=dose reduced; D▲=dose changed, new dose not specified. †Symptoms returned within 24 hours of missing 2 doses.

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Table 12. (Continued)...Summary of pharmacovigilance reports of adverse drug events in adolescents (12 years up to 16 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
	Metabolic & nutritional						
32055	weight increase	13/M	4	6 months	Prozac®	none	NR
39129	weight increase	15/M	4	3 months	NS	none	NR
37061	weight increase	15/M	2-6	7.5 months	Cogentin®	DS	U
35313	weight increase	15/M	6	4 months	NS	none	NR
26524	creatine phosphokinase increase	13/F	2	5 days	NS	DS	R
28835	alkaline phosphatase increase	15/M	4	14 weeks	Cogentin®/Prozac®	DS	R
43968	weight increase	15/M	18	NS	NS	none	NR
40186	glycosuria	13/F	4	NS	Catapres®/Depakote®/Zoloft®	DS	R
42760	weight increase	14/M	NS	8 months	Prozac®	NS	NR
40192	weight increase	NS/F	NS	NS	NS	none	NR
	Gastrointestinal						
28278	vomiting	12/M	2	1 week	NS	none	NR
36767	vomiting	13/M	2	1 day	Navane®/lithium	none	NR
37862	dysphagia	15/M	6	2 weeks	Pen-Vee K®/Benadryl®	DR/DS/Rx	NR
26087	vomiting	15/F	1	1 day	NS	DS/Rx/H	R
37255	vomiting	15/F	2	1 day	NS	Rx	NR
27698	hypersalivation	15/M	1	5 days	Prozac®/Dexedrine®	none	NR
44353	tongue edema	15/M	NS	NS	Thorazine®/Haldol®/Benadryl®	DS/Rx	R
40424	vomiting	12/M	2	1 day	NS	none	NR
	Heart rate & rhythm						
25291	tachycardia	15/M	4	6 days	lithium	Rx	NR
29263	tachycardia	15/M	2	NS	Anafranil®	none	NR
32581	tachycardia	14/F	8.5	1 day	multiple*	Rx/H	R
33236	bradycardia	14/M	3	9 weeks	Eskalith®	DS	R
41884	bundle branch block	14/F	4	20 weeks	amfebutamone	H	NR
43530	arrhythmia	13/F	NS	27 days	Catapres®	DS	NR
42071	tachycardia	NS/F	NS	NS	NS	NS	NR

*Cisapride (Propulsid®), salbutamol, phenobarbital, ranitidine (Zantac®), Augmentin®; NS=not specified; NR=not recovered at time of report; R=resolved; U=unknown; DS=drug stopped; Rx=prescription or supportive therapy; H=hospitalization; DR=dose reduced.

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Table 12. (Continued)...Summary of pharmacovigilance reports of adverse drug events in adolescents (12 years up to 16 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
	Skin & appendages						
35319	rash	13/M	2	1 day	NS	none	NR
30298	rash	14/M	3	NS	NS	Rx	R
28277	rash	14/M	1.5	7 weeks	NS	DS	R
33617	urticaria	13/M	3	7 weeks	nortriptyline	DS/Rx	NR
34337	sweating increase	14/M	4	NS	NS	none	NR
44164	alopecia	12/F	1	15 weeks	Inderal®/Cogentin®	none	NR
42296	rash	14/F	6	13 days	NS	DS	R
	Body as a whole						
29228	condition aggravated	13/M	6	5 weeks	NS	NS	NR
37357	therapeutic response decrease	15/F	10	NS	NS	none	NR
27446	therapeutic response decrease	15/F	6	7 days	NS	DI	NR
26235	edema	15/M	1	3 days	NS	DS	R
35161	edema, pharynx	13/F	2	1 day	Prozac®	DS/Rx	R
44202	chills	14/M	1	NS	NS	none	R
26776	fatigue	15/M	3	1 month	NS	NS	U
	Vision						
34607	blurred vision	13/M	4	1 week	Cylert®	none	NR
33235	blurred vision	13/M	8	NS	Prozac®/lithium	DS	R
28021	mydriasis	15/F	1	26 days	none	DR	NR
38582	blepharospasm	13/M	2	21 days	Buspar®	DS	NR
31613	diplopia	14/M	NS	3 months	NS	none	R
42114	blurred vision	14/F	2	NS	Depakote®/Zoloft®	none	NR
	Endocrine						
28860	hyperprolactinemia	15/F	6	27 days	Haldol®	DS	R
27524	gynecomastia	15/M	12	12 weeks	multiple*	DR	NR
38164	breast discharge	12/M	3	7 weeks	Ritalin®/Tenex®/nortriptyline	none	NR

*Haldol®, Depakote®, Inderal®, nitroglycerin, Prilosec®, Surfak®, scopolamine; NS=not specified; NR=not recovered at time of report; R=resolved; U=unknown; DS=drug stopped; Rx=prescription or supportive therapy; H=hospitalization; DI=dose increased; DR=dose reduced.

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Table 12. (Continued)...Summary of pharmacovigilance reports of adverse drug events in adolescents (12 years up to 16 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
	Endocrine (continued)						
40203	hyperprolactinemia	13/F	3	NS	Catapres®	NS	NR
41083	lactation, male	14/M	6	17 days	NS	DS	NR
	White cell & reticuloendothelial						
38324	neutropenia	15/M	4	15 days	Navane®	DS	R
36930	neutropenia	15/F	6	8 weeks	NS	none	R
39488	leucopenia	15/M	1	7 days	none	DS	NR
	Cardiovascular						
34990	cyanosis	13/M	2	11 weeks	Ritalin®/beclomethasone	none	NR
35932	hypotension, orthostatic	14/F	2	3 weeks	Zoloft®	DS/Rx	R
42517	hypotension, orthostatic	14/M	2	3 days	Navane®/Cogentin®	NS	U
	Liver & biliary						
29354	hepatic enzymes increase	12/NS	NS	NS	Buspar®/Depakote®	NS	U
34424	aspartate aminotransferase increase	15/M	5	NS	NS	DS	R
	Bleeding & clotting						
24118	epistaxis	15/M	1	2 days	Cogentin®/nortriptyline	DS	R
	Reproductive male						
37020	priapism	13/M	3	11 months	Elavil®/Ritalin®	DS/Rx/H	R
	Collagen disorders						
44222	antinuclear factor test positive	13/F	NS	NS	Prozac®	none	NR
	Neoplasms						
43508	pituitary neoplasm	15/F	8	1-2 months	Haldol®/Proventil®/Benadryl®	none	NR
	Respiratory						
28503	dyspnea	15/M	2	6 months	diazepam/Cogentin®	DR/Rx/H	NR
Total number of adverse events reported in adolescent patients: 115							

NS=not specified; NR=not recovered at time of report; R=resolved; U=unknown; DS=drug stopped; Rx=prescription or supportive therapy; H=hospitalization; DR=dose reduced.

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Table 13. Summary of pharmacovigilance reports of serious adverse drug events in adolescents (12 years up to 16 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
	Central & peripheral nervous						
31979	neuroleptic malignant syndrome	15/M	3	13 days	Elavil®	DS/Rx/H	NR
35872	neuroleptic malignant syndrome	15/M	2	2 weeks	lithium/Paxil®	DS/Rx/H	R
39352	neuroleptic malignant syndrome	15/M	1	1 day	Depakene®/amantadine	DS/Rx/H	R
22369	neuroleptic malignant syndrome	14/F	1	8 days	lithium/Cogentin®/Thorazine®	DS/Rx/H	R
24529	dystonia	12/M	6	5 days	Doxepin®/acetazolamide	DS/Rx/H	R
25286	tremor	14/F	14	6 days	Benadryl®	DR/H	NR
27441	convulsions	15/F	6	25 days	isoniazid/beclomethasone	DS/H	R
30197	tardive dyskinesia	15/M	3	20 weeks	NS	DS	NR
37805	tardive dyskinesia	14/F	3	6 weeks	Thorazine®	Rx	NR
39577	dyskinesia	14/F	6	NS	NS	H	R
	Psychiatric						
33067	suicide attempt	15/F	25	NS	NS	DS/Rx/H	R
45411	depression aggravated	15/F	NA †	NA †	NS	DI/H	R
40198	catatonic reaction	15/F	0.5	1 week	NS	H	NR
	Heart rate & rhythm						
32581	tachycardia	14/F	8.5	NS	multiple*	Rx/H	R
41884	bundle branch block	14/F	4	20 weeks	amfebutamone	H	NR
	Body as a whole						
35161	edema, pharynx	13/F	2	1.5 days	Prozac®	DS/Rx	R
	Neoplasms						
43508	pituitary neoplasm	15/F	8	1-2 months	Proventil®/Benadryl®	none	NR
	Gastrointestinal						
26087	vomiting	15/M	1	1 day	NS	DS/Rx/H	R

*Cisapride (Propulsid®), salbutamol, phenobarbital, ranitidine (Zantac®), Augmentin®; NS=not specified in report; NR=not recovered at time of report; R=recovered; DR=dose reduced; DS=drug stopped; Rx=prescription or supportive therapy; H=hospitalization. † Symptoms returned within 24 hours of missing 2 doses.

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Table 13. (Continued...) Summary of pharmacovigilance reports of serious adverse drug events in adolescents (12 years up to 16 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
37020	Reproductive male priapism	13/M	3	11 months	Elavil®/Ritalin®	DS/Rx/H	R
28503	Respiratory dyspnea	15/M	2	6 months	diazepam/Cogentin®	DR/Rx/H	NR
Total number of serious adverse events reported in adolescent patients: 20							

NS=not specified in report; NR=not recovered at time of report; R=recovered; DR=dose reduced; DS=drug stopped; Rx=prescription or supportive therapy; H=hospitalization.

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Table 14. Summary of pharmacovigilance reports of serious adverse drug events leading to discontinuation of treatment in adolescents (12 years up to 16 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
	Central & peripheral nervous						
31979	neuroleptic malignant syndrome	15/M	3	13 days	Elavil®	DS/Rx/H	NR
35872	neuroleptic malignant syndrome	15/M	2	2 weeks	lithium/Paxil®	DS/Rx/H	R
39352	neuroleptic malignant syndrome	15/M	1	1 day	Depakene®/amantadine	DS/Rx/H	R
22369	neuroleptic malignant syndrome	14/F	1	8 days	lithium/Cogentin®/Thorazine®	DS/Rx/H	R
27441	convulsions	15/F	6	25 days	isoniazid/beclomethasone	DS/H	R
24529	dystonia	12/M	6	5 days	Doxepin®/acetazolamide	DS/Rx/H	R
30197	tardive dyskinesia	15/M	3	20 weeks	NS	DS	NR
	Body as a whole						
35161	edema, pharynx	13/F	2	1.5 days	Prozac®	DS/Rx	R
	Gastrointestinal						
26087	vomiting	15/M	1	1 day	NS	DS/Rx/H	R
	Reproductive male						
37020	priapism	13/M	3	11 months	Elavil®/Ritalin®	DS/Rx/H	R
	Psychiatric						
33067	suicide attempt	15/F	25	NS	NS	DS/Rx/H	R
Total number of serious adverse events leading to discontinuation of treatment in adolescent patients: 11							

NS=not specified in report; NR=not recovered at time of report; R=recovered; DS=drug stopped; Rx=prescription or supportive therapy; H=hospitalization.

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Table 15. Summary of pharmacovigilance reports of treatment discontinuations due to adverse events in adolescents (12 years up to 16 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
	Central & peripheral nervous						
31979	neuroleptic malignant syndrome	15/M	3	13 days	Elavil®	DS/Rx/H	NR
35872	neuroleptic malignant syndrome	15/M	2	2 weeks	lithium/Paxil®	DS/Rx/H	R
39352	neuroleptic malignant syndrome	15/M	1	1 day	Depakene®/amantadine	DS/Rx/H	R
22369	neuroleptic malignant syndrome	14/F	1	8 days	lithium/Cogentin®/Thorazine®	DS/Rx/H	R
30197	tardive dyskinesia	15/M	3	20 weeks	NS	DS	NR
29089	dystonia	15/F	1-3	2 days	none	DS/Rx	R
24529	dystonia	12/M	6	5 days	doxepin/acetazolamide	DS/Rx/H	R
27441	convulsions	15/F	6	25 days	isoniazid/beclomethasone	DS/H	R
27684	dizziness	13/F	3	NS	lithium	DS	NR
25117	confusion	12/M	3	10 days	multiple*	DS	NR
	Reproductive female						
33238	lactation, nonpuerperal	15/F	4	5 weeks	Paxil®/Haldol®	DS	R
30926	lactation, nonpuerperal	15/F	NS	7 months	lithium	DS	R
38335	lactation, nonpuerperal	15/F	6	13 weeks	Zoloft®	DS	R
33234	lactation, nonpuerperal	15/F	2	7 days	Zoloft®/lithium	DS	NR
33242	lactation, nonpuerperal	15/F	2	6 weeks	Prozac®	DS	R
43424	lactation, nonpuerperal	15/F	NS	NS	NS	DS	NR
	Metabolic & nutritional						
37061	weight increase	15/M	2-6	7.5 months	Cogentin®	DS	U
26524	creatine phosphokinase increase	13/F	2	5 days	NS	DS	R
28835	alkaline phosphatase increase	15/M	4	14 weeks	Cogentin®/Prozac®	DS	R
40186	glycosuria	13/F	4	NS	Catapres®/Depakote®/Zoloft®	DS	R
	Gastrointestinal						
37862	vomiting	15/M	6	2 weeks	Pen-Vee K®/Benadryl®	DR/DS/Rx	NR
26087	vomiting	15/F	1	1 day	NS	DS/Rx/H	R
44353	tongue edema	15/M	NS	NS	Thorazine®/Haldol®/Benadryl®	DS/Rx	R

*Norpramin®(desipramine), Thorazine®, Stelazine®, lithium, Synthroid®, Desyrel®, Cogentin®, Depakote®; NS=not specified; NR=not recovered at time of report; R=recovered; U=unknown; H=hospitalization; DS=drug stopped; DR=dose reduced; Rx=prescription or supportive therapy.

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Table 15. (Continued)...Summary of pharmacovigilance reports of treatment discontinuations due to adverse events in adolescents (12 years up to 16 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
	Skin & appendages						
28277	rash	14/M	1.5	7 weeks	NS	DS	R
33617	urticaria	13/M	3	7 weeks	nortriptyline	DS/Rx	NR
42296	rash	14/F	6	13 days	NS	DS	R
	Vision						
33235	blurred vision	13/M	8	NS	Prozac®/lithium	DS	R
38582	blepharospasm	13/M	2	21 days	Buspar®	DS	NR
	Urinary						
26850	urinary incontinence	13/M	1	1 day	Prozac®	DS	R
44904	urinary incontinence	14/M	0.25	3 days	lithium	DS	R
	Heart rate & rhythm						
33236	bradycardia	14/M	3	9 weeks	Eskalith®	DS	R
43530	arrhythmia	13/F	NS	27 days	Catapres®	DS	NR
	Body as a whole						
26235	edema	15/M	1	3 days	NS	DS	R
35161	edema, pharynx	13/F	2	1 day	Prozac®	DS/Rx	R
	Endocrine						
28860	hyperprolactinemia	15/F	6	27 days	Haldol®	DS	R
41083	lactation, male	14/M	6	17 days	NS	DS	NR
	White cell & reticuloendothelial						
38324	neutropenia	15/M	4	15 days	Navane®	DS	R
39488	leucopenia	15/M	1	7 days	none	DS	NR
	Psychiatric						
33067	suicide attempt	15/F	25	NS	NS	DS/Rx/H	R

NS=not specified; NR=not recovered at time of report; R=recovered; U=unknown; H=hospitalization; DS=drug stopped; Rx=prescription or supportive therapy.

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Table 15. (Continued)...Summary of pharmacovigilance reports of treatment discontinuations due to adverse events in adolescents (12 years up to 16 years)

Case No.	Body System Adverse Event	Age/ Sex	Dose (mg/day) at Onset	Time on Drug at Onset	Concomitant Drugs	Action Taken	Outcome
35932	Cardiovascular hypotension, orthostatic	14/F	2	3 weeks	Zoloft®	DS/Rx	R
34424	Liver & biliary aspartate aminotransferase increase	15/M	5	NS	NS	DS	R
24118	Bleeding & clotting epistaxis	15/M	1	2 days	Cogentin®/nortriptyline	DS	R
37020	Reproductive male priapism	13/M	3	11 months	Elavil®/Ritalin®	DS/Rx/H	R
Total number of adverse events leading to discontinuation in adolescent patients: 43							

NS=not specified in report; R=recovered; DS=drug stopped; Rx=prescription or supportive therapy; H=hospitalization.

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6. SAFETY IN CHILDREN/ADOLESCENTS (AGES NOT SPECIFIED)

6.A. JANSSEN-SPONSORED CLINICAL STUDIES

The safety results of RIS-BEL-11 are summarized below. The results of this study were also included in a publication by Vanden Borre et al (*Acta Psychiatr Scand* 1993; 87:167-171.); general safety information described in the publication is summarized in Section 6.B. below.

Study No. RIS-BEL-11[15]: This was a multicenter, double-blind, randomized, parallel-group, cross-over trial comparing risperidone 4-12 mg with placebo in 37 mentally retarded patients ranging in age from 15 to 65 years. Qualifying patients for the trial were given placebo or risperidone as an oral solution. Risperidone treatment was well tolerated. Sedation was reported 10 times and dizziness 6 times as a treatment-emergent adverse event under risperidone treatment.

6.B. PUBLISHED STUDIES AND CASE REPORTS

Safety information of risperidone in children and adolescents whose ages have not been reported is summarized below and in Table 16.

Acri and Henretig[16] described (in an abstract) the results of an 8-month prospective study of 16 cases (15 adults, 1 pediatric) of risperidone overdose reported to a regional poison control center. Risperidone was the only ingestant in 9 cases (42-180 mg). Effects included lethargy (4), hypotension (2), tachycardia (6), dystonia (1), electrocardiographic changes (2), and muscle spasm (1). Treatment required included an antiarrhythmic, diphenhydramine, an anticonvulsant, mechanical ventilation, and supportive care. Risperidone toxicity manifested primarily as reversible neuromuscular and cardiovascular effects from which all patients recovered fully. Whether or not the pediatric patient experienced an adverse effect was not specified in the publication. Information regarding the age and sex of the pediatric patient also was not specified.

Armenteros et al[17] reported a study of 5 patients aged 13 to 16 years. General safety information for 4 of the 5 patients (1 transferred to another institution after 4 weeks) was reported. Risperidone was administered at doses ranging from 4 to 8 mg/day (mean: 6.4 mg/day). Adverse events were mild somnolence in 3 patients (did not interfere with their functioning), an acute dystonic reaction in 1 patient, parkinsonism requiring continuous treatment with benztropine in 1 patient, and weight gain in 3 patients. The duration of the

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study was not indicated. Three of the patients had experienced adverse events during previous neuroleptic trials. The information reported did not include patient-specific information with regard to sex, gender, adverse events, and outcomes of adverse events.

Fras and Major[12] reported preliminary observations of 6 patients ranging in age from 8 to 14 years, who were treated with risperidone for aggressive behaviors. Four patients (whose age and sex were not specified) had been diagnosed with attention-deficit hyperactivity disorder with comorbid conduct disorder; 2 patients (age and sex not specified) had been diagnosed with bipolar disorder. Following risperidone treatment, the most frequently reported side effect for all patients was sedation with a reported "spacey" look, which was dose-related. Extrapyramidal effects were also reported. The age and sex of the patients with extrapyramidal dysfunction were not specified by the authors. With daily doses of less than 3 mg in adolescents and less than 2 mg in children, the extrapyramidal side effects resolved. None of the adverse events led to discontinuation of treatment.

Grcevich et al[18] presented a poster of a retrospective efficacy and safety review of 17 patients treated with risperidone for psychotic illnesses. Of these patients, 2 were children (9 and 11 years) and 6 were adolescents (12 to 15 years of age). (Nine patients did not meet the age criteria for inclusion in this safety review.) Risperidone doses ranged from 2-4 mg/day for the children and from 3-10 mg/day for the adolescents. All patients were evaluated by 2 psychiatrists. Adverse events were observed in 7 of the 17 patients (whose age and sex were not specified) by 1 psychiatrist and in 11 of the 17 patients (whose age and sex were not specified) by the other psychiatrist. Each psychiatrist reported only one patient (age and sex not specified) of the 17 patients in whom an adverse event "significantly interfered" with the patient's activities. The adverse events were not described and no information was provided with regard to adverse events that may have led to treatment discontinuation.

Kuspis et al[19] retrospectively assessed the toxic effects of all risperidone exposures reported to a regional poison control center over a 15-month period. Of the 31 cases reported during this period, 11 were pediatric exposures (mean age: 12.1 years). The mean amount of risperidone ingested by the pediatric patients was 11.7 mg. Either as the sole ingestant or as a coingestant, risperidone overdoses were not associated with any moderate or life-threatening effects. Adverse events were lethargy or tachycardia, which required no treatment. Gastric decontamination and supportive care appeared to provide adequate intervention in all cases. Patient-specific information was not provided in the publication.

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Lombroso et al[5] reported safety information from an 11-week, open-label trial of risperidone in 7 patients with chronic tic disorders. Of the 7 patients, 5 were adolescents (ages: 12 to 13 years) and 1 was a child (age: 11 years). (One patient did not meet the age criteria for inclusion in this safety review.) Risperidone doses ranged from 1-2.5 mg/day. Following treatment with risperidone, 4 patients (whose age, sex, and patient identification number were not specified) experienced tiredness, but it was not severe or persistent and resulted in the lowering of the dose in only one case (age, sex, and patient identification number not specified). One patient (Patient 3) experienced muscle stiffness and 1 patient (whose age, sex, and patient identification number were not specified) experienced photophobia in the first 2 weeks of treatment, which spontaneously resolved thereafter. Weight gain (8 to 14 pounds) was the most frequent side effect observed in all 5 of the adolescent patients (Patients 2, 3, 4, 5, and 6) during risperidone treatment. In 4 patients (Patient 4 and three other patients whose age, sex, and patient identification number were not specified), the weight gain coincided with increases in appetite. None of the patients elected to stop risperidone treatment because of the weight gain. Safety information for the adolescent patients for whom the age and sex were specified (Patients 2, 3, 4, 5, and 6) is provided in Section 5.B.; information for the child (Patient 1) is provided in Section 4.B.

Mandoki reported (as abstracts only) the results of 3 retrospective studies of "children and adolescents" (ages not specified) treated with risperidone. In a study[20] of five children with Tourette's syndrome (risperidone 6 mg/day), the most common adverse event according to the author was weight gain; no other adverse events were specified. In a study[21] of risperidone (dose not specified) in children and adolescents who were hospital inpatients (diagnoses not reported), 15 of 30 patients experienced extrapyramidal symptoms and received anticholinergic medications. The incidence of extrapyramidal symptoms was not related to age, risperidone dose, or primary diagnosis. Other adverse events were not specified. Adverse events were not reported in a third study[22] of risperidone (dose not specified) in children and adolescents with schizophrenia.

Simeon[23] reported general safety information for 21 patients who had been treated with risperidone for a variety of psychiatric disorders. The patients ranged in age from 4 to 20 years (mean age: 11.4 years). Risperidone treatment was titrated gradually for all patients and the optimal daily dosage for the pediatric patients ranged from 0.5 to 6 mg (mean: 1.4 mg). The duration of risperidone treatment for the "pediatric patients" (age and sex not specified) ranged from 1 to 28 months (mean: 7.8 months). Four patients (age and sex not specified) experienced significant sedation, which resolved with a reduction in the daily dose. Marked weight gain was experienced by 3 patients (age and sex not specified) and 1 patient (age and sex not specified) experienced a

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dystonic reaction. Information regarding the severity of the adverse events or whether treatment was discontinued was not specified in the publication.

Vanden Borre et al[24] reported safety information for 37 mentally retarded patients between the ages of 15 and 58 years (mean age: 30.5 years) who participated in a double-blind, randomized, cross-over study comparing risperidone 4-12 mg with placebo. The number of adolescent patients who participated in the trial was not specified in the publication. Sedation was reported 10 times and drowsiness 6 times as a treatment-emergent adverse event for patients receiving risperidone. No difference in the incidence of extrapyramidal effects was observed between patients on risperidone and placebo. The severity of the adverse events and information on who experienced the events were not specified in the publication.

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Table 16 Summary of published safety information on the use of risperidone in children and adolescents (ages not specified)

Author(s) Accession No. Study No.	Age Range (years)	Number of Patients	Adverse Events (number of reports)	Dose (mg/day) at Onset	Time on Drug at Onset	Diagnosis	Action Taken	Outcome
Acri & Henretig N 114954 N/A	NS	15 adults 1 pediatric	lethargy (4) hypotension (2) tachycardia (6) dystonia (1) electrocardiographic changes (2) muscle spasm (1)	42-180 mg overdoses	NS	NS	antiarrhythmic, diphenhydramine, anticonvulsants, mechanical ventilation, supportive care	all patients recovered
Armenteros et al N 111963/1 N/A	13-16	5	somnolence (3) acute dystonic reaction (1) parkinsonism (1) weight gain (3)	4-8 mean: 6.4	NS	NS	benztropine for parkinsonism	NS
Fras & Major N 114957 N/A	8-14	6	sedation, "spacey look" (6) extrapyramidal effects (NS)	<2 in children; <3 in adolescents	NS	ADHD* (4) bipolar disorder (2)	treatment continued	NS
Grcevich et al N 118489 N/A	9-11 12-15	2 children 6 adolescents	NS	2-4 children 3-10 adolescents	NS	NS	NS	NS
Kuspis et al N 114955 N/A	mean: 12.1	11 pediatric	lethargy (NS) tachycardia (NS)	overdoses	NS	NS	gastric decontamination supportive care	NS
Lombroso et al N 118174 N/A	11, 12-13	1 child 5 adolescents	tiredness (4) muscle stiffness (1) photophobia (1) weight gain (5) increased appetite (4)	1-2.5	NS	NS	treatment continued	NS

N/A=not applicable; NS=not specified in report; *ADHD=attention-deficit hyperactivity disorder.

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Table 16 (Continued)...Summary of published safety information on the use of risperidone in children and adolescents (ages not specified)

Author(s) Accession No. Study No.	Age Range (years)	Number of Patients	Adverse Events (number of reports)	Dose (mg/day) at onset	Time on Drug at Onset	Diagnosis	Action Taken	Outcome
Mandoki N 112434/1 N/A	NS	5 children	weight gain (NS)	NS	NS	Tourette's	NS	NS
Mandoki N 112436/1 N/A	NS	30 children & adolescents	extrapyramidal symptoms (15)	NS	NS	NS	anticholinergics	NS
Mandoki N 112439/1 N/A	NS	NS	no adverse events	N/A	N/A	N/A	N/A	N/A
Simeon N 116688/1 N/A	4-20 mean: 11.4	21	sedation (4) weight gain (3) dystonic reaction (1)	0.5-6, mean: 1.4	1-28 months, mean: 7.8 months	"psychiatric disorders"	reduction in dose for sedation; no action specified for weight gain, dystonic reaction	R: sedation; NS: weight, dystonic reaction
Vanden Borre et al N 80878 RIS-BEL-11	15-58 mean: 30.5	37	sedation (10) drowsiness (6)	4-12	NS	mental retardation	NS	NS

NS=not specified in report; NR=not recovered at time of report; R=recovered; N/A=not applicable.

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7. DOSE RANGES AND EXTENT OF EXPOSURE

7.A. DOSE RANGES

Of the pediatric population (<16 years of age) described in this summary, 48% (102/223) received risperidone in doses ranging from 1.0 mg to <4.0 mg/day. Summaries of the risperidone dose ranges are provided by source of information in Table 17, by the source of information and the age category of 2 years up to 12 years in Table 18, and by the source of information and age category of 12 years up to 16 years in Table 19.

7.B. EXTENT OF EXPOSURE

More than half (60%, 133/223) of the pediatric population received risperidone for periods ranging from >0 to <3 months. The extent of the pediatric exposure to risperidone is summarized by source of information in Table 20.

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Table 17. Dose range of risperidone in pediatric population (<16 years of age) by source of data

Dose Ranges (mg/day)	Number (%) Patients			
	Clinical Trials N=14	Literature N=29*	Spontaneous Adverse Event Reports N=186	Total† N=223
0 to < 1.0	8 (57)	1 (3)	29 (16)	38 (17)
1.0 to < 4.0	5 (38)	13 (45)	84 (45)	102 (48)
4.0 to < 8.0	0	10 (34)	35 (19)	45 (20)
8.0 to < 12.0	1 (7)	5 (17)	3 (1)	9 (4)
12.0 to ≤ 16.0	0	0	1 (<1)	1 (<1)
>16.0	0	0	3 (1)	3 (1)
not specified or unknown	0	0	31 (17)	31 (14)

* Total includes count for 6 patients whose adverse events were also reported as spontaneous adverse drug events (Case Nos. 39329, 39328, 39326, 39325, 39327, and 39330).

† Total may not be the sum of the individual columns due to duplication in reporting.

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Table 18. Dose range of risperidone in children (2 years up to 12 years) by source of data

Dose Ranges (mg/day)	Number (%) Patients			
	Clinical Trials N=12	Literature N=10*	Spontaneous Adverse Event Reports N=64	Total† N=81
0 to < 1.0	7 (58)	3 (30)	14 (22)	24 (30)
1.0 to < 4.0	5 (42)	3 (30)	32 (50)	38 (47)
4.0 to < 8.0	0	4 (40)	8 (13)	9 (11)
8.0 to < 12.0	0	0	0	0
12.0 to < 16.0	0	0	0	0
>16.0	0	0	0	0
not specified or unknown	0	0	10 (16)	10 (12)

* Total includes count for 5 patients whose adverse events were also reported as spontaneous adverse drug events (Case Nos. 39329, 39328, 39326, 39325, and 39327).

† Total may not be the sum of the individual columns due to duplication in reporting.

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Table 19. Dose range of risperidone in adolescents (12 years up to 16 years) by source of data

Dose Ranges (mg/day)	Number (%) Patients			
	Clinical Trials N=2	Literature N=19*	Spontaneous Adverse Event Reports N=115	Total† N=135
0 to < 1.0	1 (50)	1 (5)	12 (10)	14 (10)
1.0 to < 4.0	0	9 (47)	52 (45)	61 (45)
4.0 to < 8.0	0	7 (37)	27 (23)	33 (24)
8.0 to < 12.0	1 (50)	2 (11)	3 (3)	6 (4)
12.0 to ≤ 16.0	0	0	1 (<1)	1 (<1)
>16.0	0	0	2 (2)	2 (1)
not specified or unknown	0	0	17 (15)	17 (13)

* Total includes count for 1 patient whose adverse events were also reported as spontaneous adverse drug events (Case No. 39330).

† Total may not be the sum of the individual columns due to duplication in reporting.

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Table 20. Extent of pediatric (<16 years of age) exposure to risperidone by source of data

Duration of exposure (30-day months)	Number (%) of patients exposed to risperidone			
	Clinical Trials N=14	Literature N=29*	Spontaneous Adverse Event Reports N=186	Total† N=223
>0 to < 3	14 (100)	13 (45)	106 (60)	133 (60)
3 to < 6	0	6 (21)	8 (4)	14 (6)
6 to < 9	0	4 (14)	7 (3)	11 (5)
9 to ≤ 12	0	3 (10)	5 (2)	8 (4)
>12	0	1 (3)	1 (<1)	2 (<1)
not specified or unknown	0	2 (7)	59 (31)	61 (27)

* Total includes count for 6 patients whose adverse events were also reported as spontaneous adverse drug events (Case Nos. 39329, 39328, 39326, 39325, 39327, and 39330).

† Total may not be the sum of the individual columns due to duplication in reporting.

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8. SUMMARY AND DISCUSSION

Four clinical studies,[2,3,4,9,15] 18 publications,[5,6,7,8,10,11,12,13,14,16,17,18,19,20,21,22,23,24] and 186 spontaneous adverse drug event reports[1] provided safety information in a total of 223 pediatric patients (<16 years of age) who received risperidone. The total number of patients (ages specified) who received risperidone and whose safety information was reviewed is summarized by age categories and by source in Table 21.

The most frequently reported treatment-emergent adverse drug events among the combined pediatric population (<16 years of age) were related to the central and peripheral nervous system, psychiatric events, metabolic and nutritional disturbances, and gastrointestinal disorders. Summaries of the most common treatment-emergent adverse drug events are presented by source of information in Tables 22, 23, and 24. Events reported by ≥1% of the pediatric population are included. Of all the adverse events reported, extrapyramidal symptoms, weight gain, and somnolence were described in all three sources of safety information (Table 25).

Serious adverse events derived from spontaneous adverse event reports occurred in 43 patients (2 neonates, 3 infants, 18 children, and 20 adolescents) and were related mostly to the central and peripheral nervous system and psychiatric events. When serious adverse events occurred, measures such as lowering the dose or discontinuing the drug, hospitalizing the patient, or discontinuing concomitant drugs were taken. At times, medications such as benztropine, paroxetine, procyclidine, or diphenhydramine were started to resolve or control the reaction.

A review of the safety information derived from clinical trials, the medical literature, and spontaneous adverse event reports show no other serious or unexpected safety concerns. The events reported in the pediatric population described in this summary are well known to occur with risperidone in adults and are tolerated by most patients or are reversible with discontinuation of treatment.

Seven publications[6,11,12,13,16,17,21] described extrapyramidal symptoms. Significant extrapyramidal symptoms that appeared after rapid titration of risperidone to 6 mg/day decreased when the dose was reduced to 1 mg twice daily.[12] In a retrospective review,[21] 15 of 30 patients who experienced extrapyramidal symptoms required anticholinergic agents.

Specific extrapyramidal symptoms are included in the published reports summarized in this review. Tongue protrusion and muscle rigidity present on the third day of treatment with risperidone (1 mg/twice daily) were successfully eliminated with benztropine.[6] In 1 patient, possible tongue protrusion was

difficult to assess because of a speech impediment.[6] A patient with akinesia and dyskinetic movements 10 days after initiation of treatment with risperidone (3 mg/twice daily) greatly improved with benztropine.[6] Muscle stiffness also responded to benztropine.[5] One instance of a dystonic reaction was reported but not discussed[17].

Tremors described in 3 published studies[6,17,11] were controlled or greatly improved with different modes of treatment – mild tremors (onset at 2 mg/twice daily) required no treatment,[6] tremors (onset at 4 mg/day) were controlled with procyclidine,[11] and Parkinsonism (onset dose not specified) required continuous treatment with benztropine.[17]

Weight gain was reported in 4 publications.[6,17,5,20] The total weight gain varied from 8 to 14 pounds over periods ranging from 8 weeks to 1 year. One patient reportedly gained 30 pounds, but no time period was indicated.[6] In some patients the weight gain coincided with increased appetite.[5] In another report,[20] weight gain was the most common adverse event. The extent to which the weight gain in these cases is in excess of the expected weight gain in a child or adolescent cannot be determined.

Somnolence was described in 3 published studies.[17,13,7] Reduction in dose from 4 mg/day to 0.75 mg/day eliminated daytime somnolence in 1 patient.[13] Somnolence reported in three other patients did not interfere with their functioning,[17] and oversedation in 1 patient (titrated to 6 mg/day) responded to a reduced dose of 2 mg/day.[7]

Determining an optimal and safe dose for children and adolescents is difficult because of the limited size of the samples, the wide age range, heterogeneous diagnoses, and the variety of doses and titration methods. Experience in adults suggests that titrating risperidone slowly might be an important factor in avoiding adverse effects in children and adolescents.

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Table 21. Total number of patients who received risperidone and whose safety information was analyzed by age categories (ages specified) and source of data

Source of Safety Information	Neonates (birth up to 1 month)	Infants (1 month up to 2 years)	Children (2 years up to 12 years)	Adolescents (12 years up to 16 years)	TOTAL
Spontaneous adverse event reports	3	4	64	115	186
Clinical trials	0	0	12	2	14
Publications	0	0	5*	18†	23
TOTAL	3	4	81	135	223

*Total excludes count for 5 patients (Case Nos 39329, 39328, 39326, 39325, and 39327 in Table 6.) whose adverse events were also reported as spontaneous adverse events. † Total excludes count for 1 patient (Case No. 39330 in Table 12.) whose adverse event was also reported as a spontaneous adverse event.

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Table 22. Most common* treatment-emergent adverse drug events (ADEs) experienced by the pediatric population (<16 years of age)† receiving risperidone in clinical trials (N=14)

Body System Adverse Events (number of events) ‡	Number (%) Patients with ADE
Psychiatric somnolence (5) insomnia (2)	7 (54)
Central & peripheral nervous absences § (2) coma ‖ (1) extrapyramidal symptoms (1) oculogyric crisis (1) dizziness (1)	4 (31)
Metabolic & nutritional weight increase (2) high alkaline phosphatase (1)	2 (15)
Gastrointestinal hypersalivation (1) vomiting (1) diarrhea (1)	2 (15)
Body as a whole fever (1) fatigue (1)	2 (15)
Heart rate & rhythm palpitation (1)	1 (8)
Respiratory rhinitis (1)	1 (8)

* Events reported by ≥1% of the pediatric population receiving risperidone and participating in clinical trials are included.

† The total number of pediatric patients who participated in clinical trials and met the age criteria for inclusion in this summary was 14.

‡ Adverse events are presented within body systems in descending order of frequency.

§ Absences=term commonly used in French for a variety of minor epileptic seizures including those covered in English by the term *petit mal*.

‖ Coma=WHOART term for "subcomatose"(event did not entail loss of consciousness).

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Table 23. Most common* treatment-emergent adverse drug events (ADEs) experienced by the pediatric (<16 years of age) population† receiving risperidone in the literature (N=29 †)

Body System Adverse Events (number of events) ‡	Number (%) Patients with ADE
Central & peripheral nervous tremors (3) tongue protrusion (2) muscle rigidity (2) extrapyramidal symptoms (2) dizziness (2) akinesia (1) dyskinesia (1) exacerbation of tics (1) leg numbness (1)	12 (41)
Psychiatric sedation (2) depression (2) psychotic symptoms (1) dysphoria (1) lethargy (1)	5 (17)
Body as a whole weakness (1) tiredness (1)	1 (3)
Metabolic & nutritional weight increase (8)	8 (28)

* Events reported by ≥1% of the pediatric population receiving risperidone and cited in the psychiatric literature are included.

† The total number of pediatric patients cited in the psychiatric literature and who met the age criteria for inclusion in this summary was 29 and includes 6 patients whose safety information was also reported as spontaneous adverse drug events.

‡ Adverse events are presented within body systems in descending order of frequency.

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Table 24. Most common* treatment-emergent adverse drug events (ADEs) experienced by the pediatric (<16 years of age) population† described in spontaneous adverse event reports (N=186)

Body System Adverse Events (number of events) ‡	Number (%) Patients
Central & peripheral nervous dyskinesia (7) dystonia (6) convulsions (6)§ tardive dyskinesia (5) dizziness (5) neuroleptic malignant syndrome (4) extrapyramidal symptoms (3)	44 (23)
Psychiatric somnolence (6) depression (3) aggressive reaction (2) nervousness (2)	22 (11)
Urinary urinary incontinence (10) urinary retention (4)	14 (8)
Reproductive female lactation, nonpuerperal (10) amenorrhea (2)	12 (7)
Gastrointestinal vomiting (5) hypersalivation (3)	16 (8)
Metabolic and nutritional weight increase (10)	13 (6)
Skin & appendages rash (5) urticaria (2)	10 (5)

* Spontaneous adverse drug events reported with a frequency of ≥1% are included.

† The total number of pediatric patients described in spontaneous adverse drug event reports and met the age criteria for inclusion in this summary was 186 and includes reports for 6 patients who were also described in the psychiatric literature (Case Nos. 39329, 39328, 39326, 39325, 39327, and 39330).

‡ Adverse events are presented by WHO terms within body systems in descending order of frequency.

§ Events included were reported as convulsions, seizures, petit mal seizures, grand mal seizures, and convulsions aggravated.

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Table 24. (Continued...) Most common* treatment-emergent adverse drug events (ADEs) experienced by the pediatric (<16 years of age) population† described in spontaneous adverse event reports (N=186)

Body System Adverse Events (number of events) ‡	Number (%) Patients
Body as a whole therapeutic response decreased (3) therapeutic response increased (2)	11 (5)
Bleeding & clotting epistaxis (5)	6(3)
Vision blurred vision (4)	8(4)
Heart rate & rhythm tachycardia (4)	7(3)
Respiratory dyspnea (2)	3 (1)
Cardiovascular hypotension, orthostatic (2)	4 (2)
White cell & reticuloendothelial neutropenia (2)	3 (1)
Endocrine hyperprolactinemia (2)	5 (2)

* Spontaneous adverse drug events reported with a frequency of ≥1% are included.

† The total number of pediatric patients described in spontaneous adverse drug event reports and met the age criteria for inclusion in this summary was 186 and includes reports for 6 patients who were also described in the psychiatric literature (Case Nos. 39329, 39328, 39326, 39325, 39327, and 39330).

‡ Adverse events are presented by WHO terms within body systems in descending order of frequency.

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Table 25. Summary of adverse events* commonly reported in all sources of safety information for neonates (birth to 1 month), infants (1 month up to 2 years), children (2 years up to 12 years), and adolescents (12 years up to 16 years)

Body System Adverse Events	Number of reports by source of information and age category												TOTAL
	Clinical Trials				Literature				Spontaneous Reports				
	Neonates	Infants	Children	Adolescents	Neonates	Infants	Children§	Adolescents‖	Neonates	Infants	Children	Adolescents	
Central & peripheral nervous† extrapyramidal symptoms	0	0	2	4	0	0	7	8	1	1	25	18	66
Metabolic & nutritional weight gain	0	0	2	0	0	0	2	6	0	0	3	7	20
Psychiatric somnolence ‡	0	0	7	0	0	0	1	2	0	0	4	3	17

*Adverse events are from patients whose ages were specified.
†Central & peripheral nervous symptoms were reported as: extrapyramidal symptoms, akinesia, dyskinesia, tremors, tongue protrusion, muscle rigidity, stupor, oculogyric crisis, tardive dyskinesia, dystonia, convulsions, petit mal seizures, grand mal seizures, seizures, tongue paralysis, abnormal gait, stupor, neuritis, dizziness, neuroleptic malignant syndrome, confusion, coma, absences, nervousness.
‡Symptoms were reported as: somnolence, sedation, insomnia, lethargy, drowsiness.
§Includes count for 5 patients (Case Nos. 39329, 39328, 393266, 39325, and 39327) whose adverse events were also reported as spontaneous adverse events.
‖Includes count for 1 patient (Case No. 39330) whose adverse event was also reported as a spontaneous adverse event.

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9. RISK BENEFIT ASSESSMENT

The efficacy and safety of risperidone have not been formally investigated in large pediatric populations (i.e., those less than 16 years of age) for any indication. Several small studies, however, have been conducted in children and adolescents, several investigator-initiated studies are in progress, and one formal program in mentally retarded children with behavioral disorders will commence in 1996. The risks of risperidone can therefore only be assessed relative to possible benefits in diverse indications. The results of these investigations may show risperidone to be beneficial to children and adolescents in controlling the symptoms of various psychiatric disorders, including schizophrenia, attention-deficit hyperactivity disorder, bi-polar disorder, depression, obsessive-compulsive disorder, mental retardation, infantile autism, conduct disorder, Tourette's syndrome, and possibly other conditions. The risks discussed below apply to all possible indications.

In the absence of formal clinical trials with defined, scheduled safety evaluations in sufficient numbers of pediatric patients, the assessment of risk is derived from the less certain sources of small clinical trials using the current market formulation of risperidone, published reports, and spontaneously reported adverse events. However, converging data from these three sources indicate that children and adolescents exposed to risperidone are at risk of extrapyramidal symptoms, sedation, and weight gain. These adverse events are more common and more severe at doses of risperidone in excess of 3 mg/day, but they were also observed at lower doses. These three adverse events were also observed in large clinical trials in adult schizophrenic patients and they do not represent new hazards.

All the well-recognized extrapyramidal symptoms have been observed in children and adolescents. These include bradykinesia, akathisia, muscle rigidity, tremor, dystonia, neuroleptic malignant syndrome, and tardive dyskinesia. Children and adolescents may be at greater risk than adult schizophrenic patients for extrapyramidal symptoms such as neuroleptic malignant syndrome because in addition to having a smaller volume of distribution they are more likely to be neuroleptic naive. Current recommendations for risperidone in children and adolescents therefore stress slow titration and careful monitoring for extrapyramidal symptoms. The dose of risperidone should be reduced if extrapyramidal symptoms emerge. Risperidone should be discontinued if dose reduction does not result in resolution of extrapyramidal symptoms. Since extrapyramidal symptoms almost always resolve with dose reduction, clinicians can weigh the risks of extrapyramidal symptoms with the anticipated benefits of risperidone treatment and safely change course if the clinical result is unsatisfactory.

Sedation was commonly reported in children, but often responded to dose reduction. The reports do not permit a distinction between development of

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tolerance and symptom resolution with dose reduction. However, sedation can be easily managed in clinical practice and does not represent a significant risk.

Weight gain has been reported with serotonin/dopamine antagonists. Weight gain in long-term risperidone trials in adults was modest, averaging only 5 to 7 pounds, although 10-20% of patients gained more than 7% of their baseline body weight. Weight gain in excess of anticipated growth-related increases in body mass may occur in children and adolescents. The weight gain occurs gradually, and risperidone can be safely discontinued in a child or adolescent who gains unanticipated weight after initiation of risperidone.

Prolactin increases were observed in controlled clinical trials with risperidone. There is limited data on prolactin levels in children and adolescents and no evidence of prolactin-related adverse events in children and adolescents. There is a possibility that risperidone-related prolactin increases could affect the onset of puberty. Planned long-term safety trials in pre-pubescent children will assess this risk.

Controlled clinical trials indicated that risperidone had a favorable safety profile. Wide market penetration and long-term clinical studies have not revealed any additional risks. We therefore conclude that the risks of risperidone in children and adolescents can be safely and reasonably assessed against any demonstrated or anticipated benefits.

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