

**One Year Post-Exclusivity
Adverse Event Review:
Risperidone
Pediatric Advisory Committee Meeting
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Background Drug Information

Drug: Risperdal[®] (risperidone)

Formulation: Tablets, oral solution, and
orally disintegrating tablets

Therapeutic Category: Antipsychotic (atypical)

Sponsor: Janssen, L.P.

Original Market Approval: December 29, 1993

Pediatric Exclusivity Granted: February 28, 2007

Background Drug Information

Indications Prior to the Exclusivity Studies:

- Treatment of schizophrenia in adults
- Short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults
- Treatment of irritability associated with autistic disorder in children and adolescents

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Drug Use Trends in Outpatient Settings During the Post-Exclusivity Period

7.8 million dispensed prescriptions for all age groups

- 781,000 (10.0%) for patients 13 to 17 years old
- 1,215,000 (15.5%) for patients 0 to 12 years old

2% increase in prescriptions for all age groups between the 12 month pre- and post-exclusivity periods

- 10% increase for patients 0 to 17 years old

SDI Vector One®: National. Mar 2007 – Feb 2008. Data Extracted 7-16-08.

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Drug Use Trends in Outpatient Settings During the Post-Exclusivity Period

Psychiatry was the top prescribing specialty[†]

- All psychiatrists - 53.4%
- Child psychiatrists - 11.4%
- Pediatricians - 3.6%
- Child neurologists - 1%

Top diagnosis codes in children 0 to 17 years old [‡]

- Infantile autism
- Attention deficit disorder

[†]SDI Vector One®: National. Mar 2007 – Feb 2008. Data Extracted 7-16-08.

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[‡]SDI Physician's Drug and Diagnosis Audit. Mar 2007 – Feb 2008. Data Extracted 7-16-08.

Pediatric Exclusivity Studies: Overview

Indications and Age Group Studied

- Schizophrenia (acute treatment)
13 to 17 year olds
- Mania in Bipolar I Disorder (acute treatment)
10 to 17 year olds

Study Types and Dosing

- 1 Pharmacokinetic (PK) Study
Risperidone 0.01 – 0.08 mg/kg
- 3 Efficacy and Safety Studies
Risperidone 0.15 – 6 mg/day
- 1 Safety Study
Risperidone 2 – 6 mg/day

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Pediatric Exclusivity Studies: Findings

Results indicate that risperidone is effective and reasonably safe for the studied indications in pediatric patients.

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Pediatric Exclusivity Studies: Labeling Changes

Labeling Sections Changed

Section 1 Indications and Usage

- 1.1 Schizophrenia – Adolescent
- 1.2 Bipolar Mania Monotherapy – Adults and Pediatrics

Section 2 Dosage and Administration

- 2.1 Schizophrenia – Adolescent
- 2.2 Bipolar Mania – Pediatrics

Section 6 Adverse Reactions

- 6.1 Commonly-Observed Adverse Reactions in Placebo-Controlled Trials – Schizophrenia
 - Pediatric Patients with Schizophrenia
- 6.2 Commonly-Observed Adverse Reactions in Placebo-Controlled Trials – Bipolar Mania
 - Pediatric Patients with Bipolar Mania

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Pediatric Exclusivity Studies: Labeling Changes

Labeling Sections Changed

Section 6 Adverse Reactions (continued)

- 6.5 Discontinuations Due to Adverse Reactions
 - Schizophrenia – Pediatrics
 - Bipolar Mania – Pediatrics
- 6.8 Changes in ECG

Section 8 Use in Specific Populations

8.4 Pediatric Use

- Weight gain
- Somnolence
- Hyperprolactinemia, Growth, and Sexual Maturation

Section 14 Clinical Studies

- 14.1 Schizophrenia – Pediatrics
- 14.2 Bipolar Mania - Pediatrics

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Pediatric Exclusivity Studies: Labeling Changes

Details of Selected Labeling Changes

Indication and Usage

- Schizophrenia indication was extended to adolescents, 13 to 17 years old
- Bipolar mania indication was extended to children and adolescents, 10 to 17 years old

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Pediatric Exclusivity Studies: Labeling Changes

Details of Selected Labeling Changes

Dosage and Administration

- Schizophrenia studies
 - No additional benefit was seen above 3 mg/day
 - Higher doses were associated with more adverse events
- Bipolar mania studies
 - No additional benefit was seen above 2.5 mg/day
 - Higher doses were associated with more adverse events

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Pediatric Exclusivity Studies: Labeling Changes

Details of Selected Labeling Changes

Adverse Reactions - Discontinuations Due to Adverse Reactions

- Schizophrenia
 - ~7% (7/106) in risperidone group vs. 4% (2/54) in placebo group
 - Adverse reactions associated with study discontinuation in risperidone group: somnolence (2%), dizziness (2%), anorexia (1%), ataxia (1%), hypotension (1%), and palpitation (1%)
- Bipolar mania
 - 12% (13/111) in risperidone group vs. 7% (4/58) in placebo group
 - Adverse reactions associated with study discontinuation in the risperidone group: somnolence (5%), nausea (3%), abdominal pain (2%), and vomiting (2%)

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Pediatric Exclusivity Studies: Labeling Changes

Details of Selected Labeling Changes

Use in Specific Populations – Pediatric Use

- Weight gain
 - Schizophrenia studies
 - 14% reported weight increase in open-label studies
 - Mean increase of 9.0 kg after 8 months of treatment in 103 adolescents
 - Bipolar mania studies
 - Increased body weight was higher in risperidone groups than placebo group, but not dose related, in a controlled trial
 - 1.9 kg (0.5 – 2.5 mg) and 1.44 kg (3 – 6 mg) for risperidone groups vs. 0.65 kg for placebo group ¹³

Pediatric Exclusivity Studies: Labeling Changes

Details of Selected Labeling Changes

Use in Specific Populations – Pediatric Use

- Somnolence
 - Most commonly observed adverse event in schizophrenia and bipolar disorder trials
- Hyperprolactinemia, Growth, and Sexual Maturation
 - 82 – 87% of children and adolescents in risperidone group vs. 3 – 7% of placebo group had elevated levels of prolactin in controlled schizophrenia or bipolar disorder trials

Adverse Event Reports Since Marketing Approval

12/29/1993 – 03/28/2008

Crude Counts*	All Reports (US)	Serious** (US)	Death (US)
Adults (≥ 17)	14,910 (10,845)	11,029 (7,077)	2,035 (1,272)
Pediatrics (0 to 16)	1,535 (1,183) [7.5% of all reports]	1,207 (860)	48 (33)
Age unknown	3,907	2,867	530
All ages	20,352	15,103	2,613

* May include duplicate cases

** Serious adverse events include death, hospitalization, life-threatening event, disability, congenital anomaly, and other (unspecified).

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Source: Adverse Event Reporting System, FDA

Pediatric Deaths Since Marketing Approval

48 Crude count reports

- 17 Duplicates

31 Unique cases

- 4 Indeterminant cause of death

27 Remaining cases

- 10 Nervous system
- 9 Cardiac system
- 8 Miscellaneous

No new safety concerns were identified.

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Source: Adverse Event Reporting System, FDA

Labeling Relevant to the Death Cases

Warnings and Precautions

- Seizures
- Neuroleptic malignant syndrome
- Hyperglycemia and diabetes mellitus (with worsening glucose control)
- Orthostatic hypotension
- Suicide

Adverse Reactions

- Controlled Clinical Trials
 - Arrhythmia
 - Hypotension
- Post-marketing Experience
 - Pulmonary embolism
 - Cardiopulmonary arrest

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Pediatric Deaths Since Marketing Approval

10 Nervous System Cases

- Five adolescents died after a seizure or related complication while on risperidone.
 - Two cases involved patients with a history of epilepsy.
 - One additional case involved concomitant paroxetine use which has a labeled seizure association.
 - Other concomitant medications (acetaminophen, diprobase cream, carbamazepine, valproate, lorazepam, clobazam, topiramate).
- 7 year old experienced encephalitis, hypotension, arrhythmia, and cerebral edema and died after 2 days of risperidone 2 mg/day prescribed for psychosis.

Unlabeled serious adverse events (SAEs) are underlined.

Source: Adverse Event Reporting System, FDA

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Pediatric Deaths Since Marketing Approval

10 Nervous System Cases (continued)

- One 8 year old and two 16 year olds died of neuroleptic malignant syndrome (NMS) or NMS-like symptoms while on risperidone.
 - One case involved concomitant medications with labeled NMS association (haloperidol, chlorpromazine, lorazepam)
- 9 year old died due to cavernous angioma 12 days after initiating risperidone therapy for attention deficit hyperactivity disorder (ADHD).
 - Concomitant medications (valproate, citalopram).

Source: Adverse Event Reporting System, FDA

¹⁹
Unlabeled SAEs are underlined.

Pediatric Deaths Since Marketing Approval

9 Cardiac System Cases

- 6 and 12 year old males died from cardiac arrest while on risperidone without concomitant medications.
 - Risperidone dose was 0.5 mg/day in one case.
 - Case reports lacked significant details.
- 10 and 12 year old with congenital heart disease died due to cardiac arrhythmia or sudden death while on risperidone 0.5 – 1 mg/day for Bipolar Disorder or conduct disorder.
 - Concomitant medication (sertraline).

Source: Adverse Event Reporting System, FDA

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Pediatric Deaths Since Marketing Approval

9 Cardiac System Cases (continued)

- 11 year old female died of myocarditis one month after initiating risperidone 2 mg/day for a mental disorder.
 - Concomitant medications (oxcarbazepine, fluphenazine, biperiden).
- 7 year old male experienced QTc prolongation and died due to a heart attack after initiating therapy with risperidone 1 mg/day.
 - Concomitant medication (sertraline).

Source: Adverse Event Reporting System, FDA

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Pediatric Deaths Since Marketing Approval

9 Cardiac System Cases (continued)

- 16 year old male with a family history of Protein S deficiency experienced an upper respiratory infection, breathing difficulty, and a massive blood clot and died three months after initiating therapy with risperidone.
 - Concomitant medication (sertraline).
- 11 and 16 year old on risperidone 2 or 4 mg/day for depression/hallucinations or developmental delay died possibly due to left ventricular hypertrophy.
 - Other possible causes of death included pneumonia or a drug interaction.
 - Concomitant medications (imipramine, sertraline).

Source: Adverse Event Reporting System, FDA

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Unlabeled SAEs are underlined.

Pediatric Deaths Since Marketing Approval

8 Miscellaneous Cases

- 14 year old had viral infection and cardiorespiratory arrest prior to death while on risperidone.
- 14 and 12 year old died from suicide (multiple medication overdose including risperidone or hanging).
- 13 year old on risperidone had pneumonia, septicemia, congestive heart failure, and cardiac arrest and died.
- 8 year old with diabetes had a hypoglycemic seizure and died while on risperidone.
- 6 year old died after the accidental ingestion of multiple medications, including risperidone.
- 5 year old died after a near drowning within three months of initiating risperidone.
- 1 year old died of suffocation after receiving her mother's risperidone 0.5 mg.

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Source: Adverse Event Reporting System, FDA

Unlabeled SAEs are underlined.

Adverse Event Reports Since Marketing Approval

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Age unknown	3,907	2,867	530
All ages	20,352	15,103	2,613

* May include duplicate cases

** Serious adverse events include death, hospitalization, life-threatening event, disability, congenital anomaly, and other (unspecified).

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Source: Adverse Event Reporting System, FDA

Adverse Event Reports During the Post-Exclusivity Period			
02/28/2007 – 03/28/2008			
Crude Counts*	All Reports (US)	Serious** (US)	Death (US)
Adults (≥ 17)	1,230 (488)	1,155 (421)	189 (97)
Pediatrics (0 to 16)	150 (56)	131 (42)	8 (8)
Age unknown	411	378	47
All ages	1,791	1,671	244

* May include duplicate cases
** Serious adverse events include death, hospitalization, life-threatening event, disability, congenital anomaly, and other (unspecified).
Source: Adverse Event Reporting System, FDA

Serious Adverse Events During the Post-Exclusivity Period	
131 Crude count reports	
• 15 Duplicates	
116 Unique cases	
• No new safety concerns	
• Areas of focus	
• 15 Metabolic	
• 14 Extrapiramidal	
• 6 Gynecomastia/hyperprolactinemia	

Source: Adverse Event Reporting System, FDA

Labeling Relevant to Serious Adverse Events

Warnings and Precautions

- Hyperglycemia and diabetes mellitus (associated with ketoacidosis)
- Tardive dyskinesia
- Hyperprolactinemia

Adverse Reactions

- Extrapyramidal symptoms
- Gynecomastia

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Serious Adverse Events During the Post-Exclusivity Period

15 Metabolic

- Increased weight, diabetes mellitus, diabetic ketoacidosis, and/or glycosuria

14 Extrapyramidal

- 3 Tardive dyskinesia
- 11 Other extrapyramidal effects

6 Gynecomastia/hyperprolactinemia

- 4 Gynecomastia
- 2 Hyperprolactinemia

Source: Adverse Event Reporting System, FDA

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Metabolic Serious Adverse Events During the Post-Exclusivity Period (n=15)

Number of Cases	Metabolic Serious Adverse Event
6	Increased weight
4	Diabetes mellitus + increased weight
2	Diabetes mellitus + diabetic ketoacidosis
2	Diabetes mellitus
1	Glycosuria

Source: Adverse Event Reporting System, FDA

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Other Serious Adverse Events During the Post-Exclusivity Period

Case Counts

- 20 Non-therapeutic use
- 15 Hematologic
- 11 Neurologic
- 9 Psychiatric
- 9 Miscellaneous
- 6 Biochemical laboratory tests and toxins
- 6 Cardiac
- 3 Gastrointestinal
- 2 Drug exposure in utero

29 cases with labeled events

52 cases with unlabeled events

Source: Adverse Event Reporting System, FDA

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Labeling Relevant to the Other Serious Adverse Events

Contraindications

- Hypersensitivity reactions, including angioedema

Warnings and Precautions

- Cerebrovascular events
(e.g., stroke, transient ischemic attack)
- Neuroleptic malignant syndrome
- Tardive dyskinesia
- Hyperglycemia and diabetes mellitus
(with worsening glucose control)
- Hyperprolactinemia
- Orthostatic hypotension
- Seizures
- Suicide

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Labeling Relevant to the Other Serious Adverse Events

Adverse Reactions

- Controlled Clinical Trials
 - Arrhythmia, bradycardia, tachycardia
 - Leukopenia
 - Anxiety
 - Tremor
 - SGOT increased, SGPT increased
 - Edema
 - Vomiting
- Post-marketing Experience
 - Pulmonary embolism
 - Cardiopulmonary arrest
 - Thrombocytopenia
 - Precocious puberty
 - Angioedema
 - Pancreatitis

Drug Interactions

- Increased valproate plasma concentration

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Other Serious Adverse Events During the Post-Exclusivity Period

Summary of Unlabeled Events

- No new safety concern
 - 20 Non-therapeutic uses
 - 14 Events with a single case report
 - 4 Agitation during switch from risperidone to methylphenidate
 - 3 Hallucinations
 - 3 Neutropenia
 - 2 Aggression
 - 2 Self-injurious behavior
 - 2 Increased alkaline phosphatase
 - 2 Drug exposure in utero

Source: Adverse Event Reporting System, FDA

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Summary: Risperidone

- This completes the one year post-exclusivity adverse event reporting.
- The safety review did not reveal any new safety concerns for oral risperidone.
- FDA will continue its standard, ongoing safety monitoring for oral risperidone.
- Does the Advisory Committee concur?

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