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

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

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

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

Pediatric Exclusivity Studies: Findings

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

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
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

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
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

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%)
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

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

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

* 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

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### 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.

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

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
**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

**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
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

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

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.

Source: Adverse Event Reporting System, FDA

Unlabeled SAEs are underlined.

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12/29/1993 – 03/28/2008

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Source: Adverse Event Reporting System, FDA
### Adverse Event Reports
**During the Post-Exclusivity Period**
02/28/2007 – 03/28/2008

<table>
<thead>
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<th>Crude Counts*</th>
<th>All Reports (US)</th>
<th>Serious** (US)</th>
<th>Death (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥ 17)</td>
<td>1,230 (488)</td>
<td>1,155 (421)</td>
<td>189 (97)</td>
</tr>
<tr>
<td>Pediatrics (0 to 16)</td>
<td>150 (56)</td>
<td>131 (42)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Age unknown</td>
<td>411</td>
<td>378</td>
<td>47</td>
</tr>
<tr>
<td>All ages</td>
<td>1,791</td>
<td>1,671</td>
<td>244</td>
</tr>
</tbody>
</table>

* 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

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

<table>
<thead>
<tr>
<th>Number of Cases</th>
<th>Metabolic Serious Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Increased weight</td>
</tr>
<tr>
<td>4</td>
<td>Diabetes mellitus + increased weight</td>
</tr>
<tr>
<td>2</td>
<td>Diabetes mellitus + diabetic ketoacidosis</td>
</tr>
<tr>
<td>2</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>1</td>
<td>Glycosuria</td>
</tr>
</tbody>
</table>

Source: Adverse Event Reporting System, FDA

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
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

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
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

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?
## Acknowledgements

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