

**CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW**

**DRUG:** Risperidone

**PRIMARY REVIEWER:** Andre Jackson

**NDA:** 20272/SE5-046,047

**TYPE:** NDA

20588/SE5-036,037

2144/ SE5-020,021

**FORMULATION:** Oral Tablet

**STRENGTH:** 0.25mg, 0.5mg, 1 mg,  
2mg, 3mg and 4mg

**APPLICANT:** Johnson and Johnson Submission Dates: June 25, 2007

**INDICATIONS:** Schizophrenia , Bipolar Disorder

**REVIEW OF A LABELLING SUPPLEMENT**

➤ New Label Entry 1

**-----DOSAGE AND ADMINISTRATION-----**

	Initial Dose	Titration	Target Dose	Effective Dose Range
Schizophrenia - adults (2.1)	2 mg /day	1-2 mg daily	4-8 mg daily	4-16 mg /day
Schizophrenia - adolescents (2.1)	0.5mg /day	0.5- 1 mg daily	3mg /day	1-6 mg /day
Bipolar mania - adults (2.2)	2-3 mg /day	1mg daily	1-6mg /day	1-6 mg /day
Bipolar mania in children/ adolescents (2.2)	0.5 mg /day	0.5-1mg daily	2.5mg /day	0.5-6 mg /day
Irritability associated with autistic disorder (2.3)	0.25 mg /day (<20 kg) 0.5 mg /day (≥20 kg)	0.25-0.5 mg at ≥ 2 weeks	0.5 mg /day (<20 kg) 1 mg /day (≥20 kg)	0.5-3 mg /day

FDA Comment:

The entry is acceptable and is supported by information either in the current label under Dosage and Administration or in the NDA 20272.

➤ New Label Entry 2

## **DOSAGE AND ADMINISTRATION**

### ***Schizophrenia***

#### **Adolescents**

The dosage of RISPERDAL<sup>®</sup> should be initiated at 0.5 mg once daily, administered as a single-daily dose in either the morning or evening. Dosage adjustments, if indicated, should occur at intervals not less than 24 hours, in increments of 0.5 or 1 mg/day, as tolerated, to a recommended dose of 3 mg/day. Although efficacy has been demonstrated in studies of adolescent patients with schizophrenia at doses between 1 and 6 mg/day, no additional benefit was seen above 3 mg/day, and higher doses were associated with more adverse events. Doses higher than 6 mg/day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

There are no controlled data to support the longer term use of RISPERDAL<sup>®</sup> beyond 8 weeks in adolescents with schizophrenia. The physician who elects to use RISPERDAL<sup>®</sup> for extended periods in adolescents with schizophrenia should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

#### **FDA Comment:**

The entry is acceptable and is supported by information either in the current label under Dosage and Administration or in the NDA 20272.

➤ New Label Entry 3

### ***Bipolar Mania***

#### **Pediatrics**

The dosage of RISPERDAL<sup>®</sup> should be initiated at 0.5mg once daily, administered as a single-daily dose in either the morning or evening. Dosage adjustments, if indicated, should occur at intervals not less than 24 hours, in increments of 0.5 or 1 mg/day, as tolerated, to a recommended dose of 2.5 mg/day. Although efficacy has been demonstrated in studies of pediatric patients with bipolar mania at doses between 0.5 and

6 mg/day, no additional benefit was seen above 2.5 mg/day, and higher doses were associated with more adverse events. Doses higher than 6 mg/day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

FDA Comment:

The entry is acceptable and is supported by information either in the current label under Dosage and Administration or in the NDA 20272.

➤ New Label Entry 3

### ***Irritability Associated with Autistic Disorder – Pediatrics (Children and Adolescents)***

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

The dosage of RISPERDAL<sup>®</sup> should be individualized according to the response and tolerability of the patient. The total daily dose of RISPERDAL<sup>®</sup> can be administered once daily, or half the total daily dose can be administered twice daily.

Dosing should be initiated at 0.25 mg per day for patients < 20 kg and 0.5 mg per day for patients ≥ 20 kg. After a minimum of four days from treatment initiation, the dose may be increased to the recommended dose of 0.5 mg per day for patients < 20 kg and 1 mg per day for patients ≥ 20 kg. This dose should be maintained for a minimum of 14 days. In patients not achieving sufficient clinical response, dose increases may be considered at ≥ 2-week intervals in increments of 0.25 mg per day for patients < 20 kg or 0.5 mg per day for patients ≥ 20 kg. Caution should be exercised with dosage for smaller children who weigh less than 15 kg.

FDA Comment:

The entry is acceptable and is identical to that in the approvable letter to the firm dated 6/07.

➤ Drug Interactions

The firm has incorporated the requested changes

➤ Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

FDA Comment:

The entry is acceptable and is identical to that in the approvable letter to the firm dated 6/07.

➤ Carbamazepine and Other Enzyme Inducers

FDA Comment:

The entry is acceptable and is identical to that in the approvable letter to the firm dated 6/07.

➤ Drugs Metabolized by CYP 2D6

FDA Comment:

The entry is acceptable and is identical to that in the approvable letter to the firm dated 6/07.

**SIGNATURES**

Andre Jackson \_\_\_\_\_  
Reviewer, Psychiatric Drug Products, DCP I  
Office of Clinical Pharmacology and Biopharmaceutics

RD/FTinitialized by Raman Baweja, Ph.D. \_\_\_\_\_

Team Leader, Psychiatry Drug Section, DCP I  
Office of Clinical Pharmacology  
cc: NDA 20-272, HFD-860(Mehta, Baweja, Jackson)  
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/s/

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Andre Jackson  
8/1/2007 10:37:45 AM  
BIOPHARMACEUTICS

Raman Baweja  
8/1/2007 05:34:53 PM  
BIOPHARMACEUTICS  
This DFS signoff for NDA 20272/046 & 047 also  
serves as signoff for NDA 20588/036 & 037,  
and NDA 21444/020 & 021.