M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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FROM: Mitchell V. Mathis, M.D.
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TO: File NDA 20-272 SE5 046/047, NDA 20-588 SE5 036/037, NDA 21-444 SE5 020/021

SUBJECT: Recommendation of Approvable Action for risperidone (Risperdal®) for the Treatment of Schizophrenia and Bipolar I Disorder in Pediatric Patients (response to PWR)

1 BACKGROUND AND REGULATORY HISTORY

Risperidone is a second-generation (atypical) antipsychotic approved for the acute and maintenance treatment of schizophrenia in adults, the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder in adults, and for the irritability associated with autistic disorder in children and adolescents. In this application, Johnson and Johnson Pharmaceutical Research and Development has responded to a DPP-issued Pediatric Written Request (PWR) with studies of risperidone for the short-term treatment of schizophrenia and the acute manic and mixed episodes of bipolar I disorder in the pediatric population.

The PWR for studying both indications (schizophrenia in adolescents and bipolar I disorder in children and adolescents) was issued on November 25, 2002. The main requirements were to conduct a pediatric PK study, efficacy studies in pediatric schizophrenia and bipolar I disorder, and a long-term pediatric safety study. The PWR required that a sufficient number of pediatric patients be included in the trial to allow for the statistical power required to discern a difference between drug and placebo groups in both disorders, and that at least 6 months of safety data be collected from the long-term safety study. The age groups for study were defined as adolescents (13-17 years old) for schizophrenia, and children and adolescents (10-17 years old) for bipolar I disorder.

The Division met with the sponsor in May and August 2003 to clarify the requirements of the PWR. These discussions centered on study design and proposed dose ranges to be explored. On September 19, 2006, the Division held a Type B Meeting with the sponsor to discuss plans for supplemental new drug applications for pediatric schizophrenia and bipolar I disorder as outlined in the PWR.

The Agency Pediatric Exclusivity Board met on 28 February 2007, determined that the sponsor had met the requirements of the PWR, and granted exclusivity.

This NDA has been reviewed by June Cai, M.D., Medical Officer, DPP, John Lawrence, Ph.D., Office of Biostatistics, Andre Jackson, Ph.D., Office of Clinical Pharmacology, Barry Rosloff, Ph.D., Pharmacology/Toxicology, and N. Chidambaram, Ph.D., Chemistry.

2 CHEMISTRY

The chemists recommend an APPROVAL action pending the sponsor accepting minor editorial changes to labeling.

3 PHARMACOLOGY/TOXICOLOGY

Dr. Rosloff has noted that the sponsor is currently performing juvenile rat and dog studies as part of a Phase 4 commitment to the irritability associated with autistic disorder clam. These same studies will be used to support the current applications.

4 CLINICAL PHARMACOLOGY

The Clinical Pharmacologists have recommended an APPROVABLE action for these applications. They have concluded that weight normalized mean exposures based upon trough levels prior to next dose in children, adolescents, and adults are comparable and that dose adjustments based on body weight are not warranted for risperidone in children and adolescents. They agree with the sponsor's recommended pediatric target dose of 3 mg/day for schizophrenia and 2.5 mg/day for bipolar I disorder. They have reviewed and are in agreement with the clinical pharmacology sections of the sponsor's proposed labeling.

5 CLINICAL DATA

5.1 Overview of Studies

The response to the Agency-issued PWR consists of two studies in schizophrenia and one in bipolar I disorder. Studies RIS-SCH302 and RIS-USA-231 evaluated the safety and efficacy of risperidone in adolescents with schizophrenia. RIS-BIM-301 evaluated the safety and efficacy of risperidone in children and adolescents with bipolar I disorder.

5.2 Efficacy Findings

Schizophrenia

RIS-SCH-302 was a randomized, double-blind, placebo-controlled, multi-center study conducted at 23 sites in 4 countries. It included 3 treatment groups: placebo, risperidone 1-3 mg/day, and risperidone 4-6 mg/day. After a screening/washout phase, pediatric patients with schizophrenia were entered into a six week double-blind treatment phase. Risperidone was titrated within the assigned dose range to the maximum tolerated dose by Day 14.

The primary efficacy measure was change from baseline in the Positive and Negative Symptom Scale for Schizophrenia (PANSS) at 6 weeks. Last observations were carried forward to week 6. The results are shown in the table below.

Study RIS-USA-302: PANSS Total Score Changes Baseline to Day 43 End Point Efficacy Analysis Set

	PLACEBO	RIS 1-3 mg	RIS 4-6 mg
Baseline			
N	54	54	50
Mean (SD)	93.2 (10.27)	95.4 (11.01)	93.0 (11.87)
Median (Range)	94.0 (62;120)	96.0 (67;120)	90.0 (71;117)
Day 43 End Point			
N	54	54	50
Mean (SD)	84.4 (16.59)	74.1 (17.79)	71.8 (18.35)
Median (Range)	86.0 (42;126)	74.5 (34;124)	71.0 (34;117)
Change from Baseline			
N	54	54	50
Mean (SD)	-8.9 (16.11)	-21.3 (19.61)	-21.2 (18.29)
Median (Range)	-7.0 (-53;21)	-19.0 (-69;38)	-20.0 (-60;22)
P-value(minus PLACEBO)[a,b]		<0.001	<0.001
Diff. of LS Means (SE)		-12.0 (3.02)	-12.8 (3.07)
95% CI		(-17.95;-5.99)	(-18.83;-6.71)

Source: Dr. Lawrence's Review

Team Leader Comment: Both dose ranges of risperidone demonstrated statistically significant and clinically important decreases in the mean PANSS scores at endpoint (primary measure of efficacy) compared to placebo.

RIS-USA-231 was a randomized, double-blind, low-dose-controlled, multi-center study conducted at 41 sites in 8 countries. It included 2 treatment groups—high dose and low dose as shown in the sponsor's table below.

	Risperidone low-dose group		Risperidone high-dose group	
	<50 kg (mg/kg/day)	≥50 kg (mg/day)	<50 kg (mg/kg/day)	≥50 kg (mg/day)
Pre-Amendment 3[a]	0.003 to 0.008	0.15 to 0.4	0.03 to 0.08	1.5 to 4
Post-Amendment 3[b]	0.007 to 0.012	0.35 to 0.6	0.07 to 0.12	3.5 to 6

[a] The maximum dose was 4 mL/day (0.4 mg/day [low-dose group] or 4 mg/day [high-dose group]), irrespective of body weight.

[b] The maximum dose was 6 mL/day (0.6 mg/day [low-dose group] or 6 mg/day [high-dose group]), irrespective of body weight.

After a screening/washout phase, pediatric patients with schizophrenia were entered into an eight week double-blind treatment phase. Risperidone was titrated to the assigned target dose by Day 12.

The primary efficacy measure was change from baseline in the Positive and Negative Symptom Scale for Schizophrenia (PANSS) at 8 weeks. Last observations were carried forward to week 8. The results are shown in the table below.

Study RIS-USA-231: PANSS Total Score Change from Baseline To Day 56—Efficacy Analysis Set

	RIS LOW DOSE	RIS HIGH DOSE
Baseline		
N	131	124
Mean (SD)	93.3 (14.14)	96.4 (15.39)
Median (Range)	94.0 (61;119)	97.0 (63;126)
Day 56 End Point		
N	131	124
Mean (SD)	80.8 (24.33)	72.8 (22.52)
Median (Range)	80.0 (33;132)	71.0 (32;146)
Change from Baseline		
N	131	124
Mean (SD)	-12.5 (20.32)	-23.6 (22.83)
Median (Range)	-11.0 (-68;29)	-23.0 (-94;51)
P-value (minus RIS LOW DOSE)*		<0.001
Diff. of LS Means (SE)		-10.3 (2.65)
95% CI		(-15.53;-5.09)

Source: Study Report, p 103 and FDA analysis.

Team Leader Comment: The high dose risperidone group demonstrated a statistically significant and clinically important decrease in the mean PANSS scores at endpoint (primary measure of efficacy) compared to low dose risperidone.

Bipolar I Disorder

RIS-BIM-301 evaluated the safety and efficacy of 2 dose ranges of risperidone monotherapy compared to placebo in pediatric patients with a diagnosis of bipolar I disorder. The dose ranges were 0.5-2.5 mg/day and 3-6 mg/day. This study was a randomized, double-blind, placebo-controlled, multi-center study of patients with bipolar I disorder between 10 and 17 years of age who were experiencing a manic or mixed mood episode at enrollment. After a screening/washout phase, patients were entered into a three week double-blind treatment phase. Risperidone was titrated to a target dose range by Day 7 and to maximum tolerated dose within the range by Day 10.

The primary efficacy measure was change from baseline in the Young Mania Rating Scale (YMRS) at 3 weeks. Last observations were carried forward to week 3. The results are shown in the table below.

Study RIS-BIM-301: YMRS Change from Baseline to Day 21

	PLACEBO	RIS 0.5-2.5 mg	RIS 3-6 mg
Baseline			
N	57	49	60
Mean (SD)	31.0 (7.46)	31.1 (5.97)	30.5 (5.92)
Median (Range)	31.0 (19;45)	31.0 (16;44)	31.0 (20;44)
Day 21 endpoint			
N	57	49	60
Mean (SD)	21.9 (9.51)	12.6 (7.22)	13.9 (9.70)
Median (Range)	22.0 (3;44)	12.0 (0;30)	11.5 (0;40)
Change from Baseline			
N	57	49	60
Mean (SD)	-9.1 (10.95)	-18.5 (9.70)	-16.5 (10.29)
Median (Range)	-8.0 (-36;22)	-17.0 (-39;-3)	-18.0 (-35;6)
P-value(minus PLACEBO)(a,b)		<0.001	<0.001
Diff. of LS Means (SE)		-9.2 (1.76)	-8.0 (1.70)
95% CI		(-12.69;-5.74)	(-11.33;-4.62)

Source: Study Report, p 120 and FDA analysis.

Team Leader Comment: Both dose ranges demonstrate efficacy, i.e., statistically significant and clinically meaningful lower mean YMRS scores compared to placebo at 21 days.

5.3 Efficacy Conclusions

It is clear from the data presented above that risperidone is effective in treating pediatric schizophrenia and bipolar I disorder. Dr. Cai has noted in her reviews that doses above 3 mg/day for schizophrenia and 2.5 mg/day for bipolar I disorder do not show additional benefit and are associated with greater side effects (see safety review below) in the populations studied. She has therefore recommended that pediatric doses be limited in labeling to 3 mg/day for schizophrenia and 2.5 mg/day for bipolar I disorder. While I believe we should certainly label the drug with the information learned from the clinical trials, and even identify target doses of 3 mg/day for pediatric schizophrenia and 2.5 mg/day for pediatric bipolar I disorder, I think it would be too restrictive to the prescriber to limit the dose to a maximum when we know that doses up to 6 mg/day were also shown to be efficacious in the same studies that demonstrated efficacy for the lower dose ranges.

In addition, as pointed out above in the description of the controlled studies in pediatric schizophrenia and bipolar I disorder, the dose was titrated to the maximum tolerated dose within the assigned dose group, which put most patients at the higher end of their assigned dose range for the fixed dose phase of the study. In fact, the median modal dose during the fixed-dose phase (Days 15-42) of RIS-SCH-302 was 3 mg/day in the 1-3 mg/day dose group and 6 mg/day in the 4-6 mg/day dose group. Likewise, the median modal dose during the fixed dose phase (Days 11-21) of RIS-BIM-301 was 2.5 mg in the 0.5-2.5 mg/day dose group and 5 mg/day in the 3-6 mg/day dose group. Therefore, the median modal doses in both trials were at or near the top of their respective dose ranges, and the efficacy results (and adverse events) noted from the trials come from the higher doses in both groups for both study populations. As a result, we don't know the exact range of effectiveness with certainty, but we do know that doses up to 6 mg/day are effective for

schizophrenia in adolescent patients, and for mania/mixed mood episodes of bipolar I disorder in children and adolescents. I would not, therefore, restrict labeling to the lower dose range, but would recommend that we define 6 mg/day as the upper boundary for the effective dose range for both disorders in pediatric patients.

6.0 Safety Data

Treatment of pediatric patients with risperidone has been reasonably safe and well tolerated. The safety profile for use in pediatric patients appears similar to that in adults.

6.1 Studies Used to Assess Safety

Schizophrenia

The safety evaluation for schizophrenia is based upon three studies conducted in adolescents with schizophrenia. Two of these studies were the same trials used to demonstrate efficacy. One was placebo-controlled (RIS-SCH-302[6 weeks]), one low-dose controlled (RIS-USA-231 [8 weeks]), and one was open-label (RIS-USA-234 [6 months]).

Bipolar I Disorder

The safety evaluation for bipolar I disorder is based on three studies of adolescents and children. One of these studies was placebo-controlled (the same trial used to demonstrate efficacy) and conducted in pediatric patients with bipolar I disorder (RIS-BIM-301[3 weeks]), one was the same long-term open-label study in adolescents with schizophrenia (RIS-USA-234 [6 months]) mentioned above, and one was a pharmacokinetic study in which subjects (5-17 years old) took risperidone at a daily dose of 0.01-0.08 mg/kg/day with a maximum daily dose of 4 mg.

6.2 Deaths

There were no deaths in any of the controlled trials.

6.3 Adverse Events Leading to Dropout

Schizophrenia

The events leading to discontinuation of the study medication in the two controlled trials of pediatric patients with schizophrenia are similar to those seen in adults and are summarized in the tables below.

RIS-SCH-302: Treatment-emergent Adverse Events Resulting in Discontinuation

AE System Organ Class Adverse Event Preferred Term	Placebo (N=54) n (%)	RIS 1-3 mg (N=55) n (%)	RIS 4-6 mg (N=51) n (%)	ALL RIS (N=106) n (%)
Total no. subjects with perm stop med	2 (4)	3 (5)	4 (8)	7 (7)
Psychiatric disorders	2 (4)	2 (4)	4 (8)	6 (6)
Somnolence	0	0	2 (4)	2 (2)
Anorexia	0	0	1 (2)	1 (1)
Anxiety	0	0	1 (2)	1 (1)
Psychosis	2 (4)	2 (4)	1 (2)	3 (3)
Centr & periph nervous system disorders	0	1 (2)	2 (4)	3 (3)
Ataxia	0	0	1 (2)	1 (1)
Dizziness	0	1 (2)	1 (2)	2 (2)
Cardiovascular disorders, general	0	0	1 (2)	1 (1)
Hypotension	0	0	1 (2)	1 (1)
Heart rate and rhythm disorders	0	0	1 (2)	1 (1)
Palpitation	0	0	1 (2)	1 (1)
Body as a whole - general disorders	1 (2)	0	0	0
Fever	1 (2)	0	0	0

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Source: Dr. Cai's review

RIS-SCH-231: Treatment-emergent Adverse Events Resulting in Discontinuation

AE System Organ Class Adverse Event Preferred Term	RIS 0.15-0.6 mg (N=132) n (%)	RIS 1.5-6 mg (N=125) n (%)
Total no. subjects with perm stop med	6 (4.5)	5 (4.0)
Psychiatric disorders	4 (3.0)	3 (2.4)
Psychosis	3 (2.3)	2 (1.6)
Agitation	1 (0.8)	1 (0.8)
Insomnia	0	1 (0.8)
Suicide attempt[a]	1 (0.8)	0
Cardiovascular disorders, general	1 (0.8)	1 (0.8)
ECG abnormal	0	1 (0.8)
Hypertension	1 (0.8)	0
Centr & periph nervous system disorders	1 (0.8)	1 (0.8)
EEG abnormal	0	1 (0.8)
Oedema cerebral	1 (0.8)	0
Respiratory system disorders	0	1 (0.8)
Upper resp tract infection	0	1 (0.8)
Heart rate and rhythm disorders	1 (0.8)	0
Tachycardia	1 (0.8)	0
Liver and biliary system disorders	1 (0.8)	0
SGOT increased	1 (0.8)	0
SGPT increased	1 (0.8)	0

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events. [a] Verbatim term: suicidal ideation.
EEG= electroencephalogram.
Source: Dr. Cai's review.

Bipolar I Disorder

There were no adverse events leading to discontinuation in Study RIS-USA-160.

Adverse events leading to discontinuation of risperidone in the single controlled trial of bipolar I disorder in children and adolescents are listed in the table below.

RIS-BIM-301: Treatment-emergent Adverse Events Resulting in Discontinuation

Study Phase: Treatment AE System Organ Class Adverse Event Preferred Term	PLACEBO (N=58) n (%)	RIS 0.5-2.5 mg (N=50) n (%)	RIS 3-6 mg (N=61) n (%)	ALL RIS (N=111) n (%)
Total no. subjects with perm stop med	4 (7)	3 (6)	10 (16)	13 (12)
Psychiatric disorders	3 (5)	1 (2)	7 (11)	8 (7)
Somnolence	0	1 (2)	4 (7)	5 (5)
Psychosis manic-depressive	3 (5)	0	3 (5)	3 (3)
Aggressive reaction	0	0	1 (2)	1 (1)
Nervousness	0	0	1 (2)	1 (1)
Suicide attempt	2 (3)	0	1 (2)	1 (1)
Centr & periph nervous system disorders	0	1 (2)	3 (5)	4 (4)
Bradykinesia	0	0	1 (2)	1 (1)
Hyperkinesia	0	0	1 (2)	1 (1)
Hypertonia	0	0	1 (2)	1 (1)
Speech disorder	0	0	1 (2)	1 (1)
Vertigo	0	1 (2)	0	1 (1)
Gastro-intestinal system disorders	0	2 (4)	3 (5)	5 (5)
Abdominal pain	0	1 (2)	1 (2)	2 (2)
Nausea	0	2 (4)	1 (2)	3 (3)
Saliva increased	0	0	1 (2)	1 (1)
Vomiting	0	1 (2)	1 (2)	2 (2)
Body as a whole - general disorders	1 (2)	0	1 (2)	1 (1)
Allergic reaction	0	0	1 (2)	1 (1)
Syncope	1 (2)	0	0	0

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
AE = adverse event; med = medication; N = total sample size; n = number with adverse event; no. = number; perm = permanent; RIS = risperidone
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Source: Dr. Cai's review.

From the table above it is notable that 12% (13/111) of pediatric patients treated with risperidone discontinued treatment due to an adverse event compared to 7% (4/58) of patients taking placebo. Adverse events leading to discontinuation in more than one patient include somnolence, nausea, abdominal pain, and vomiting.

Team Leader Comment: Overall, events leading to dropout from the pediatric trials are similar to those seen in the adult trials of risperidone.

6.4 Serious Adverse Events (SAEs)

RIS-SCH-302

Two SAEs were reported for patients taking drug in this study, one in each of the risperidone treatment groups and both while each patient was taking 1 mg/day. Both events were related to

psychosis requiring hospitalization and treatment with other antipsychotics, and neither is considered related to study drug.

RIS-USA-231

Nine SAEs were reported as psychosis, one occurred in a patient who also had cerebral edema in the low-dose risperidone group. It is unclear if this SAE was related to risperidone.

US-BIM-301

The following table of SAEs includes events occurring during the treatment phase and for 30 days after the last dose of risperidone.

RIS-BIM-301: ITT Analysis Set, SAEs Occurring During Treatment or Within 30 Days of Last Medication Dose

AE System Organ Class Adverse Event Preferred Term	Placebo (N=58) n (%)	Risperidone 0.5–2.5 mg (N=50) n (%)	Risperidone 3–6 mg (N=61) n (%)	All Risperidone (N=111) n (%)
Total no. subjects with serious AEs	3 (5)	3 (6)	5 (8)	8 (7)
Psychiatric disorders	3 (5)	2 (4)	4 (7)	6 (5)
Psychosis manic-depressive	2 (3)	1 (2)	4 (7)	5 (5)
Suicide attempt	1 (2)	2 (4)	2 (3)	4 (4)
Manic reaction	1 (2)	0	0	0
Body as a whole - general disorders	0	0	1 (2)	1 (1)
Allergic reaction	0	0	1 (2)	1 (1)
Respiratory system disorders	0	1 (2)	0	1 (1)
Asthma	0	1 (2)	0	1 (1)
Bronchospasm	0	1 (2)	0	1 (1)

Team Leader Comment: Although the numbers are small, the majority of SAEs in Study 301 are psychiatric, and many of those (e.g. psychosis, manic-depressive) are related to bipolar I disorder. Dr. Cai has reviewed the cases of "suicide attempt" listed above, as well as the sponsor's subsequent analysis of the data related to this category. The sponsor's analysis includes all incidences of suicide attempts, suicidal ideation, self injurious behaviors, falls, injuries, and aggressive reaction. Dr. Cai points out, and I agree, that self-injurious behavior with no intent to produce harm is common in the pediatric population, and that indeed the only genuine suicide attempt in Study 301 occurred in a patient taking placebo. I also agree with Dr. Cai that due to the small number of subjects in the study, no meaningful conclusions can be drawn about drug effect on suicidal ideation (see Dr. Cai's review for a more detailed analysis).

RIS-USA-234

This six month, open-label safety study did not reveal any unexpected serious adverse events in the pediatric population.

6.5 Common and Drug-Related Adverse Events

Schizophrenia

The table below represents common and therefore likely drug-related adverse events that occurred in at least 5% in any treatment group with rates at least twice that of placebo from Study RIS-SCH-302.

Common Adverse Events in Study RIS-SCH-302

Subject N / Adverse Events (%)	Placebo	RIS 1-3 mg	RIS 4-6 mg	All RIS
	54	55	51	106
Extrapyramidal disorder	2 (4)	5 (9)	8 (16)	13 (12)
Dizziness	1 (2)	4 (7)	7 (14)	11 (10)
Hypertonia	4 (7)	3 (5)	7 (14)	10 (9)
Somnolence	2 (4)	13 (24)	6 (12)	19 (18)
Agitation	4 (7)	8 (15)	4 (8)	12 (11)
Anxiety	0	4 (7)	3 (6)	7 (7)
Saliva Increased	1 (2)	0	5 (10)	5 (5)

Source: Dr. Cai's review

Team Leader Comment: From the table above it is clear that the higher-dose risperidone group experienced more extrapyramidal symptoms, hypertonia, and dizziness. It is also clear that the lower dose group had more anxiety and agitation, which may represent partially-treated symptoms of schizophrenia. Somnolence was more common in the lower dose group.

Bipolar I Disorder

The table below represents common and therefore potentially drug-related adverse events that occurred in at least 5% in any treatment group with rates at least twice that of placebo (bold type).

Common Adverse Events in Study RIS-BIM-301

AE System Organ Class / Adverse Event Preferred Term	**PLACEBO (N=58)** n (%)	**RIS 0.5-2.5 mg (N=50)** n (%)	**RIS 3-6 mg (N=61)** n (%)
Total no. subjects with AEs	44 (76)	45 (90)	58 (95)
Psychiatric disorders	20 (34)	24 (48)	**45 (74)**
Somnolence	11 (19)	**21 (42)**	**34 (56)**
Anxiety	2 (3)	0	**5 (8)**
Appetite increased	1 (2)	**2 (4)**	**4 (7)**
Suicide attempt	2 (3)	1 (2)	**4 (7)**
Centr & periph nervous system disorders	22 (38)	27 (54)	34 (56)
Dizziness	3 (5)	**8 (16)**	**8 (13)**
Hypertonia	1 (2)	**2 (4)**	**5 (8)**
Hyperkinesia	1 (2)	0	**4 (7)**
Extrapyramidal disorder	1 (2)	1 (2)	**3 (5)**
Dystonia	0	**3 (6)**	**2 (3)**
Gastro-intestinal system disorders	14 (24)	**25 (50)**	26 (43)
Abdominal pain	3 (5)	**9 (18)**	**9 (15)**
Nausea	4 (7)	**8 (16)**	8 (13)

Diarrhea	1 (2)	**4 (8)**	**4 (7)**
Dyspepsia	2 (3)	**8 (16)**	3 (5)
Body as a whole - general disorders	13 (22)	18 (36)	23 (38)
Fatigue	2 (3)	**9 (18)**	**18 (30)**
Injury	2 (3)	**3 (6)**	1 (2)
Respiratory system disorders	12 (21)	12 (24)	17 (28)
Dyspnea	0	**1 (2)**	**3 (5)**
Pharyngitis	3 (5)	**5 (10)**	2 (3)
Sinusitis	2 (3)	**3 (6)**	1 (2)
Skin and appendages disorders	3 (5)	**5 (10)**	**7 (11)**
Rash	1 (2)	0	**4 (7)**
Heart rate and rhythm disorders	1 (2)	0	**6 (10)**
Tachycardia	1 (2)	0	**3 (5)**
Reproductive disorders, female	4 (7)	1 (2)	**4 (7)**
Lactation nonpuerperal	0	1 (2)	**3 (5)**
Urinary system disorders	0	0	**4 (7)**
Urinary incontinence	0	0	**3 (5)**
Vision disorders	2 (3)	**3 (6)**	**4 (7)**
Vision abnormal	0	**2 (4)**	**4 (7)**

Source: Dr. Cai's review.

Extrapyramidal AEs

Dr. Cai has pointed out in her review that AEs which likely represent treatment-emergent extrapyramidal symptoms include the categories listed above as hypertonia, hyperkinesia, extrapyramidal disorder, and dystonia. She combined these categories and calculated the combined incidence rates for extrapyramidal disorder as 23% (14/61) for the risperidone 3-6 mg/day group, 12% (6/50) in the risperidone 0.5-2.5 mg/day group, and 5.1% (3/58) for the placebo group.

Team Leader Comment: I agree that we should include all extrapyramidal symptoms in one category. As with adults, the higher dose group has a predictably higher incidence of treatment-emergent extrapyramidal symptoms. There were no reports of tardive dyskinesia in the pediatric study populations.

Somnolence

Somnolence is a very commonly observed treatment-emergent adverse event with risperidone in controlled studies for both pediatric schizophrenia and bipolar I disorder.

Team Leader Comment: Somnolence is a known adverse event seen with use of risperidone and it will be included in Warnings and Precautions section of labeling.

Suicide-Related AEs

There were 7 reports of adverse events coded to "suicide attempt" during the treatment phase of Study RIS-BIM-301, but not all of these were also coded as serious adverse events. The suicide attempts considered serious by the sponsor include 1 in the placebo group and 2 in the risperidone 3-6 mg/day group. All of these events coded as serious in the risperdidone group were suicidal ideation. Three subjects in the risperidone groups had events coded at least 4 days after the last dose of risperidone and so these events were not considered treatment-emergent. The sponsor conducted a blinded (done by an external consultant) review of all potentially suicide-related

adverse events (including all potentially self-injurious behaviors) and concluded that there was no clinically meaningful imbalance between placebo and risperidone treatment groups.

Dr. Cai reviewed the potentially suicide-related cases and confirmed that all 4 cases of treatment-emergent adverse events coded to suicide attempt in the risperdone 3-6 mg/day group were actually suicidal ideation and not suicide attempts. She concluded that significant differences could not be discerned between placebo and risperidone treatment groups.

Team Leader Comment: I agree with Dr. Cai that no meaningful conclusions about potentially suicide-related AEs can be drawn from study RIS-BIM-301.

6.6 Vital Sign Changes

RIS-SCH-302

The only clinically relevant mean vital sign change was an increase in standing pulse rate of +5.75 bpm and supine pulse rate of +4.39 bpm on Day 15 in the risperidone 1-3 mg/day dose group.

RIS-BIM-301

There were no clinically relevant changes in mean vital signs parameters (including supine and standing pulse rate, systolic blood pressure, and diastolic blood pressure). There was an increase in the number of subjects with clinically important changes in standing pulse rate (increase greater than 15 bpm or increase to above 120 bpm from a normal pre-treatment pulse rate) during risperidone therapy (risperidone 0.5-2.5 mg group, 2 [4%] subjects; risperidone 3-6 mg group, 8 [14%] subjects); 1 subject (2%) in the placebo group had a change of clinical importance in standing pulse rate. No subject in the study met the criteria for orthostatic hypotension.

Team Leader Comment: Decreased blood pressure, orthostatic hypotension, and tachycardia are known adverse events associated with the use of risperidone and are prominently labeled.

6.7 Changes in Body Weight and Height

Schizophrenia Trials

A clinically significant increase (>7%) in body weight was observed for 15% and 16% of subjects receiving risperidone 1-3 mg/day or 4-6 mg/day, respectively, in RIS-SCH-302 (compared with 2% of placebo subjects). This same increase of >7% in body weight was seen in 39% of subjects receiving risperidone 1.5-6 mg/day in RIS-USA-231 (compared with 16% in subjects receiving low-dose risperidone 0.15-0.6 mg/day). None of the adverse events of weight increase were considered serious or led to discontinuation of study drug.

In the long-term open-label study (RIS-USA-234), mean (SD) body weight and BMI increased by 4.21 kg (5.33 kg) and 1.25 kg/m2 (1.83 kg/m2), respectively, from baseline to the Month 6 endpoint. Height showed a small increase over the treatment period with the mean (SD) change from baseline of 0.96 cm (1.55) at the Month 6 end point and 1.10 cm (1.87) at the overall end point.

Bipolar I Disorder Trial

In the risperidone groups, mean increases in body weight were higher than placebo but were not dose related (risperidone 0.5–2.5 mg group, 1.90 kg [SD, 1.68]; risperidone 3-6 mg group, 1.44 kg [SD, 2.41]). A similar trend was observed in the mean change from baseline in BMI.

Team Leader Comment: Increase in body weight is a known and labeled adverse event associated with the use of risperidone.

6.8 Laboratory Findings

Prolactin

Risperidone is known to increase mean prolactin levels and an increase in mean prolactin levels from baseline to end point was observed in the pediatric studies. The increases in mean prolactin appeared to be dose-dependent and the clinical relevance of such increases is unknown.

RIS-SCH-302

In study RIS-SCH-302 the mean increase in prolactin was 25.65 ng/mL (SD, 34.29) in the 1-3 mg dose group and 40.63 ng/mL (SD, 45.61) in the 4-6 mg dose group. The increase in prolactin was most pronounced over the first 4 weeks of treatment and the mean increases were greater in female patients. No potentially prolactin-related adverse events were observed.

RIS-BIM-301

One female subject in the placebo group, 2 subjects (1 female, 1 male) in the risperidone 0.5-2.5 mg group, and 3 subjects (all female) in the risperidone 3–6 mg group experienced prolactin-related adverse events. The main prolactin-related adverse event was lactation nonpuerperal, which was experienced by 4 subjects in the risperidone groups but no subjects in the placebo group. See the table below for more information.

Incidence of Treatment-Emergent Prolactin-Related Adverse Events (RIS-BIM-301; Intent-to-Treat Analysis Set)

AE System Organ Class Adverse Event Preferred Term	Placebo (N=58) n (%)	Risperidone 0.5–2.5 mg (N=50) n (%)	Risperidone 3–6 mg (N=61) n (%)	All Risperidone (N=111) n (%)
Total no. subjects with prolactin-related AEs	1 (2)	2 (4)	3 (5)	5 (5)
Reproductive disorders, female	1 (2)	1 (2)	3 (5)	4 (4)
Lactation nonpuerperal	0	1 (2)	3 (5)	4 (4)
Breast enlargement	1 (2)	0	0	0
Breast pain female	1 (2)	0	0	0
Reproductive disorders, male	0	1 (2)	0	1 (1)
Ejaculation disorder	0	1 (2)	0	1 (1)

Note: Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events

Team Leader Comment: Risperidone is known to increase serum prolactin, the clinical significance of which is unknown. This information is included in current labeling. Updated labeling (PLR format) will retain this information in the Warnings and Precautions section.

Glucose

RIS-SCH-302

There was a small mean increase in fasting glucose levels from baseline to endpoint in the higher dose group of this study. The magnitude of the change in serum glucose was small; there were a few subjects in each study with post-baseline values above the potentially clinically important upper

limit of 6.4 mmol/L, but no glucose-related adverse events, including new onset diabetes, were reported.

RIS-BIM-301
There were no glucose-related adverse events from this short trial.

Team Leader Comment: The potential for hyperglycemia with risperidone use is included in current labeling and will remain in the Warnings and Precautions section.

6.9 Long-term Open-label Studies

Common adverse events occurring at a greater frequency in the in the long-term study RIS-USA-234 (median treatment duration of 6 months) compared with the 2 short-term studies RIS-USA-231 and RIS-SCH-302 include weight gain and psychosis, but no new adverse events emerged with long-term treatment.

The overall incidence of serious adverse events with risperidone treatment in the long-term study (RIS-USA-234) was higher (15%) than in the 2 short-term studies (RIS-USA-231 and RIS-SCH-302 (2-3.5%)).

6.10 Postmarketing Experience

The sponsor reports 27 million patient-years of cumulative exposure to oral risperidone. The worldwide exposure in pediatric patients (ages 5-17 years) was estimated at 1,117,689 patient-years as of August 31, 2006.

There have been fewer serious adverse events involving pediatric patients in postmarketing reports than in all other age groups. There has been no newly identified pattern of adverse drug reactions specific for the pediatric population on the basis of cumulative review other than weight gain.

6.11 Literature Review

The sponsor has conducted a comprehensive literature search (current as of August, 31, 2006) and summarized the results of articles containing original clinical data on the use of risperidone in children and adolescents as part of this submission. These articles included 17 double-blind, placebo-controlled studies and 6 reference drug-controlled studies in children and adolescents, as well as 75 open-label studies and 30 chart reviews. In total there were data on more than 5,400 pediatric subjects and safety results from 206 articles. Risperidone doses administered ranged from 0.25mg–12 mg/day or 0.01-0.06 mg/kg/day, and the duration of treatment was up to 7 years.

In general, the adverse events reported in the published articles were consistent with the established adverse event profile of risperidone. The most frequently reported adverse events were: weight gain (75 articles), sedation (47 articles), and EPS (32 articles).

Discontinuation of treatment with risperidone was discussed in 67 articles. The most commonly reported reasons to discontinue treatment were: weight gain (18 articles), EPS (11 articles), hyperprolactinemia (8 articles), and sedation (7 articles).

Six nonfatal overdoses were reported, and no deaths were reported in children or adolescents. Serious adverse events were reported for 19 subjects: neuroleptic malignant syndrome (9), tardive dyskinesia (4), pancreatitis (2), acute dystonia (1), probable viral encephalitis (1), worsening mitochondrial disorder (1), and increased carbamazepine level (1).

6.12 Conclusion Regarding Safety

Short-term treatment of pediatric patients with risperidone appears to have been reasonably safe and there were no unexpected adverse events.

7.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

This NDA was not presented to the PDAC.

8.0 DSI INSPECTIONS

Three clinical investigator sites were inspected by DSI and it was determined that the data generated to support RIS-BIM-301 and RIS-SCH-302 were acceptable.

9.0 LABELING AND ACTION LETTER

9.1 Final Draft of Labeling Attached to the Action Package

The sponsor's proposed labeling is presented in the new PLR format and will require some modification as described throughout this review. We will need to re-order the Warnings/Precautions section and include all relevant potential adverse events prominently.

9.2 DMETS

Risperdal™ is an approved trade name.

10.0 PHASE 4 COMMITMENTS

No Phase 4 requirements have been identified.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to support that risperidone is effective and reasonably safe in the treatment of pediatric schizophrenia and bipolar I disorder, and we should proceed with an APPROVABLE action pending negotiation of labeling. Annotated Draft Labeling as revised by the Division should be attached to the Action Letter.

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/s/

Mitchell Mathis
6/18/2007 04:05:12 PM
MEDICAL OFFICER