DEPARTMENT OF HEALTH AND HUMAN SERVICES

CONSULTATION

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: June 4, 2012

FROM: Ali Mohamadi, MD, Division of Metabolism and Endocrinology Products (DMEP)

THROUGH: Dragos Roman, MD, Team Leader, DMEP
Mary Parks, MD, Division Director, DMEP

TO: Robert Levin, MD, Medical Officer, Division of Psychiatry Products (DPP)
Ann Sohn, PharmD, Regulatory Project Manager, DPP

SUBJECT: Effect of Risperidone on biochemical markers of linear growth in post-marketing clinical trial 4002

ASSOCIATED NDA#s: 20272; 20588; 21444

I. Background and basis for consult

On May 4, 2012, the Division of Metabolism and Endocrinology Products (DMEP) received a consultation request from the Division of Psychiatry Products (DPP) regarding risperidone, an atypical antipsychotic drug approved in the United States for a number of indications, including treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years. The drug was approved for this indication based on the results of two separate Phase 3, 8-week placebo controlled trials of risperidone in oral doses ranging from 0.5 to 3 mg per day.

In its pivotal Phase 3 clinical trials from NDA 20-272/s036 (originally submitted in December 2003), DPP discovered a number of potentially concerning findings related to endocrine function in pediatric patients, including a number of patients with abnormalities of glucose metabolism and 12 patients who were reported to have the adverse event of "growth hormone excess" during pediatric studies with risperidone. This finding was notable because according to the sponsor these same patients were found to have an increase in body weight, height, and body mass index "greater than expected" for their age and gender; however, it is not currently included in the approved risperidone label.

In the FDA approval letter of October 6, 2006, a Phase 4 Commitment was requested in the form of a fixed-dose, parallel group, placebo-controlled trial to determine the lowest effective dose of risperidone in the treatment of irritability associated with autistic disorder. In addition, the study (known as RIS-AUT-4002 and hereafter referred to as "Study 4002") was requested to evaluate the effect of risperidone treatment on fasting glucose, fasting insulin, insulin resistance, growth hormone (GH) and Insulin-like Growth Factor (IGF-1) in this population.

In its consultation request, DPP has requested that DMEP independently evaluate the safety results of Risperdal in its postmarketing study RIS-AUT-4002 as they relate to drug effect on parameters of glucose metabolism and growth. DPP has submitted the following questions for consideration:

1. What is your assessment of the metabolic and endocrine findings from the controlled and long-term studies.
2. Are any of these findings potentially significant?
3. Would it be useful to include any of the findings in labeling?

Please note that this consult covers evaluation of biochemical testing for the evaluation of growth. Evaluation of glucose metabolism is covered in a separate consult written by Dr. Lisa Yanoff, Medical Officer, DMEP.

II. Materials reviewed for consult

1. Clinical trial protocols and clinical study reports for risperidone Phase 3 studies.
2. Study 4002 clinical study report.
3. Currently approved labeling for risperidone.

III. DMEP Comments

Study 4002 is a prospective, randomized, 6-week, double-blind, fixed-dose, placebo-controlled study followed by a 6-month, flexible-dose, open-label, uncontrolled extension phase designed to evaluated the safety and efficacy of a 0.125 mg/day dose of risperidone (lower than the recommended daily dose of 1 mg/day) in pediatric and adolescent patients with irritability due to Autism. The Phase 4 study specifically assessed the effect of fixed doses of risperidone on insulin resistance and glucose metabolism, and the growth hormone axis. Moreover, the extended safety and tolerability, particularly in relation to effects on glucose metabolism, insulin resistance, growth hormone axis, height and weight, in children and adolescents with Autistic Disorder treated with risperidone was documented over a 6-month period of open-label treatment.

Study design: double-blind phase
In the double-blind phase, patients were randomized to receive either placebo or 1 of 2 dosages of risperidone, for up to 6 weeks. The randomization was stratified by center and baseline weight (20 kg to <45 kg; or ≥45 kg). The dose levels of risperidone were: 0.125 mg/day and 1.25 mg/day for patients with a baseline weight of 20 kg to less than 45 kg; and 0.175 mg/day and 1.75 mg/day for patients with a baseline weight of 45 kg or more. The dose of risperidone was titrated upward as follows:

- Low-dose, 20 to <45 kg: started at 0.05 mg and titrated up to 0.125 mg on Day 4;
- High-dose, ≥45 kg: started at 0.5 mg and titrated up to 1.25 mg on Day 4;
- Low-dose, 20 to <45 kg: started at 0.075 mg and titrated up to 0.175 mg on Day 4;
- High-dose, ≥45 kg: started at 0.75 mg and titrated up to 1.75 mg on Day 4.

Study drug (risperidone or placebo) was administered once-daily in the morning (or evening, if sedation occurred). Efficacy and safety evaluations were completed during visits at baseline, Day 4, and Weeks 1, 2, 4, 6, and, if applicable, upon early withdrawal from the double-blind phase. Plasma concentrations of risperidone and 9-hydroxy-risperidone were determined at Week 6 as a measure of exposure.

Study design: open-label phase

The open-label extension phase was conducted in patients from the double-blind phase who required further treatment with risperidone. It consisted of the baseline visit followed by an open-label treatment phase up to 26 weeks (6 visits), during which patients received flexible doses of risperidone. The initial starting dose of risperidone for 3 days was 0.125 mg/day for patients with a baseline weight of 20 kg to less than 45 kg or 0.175 mg/day for patients with a baseline weight of 45 kg or more. The dose was then increased to 0.25 mg for all patients on Day 4. Thereafter, additions of 0.25 mg or 0.5 mg to the initial starting dose (upon the judgment of the investigator) were allowed every 2 weeks. The dose ranges were: 0.125 mg/day to 1.25 mg/day for patients with a baseline weight of 20 kg to <45 kg; and 0.175 mg/day to 1.75 mg/day for patients with a baseline weight of ≥45 kg.

Efficacy and safety evaluations were completed during visits at baseline (open-label Week 0), and open-label Weeks 1, 2, 4, 13, 26, and, if applicable, upon early withdrawal from the open-label extension phase.

Evaluation of growth hormone axis

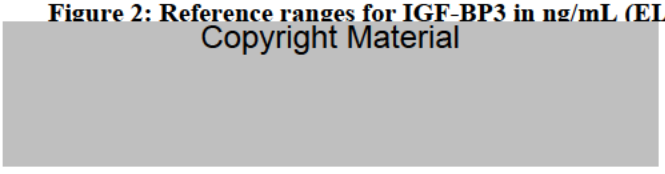
There were 96 patients randomized into the trial, with 77 (80%) completing the placebo-controlled phase. Seventy-nine patients continued into the open-label period, with 56 (77%) completing this phase. Overall completion rates for the double-blind phase across the treatment groups were comparable in both phases, although reasons for withdrawal varied somewhat across treatment groups with a higher rate of discontinuation due to inadequate response in the placebo group versus the two risperidone groups. In the entire study period, there were no serious adverse events or adverse events leading to discontinuation due to factors related to growth, development, or their associated biochemical evaluations (IGF-1 or IGF-BP3).

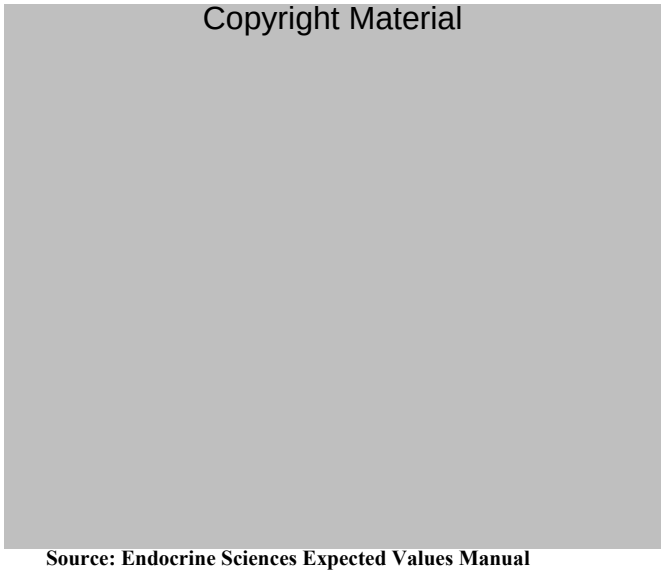
To help establish a frame of reference for the results presented later in this consultation review, Figures 1 and 2 below include the normal ranges for enzyme immunoassay (EIA) assays by age for IGF-1 (ng/mL) and IGF-BP3 (ng/mL) as established by Endocrine Sciences Laboratories:

Figure 1: Reference ranges for IGF-1 in ng/mL (EIA assays) from Endocrine Sciences

Source: Endocrine Sciences Expected Values Manual

Figure 2: Reference ranges for IGF-BP3 in ng/mL (EIA assays) from Endocrine Sciences





Source: Endocrine Sciences Expected Values Manual

Placebo-controlled phase

At baseline mean IGF-1 levels (both in ng/mL and standard deviation scores (SDS)) and mean IGF-BP3 levels (ng/mL) were similar among treatment groups (Table 1). There was no apparent clinically relevant change in values from baseline to the end of the double-blind treatment period either within or between treatment groups for any of these parameters.

Table 1: Mean Change in IGF-1 (ng/mL, SDS) and IGF-BP3 (ng/mL) by EIA – Double-Blind Treatment Period –ITT Population

	Placebo N=35	**Risperidone Low Dose N=30**	**Risperidone High Dose N=31**
IGF-1 (ng/mL)			
N	31	26	27
Mean baseline	161.7	167.8	144.0
Mean Week 6	186.9	179.7	176.9
Change (SD)	25.2 (38.1)	11.9 (39.7)	32.8 (63.7)
IGF-1 SDS			
N	31	26	27
Mean baseline	0.02	-0.60	-0.60
Mean Week 6	0.33	-0.35	-0.03
Change (SD)	0.30 (0.53)	0.25 (0.76)	0.55 (0.94)
IGF-BP3 (ng/mL)			
N	30	26	27
Mean baseline	2979.9	2701.5	2836.9
Mean Week 6	2810.4	2783.4	2917.4
Change (SD)	-169.5 (727.75)	81.9 (491.04)	80.5 (913.14)

Source: Table 55 Clinical Study Report RIS-AUT-4002

The sponsor conducted subgroup analysis of IGF-1 and IGF-BP3 by age group (12 years or greater and less than 12 years), which also did not show any clinically significant changes from baseline to end of the placebo phase (Tables 2 and 3).

Table 2: Mean Change in IGF-1 (ng/mL, SDS) and IGF-BP3 (ng/mL) by age <12 years – Double-Blind Treatment Period –ITT Population

	Placebo N=30	**Risperidone Low Dose N=20**	**Risperidone High Dose N=24**
IGF-1 (ng/mL)			

N	27	18	22
Mean baseline	149.0	132.3	126.0
Mean Week 6	173.7	147.1	158.5
Change (SD)	22.2 (39.3)	14.7 (33.5)	32.5 (53.7)
IGF-1 SDS			
N	27	18	22
Mean baseline	0.13	-0.35	-0.43
Mean Week 6	0.39	-0.09	0.13
Change (SD)	0.27 (0.56)	0.25 (0.57)	0.56 (0.91)
IGF-BP3 (ng/mL)			
N	26	18	22
Mean baseline	2746.3	2497.2	2857.9
Mean Week 6	2870.0	2632.7	2901.6
Change (SD)	-123.7 (749.2)	135.4 (465.8)	43.8 (515.2)

Source: Attachment 5.27 Clinical Study Report RIS-AUT-4002

Table 3: Mean Change in IGF-1 (ng/mL, SDS) and IGF-BP3 (ng/mL) by age ≥12 years – Double-Blind Treatment Period –ITT Population

	Placebo N=5	**Risperidone Low Dose N=10**	**Risperidone High Dose N=7**
IGF-1 (ng/mL)			
N	4	8	5
Mean baseline	230.8	247.8	223.2
Mean Week 6	276.0	253.3	257.6
Change (SD)	45.3 (22.4)	5.5 (53.3)	34.4 (105.9)
IGF-1 SDS			
N	4	8	5
Mean baseline	-0.7	-1.2	-1.2
Mean Week 6	-0.2	-0.9	-0.7
Change (SD)	0.5 (0.23)	0.2 (1.1)	0.5 (1.2)
IGF-BP3 (ng/mL)			
N	4	8	5
Mean baseline	3694.3	3161.3	2744.4
Mean Week 6	3227.3	3122.6	2986.6
Change (SD)	-467.0 (553.7)	-38.6 (557.0)	242.2 (1996.6)

Source: Attachment 5.27 Clinical Study Report RIS-AUT-4002

To corroborate the laboratory findings, Table 4 below illustrates changes in height from baseline for all patients in the placebo-controlled phase of Study 4002. These results are consistent with those of the biochemical endpoints (IGF-1 and IGF-BP3), which show no significant difference between linear growth between placebo and either treatment group at the end of 6 weeks of dosing.

Table 4: Height at Double Blind Treatment Endpoint, Study 4002

	Placebo (N=35)	Ris Low Dose (N=30)	Ris High Dose (N=31)
Height, cm			
N	33	24	27
Mean baseline	136.1	137.4	135.5
Mean value (SD)	137.1 (16.49)	138.5 (20.05)	135.5 (15.69)
Mean change (SD)	0.9 (1.07)	1.2 (1.33)	0.0 (4.29)

Source: Table 65 Clinical Study Report RIS-AUT-4002

Open-label phase

At baseline mean IGF-1 levels (both in ng/mL and standard deviation scores (SDS)) and mean IGF-BP3 levels (ng/mL) were similar among treatment groups (Table 5). There was no apparent clinically relevant change in values from baseline to the end of the double-blind treatment period either within or between treatment groups for any of these parameters. Interestingly, patients in both risperidone treatment groups demonstrated decreases in mean IGF-1 SDS and IGF-BP3 levels over the six-month open-label course.

Table 5: Mean Change in IGF-1 (ng/mL, SDS) and IGF-BP3 (ng/mL) by EIA – Open Label Treatment Period –ITT Population

	Placebo N=30	**Risperidone Low Dose N=24**	**Risperidone High Dose N=25**
IGF-1 (ng/mL)			
N	26	20	21
Mean baseline	167.3	153.9	129.1
Mean Month 6	206.4	194.5	182.2
Change (SD)	39.2 (71.4)	40.6 (59.80)	53.1 (73.7)
IGF-1 SDS			
N	26	20	21
Mean baseline	0.0953	-0.6543	-0.8530
Mean Month 6	0.5018	-0.1190	-0.2959
Change (SD)	0.41 (0.96)	0.54 (0.98)	0.56 (1.01)
IGFBP-3 (ng/mL)			
N	26	21	21
Mean baseline	3002.4	2709.1	2813.2
Mean Month 6	2770.7	2667.6	2654.1
Change (SD)	-231.7 (707.34)	-41.5 (517.87)	-159.1 (715.06)

Source: Table 56 Clinical Study Report RIS-AUT-4002

The sponsor conducted subgroup analysis of IGF-1 and IGF-BP3 by age group (12 years or greater and less than 12 years), which also did not show any clinically significant changes from baseline to end of the open label phase (Tables 6 and 7).

Table 6: Mean Change in IGF-1 (ng/mL, SDS) and IGF-BP3 (ng/mL) by age <12 years – Open Label Treatment Period –ITT Population

	Placebo N=27	**Risperidone Low Dose N=17**	**Risperidone High Dose N=20**
IGF-1 (ng/mL)			
N	24	15	17
Mean Week 26	206.3	183.2	169.7
Change from Week 0 baseline (SD)	44.9 (71.2)	51.5 (61.4)	49.3 (64.0)
IGF-1 SDS			
N	24	15	17
Mean Week 26	0.7	0.3	0.01
Change from Week 0 baseline (SD)	0.5 (0.9)	0.6 (0.9)	0.6 (0.9)
IGFBP-3 (ng/mL)			
N	24	16	17
Mean Week 26	2779.8	2629.2	2690.2
Change from Week 0 baseline (SD)	-202.7 (727.8)	32.7 (539.1)	-187.9 (640.4)

Source: Attachment 5.34 Clinical Study Report RIS-AUT-4002

Table 7: Mean Change in IGF-1 (ng/mL, SDS) and IGF-BP3 (ng/mL) by age ≥12 years – Open Label Treatment Period –ITT Population

	Placebo N=3	**Risperidone Low Dose N=7**	**Risperidone High Dose N=5**
IGF-1 (ng/mL)			
N	2	4	4
Mean Week 26	207.5	228.2	235.3
Change from Week 0 baseline (SD)	-29.5 (27.6)	8.0 (44.8)	69.3 (117.9)
IGF-1 SDS			
N	2	5	4
Mean Week 26	-1.7	-1.5	-1.6
Change from Week 0 baseline (SD)	-0.7 (0.06)	0.3 (1.2)	0.3 (1.5)
IGFBP-3 (ng/mL)			
N	2	5	4
Mean Week 26	2662.5	2790.6	2500.5
Change from Week 0 baseline (SD)	-579.5 (249.6)	-278.8 (398.27)	-36.5 (1094.1)

Source: Attachment 5.34 Clinical Study Report RIS-AUT-4002

To corroborate the laboratory findings, Table 4 below illustrates changes in height from baseline for all patients in the placebo-controlled phase of Study 4002. These results are consistent with those of the biochemical endpoints (IGF-1 and IGF-BP3), which show no significant difference in linear growth changes between placebo and either treatment group at the end of 26 weeks of dosing.

Table 8: Height at Double Blind Treatment Endpoint, Study 4002

	Placebo/RIS (N=30)	Ris Low Dose/RIS (N=24)	Ris High Dose/RIS (N=25)	Total (N=79)
Height, cm				
Open-label				
N	29	22	23	74
Mean baseline	136.4	136.0	136.8	136.4
Mean value (SD)	139.9 (16.41)	140.1 (19.17)	139.5 (15.96)	139.8 (16.91)
Mean change (SD)	3.6 (2.66)	4.1 (2.60)	2.7 (4.64)	3.4 (3.39)

Source: Table 65 Clinical Study Report RIS-AUT-4002

IV. DMEP responses to DDDP questions

1. What is your assessment of the metabolic and endocrine findings from the controlled and long-term studies.

Over the 6-week double-blind study period there was a marginally greater increase in IGF-1 (ng/mL and SDS) in the high dose risperidone group compared to placebo from baseline, but this change was small and the totality of data suggests that the risperidone doses evaluated do not result in a clinically meaningful effect on parameters of growth in children and adolescents. The same can be said for IGF-BP3, which was marginally, but not significantly higher at the end of the study in both treatment groups compared to placebo. The lack of clinical significance of these findings is corroborated by height data collected among patients receiving placebo or low/high dose risperidone, which showed no difference among groups during the placebo-controlled phase.

Similar findings were observed in the six-month, open-label extension phase of the study.

There are major limitations, however, regarding the strength of evidence provided by the results of Study 4002. First of all, the study was quite small and was not powered for IGF-1, IGFBP-3, or height analyses; subgroup analyses were conducted with even smaller numbers of patients. As such, all analyses should be seen as exploratory or hypothesis generating at best. In addition, analyses of height over a 6-week period are by definition not informative because longer periods of time (e.g. 6-12 months) are required to observe clinically meaningful changes in height (be it height suppression or height stimulation) that exceed the range of variability expected from height measurements. Therefore, the results of this study, although reassuring that there is no striking effect of risperidone on height, are not label-worthy, nor should they be seen as irrefutable evidence that risperidone does not have an influence on height, particularly since the doses of risperidone assessed in this trial are below those currently labeled.

2. Are any of these findings potentially significant?
Please refer to the response to Question 1. In this reviewer's opinion, and especially when pairing the results of the biochemical tests with the auxological markers, these findings are not clinically significant.

3. Would it be useful to include any of the findings in labeling?
Although these data suggest no clinically significant change in biochemical markers of linear growth with risperidone use at doses administered in the current study, they are limited by the limited size and duration of the trial. Therefore, DMEP does not consider the data from the current study to be a useful addition to the label. Please refer to the response to Question 1 for a more in-depth explanation.

Ali Mohamadi, MD
Medical Officer

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/s/

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