DEPARTMENT OF HEALTH AND HUMAN SERVICES

CONSULTATION

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

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SUBJECT: Consult review for clinical trial 4002 report: Risperidone in the Treatment of Children and Adolescents With Autistic Disorder: A Double-Blind, Placebo-Controlled Study of Efficacy and Safety, Followed by an Open-Label Extension Study of Safety (NDA 20272; 20588; 21444)

SUBMISSION NUMBER : SDN 409

I. Introduction

DPP requests DMEP's evaluation of metabolic and endocrine findings from a study in pediatric patients with Autism treated with risperidone entitled: **Risperidone in the Treatment of Children and Adolescents With Autistic Disorder: A Double-Blind, Placebo-Controlled Study of Efficacy and Safety, Followed by an Open-Label Extension Study of Safety; Protocol RIS-AUT-4002**

DPP has the following questions:
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 glucose metabolism. Evaluation of growth is covered in a separate consult written by Dr. Ali Mohamadi, Medical Officer, DMEP.

Materials reviewed for this consult included the full clinical study report and the currently approved labeling for risperidone.

II. DMEP Recommendations for Regulatory Action

None; we do not recommend any labeling language related to the glucose metabolism findings from the reviewed clinical study.

III. Background

Risperidone is an atypical antipsychotic agent indicated for:
• Treatment of schizophrenia in adults and adolescents aged 13-17 years
• Alone, or in combination with lithium or valproate, for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults, and alone in children and adolescents aged 10-17 years
• Treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years

According to the DPP consult, "the sponsor had demonstrated efficacy and safety in two 8-week, placebo-controlled trials of risperidone 0.5 mg to 3 mg (with weight based dosing). As a postmarketing commitment, at the time of approval, the Division requested that the sponsor study lower, fixed doses of risperidone to determine the lowest effective dose. In addition, we requested that the study include assessments of fasting glucose, fasting insulin, insulin resistance, growth hormone, and IGF-1). In the earlier studies, there was substantial weight gain and modest increases in glucose concentration. The effects on lipids were minimal."

The current labeling for risperidone includes a warning regarding unfavorable changes in glucose metabolism observed with risperidone as follows:

• Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. (5.5)
• *Hyperglycemia and Diabetes Mellitus:* Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. (5.5)

A snapshot of the current labeling is shown below:

5.5 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics, including RISPERDAL®, should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics, including RISPERDAL®, should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics, including RISPERDAL®, should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics, including RISPERDAL®, should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic, including RISPERDAL®, was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of RISPERDAL®.

Pooled data from three double-blind, placebo-controlled schizophrenia studies and four double-blind, placebo-controlled bipolar monotherapy studies are presented in Table 1a.

Table 1a. Change in Random Glucose from Seven Placebo-Controlled, 3- to 8-Week, Fixed- or Flexible-Dose Studies in Adult Subjects with Schizophrenia or Bipolar Mania

		RISPERDAL®	
	Placebo	1-8 mg/day	>8-16 mg/day
	Mean change from baseline (mg/dL)		
	n=555	**n=748**	**n=164**
Serum Glucose	-1.4	0.8	0.6
	Proportion of patients with shifts		
Serum Glucose (<140 mg/dL to ≥200 mg/dL)	0.6% (3/525)	0.4% (3/702)	0% (0/158)

In longer-term, controlled and uncontrolled studies, RISPERDAL® was associated with a mean change in glucose of +2.8 mg/dL at Week 24 (n=151) and +4.1 mg/dL at Week 48 (n=50).

Data from the placebo-controlled 3- to 6-week study in children and adolescents with schizophrenia (13-17 years of age), bipolar mania (10-17 years of age), or autistic disorder (5 to 17 years of age) are presented in Table 1b.

Table 1b. Change in Fasting Glucose from Three Placebo-Controlled, 3- to 6-Week, Fixed-Dose Studies in Children and Adolescents with Schizophrenia (13-17 years of age), Bipolar Mania (10-17 years of age), or Autistic Disorder (5 to 17 years of age)

	Placebo	RISPERDAL® 0.5-6 mg/day
	Mean change from baseline (mg/dL)	
	n=76	**n=135**
Serum Glucose	-1.3	2.6
	Proportion of patients with shifts	
Serum Glucose (<100 mg/dL to ≥126 mg/dL)	0% (0/64)	0.8% (1/120)

In longer-term, uncontrolled, open-label extension pediatric studies, RISPERDAL® was associated with a mean change in fasting glucose of +5.2 mg/dL at Week 24 (n=119).

IV. Clinical study

The current clinical study report is reviewed in this section.

Title: Risperidone in the Treatment of Children and Adolescents With Autistic Disorder: A Double-Blind, Placebo-Controlled Study of Efficacy and Safety, Followed by an Open-Label Extension Study of Safety; Protocol RIS-AUT-4002

Phase: 4

Study Design: prospective, randomized, 6-week, double-blind, fixed-dose placebo-controlled study followed by a 6-month, flexible dose, open-label, uncontrolled extension phase. The open-label phase was for eligible subjects who continued to need risperidone treatment as per the clinical judgment of the investigator, hence was voluntary. See the study schematic in Figure 1 below.

In the study report the Sponsor attempts to provide a rationale for the acceptability of the 6-week duration for assessment of endpoints related to glucose metabolism by noting that in studies assessing glucose homeostasis in subjects receiving treatment with an atypical antipsychotic, insulin resistance was generally evident within a treatment period of 6 weeks. However, at least for diabetes products, DMEP prefers a minimum of 12 weeks for assessment of changes in glucose metabolism.

Figure 1: Study Flow Diagram
Study: RIS-AUT-4002

Phase	Screening	Baseline	Double-Blind Treatment Phase					Open-Label Extension Phase					
Visit	1	2	3	4	5	6	7[a]	8[b]	9	10	11	12	13[c]
Week	-2 to 0	0		1	2	4	6[a]	0[b]	1	2	4	13	26[c]
Day	-21 to -1	1	4	8	15	29	43/EP[a]	1[b]	8	15	29	92	183/EP[c]
Treatment			3 groups with 31 subjects per group (93 subjects in total): Placebo and 2 fixed dose levels of risperidone based on 2 different weight class groups:					2 different weight class groups:					
			Lower weight class: 20 kg - <45 kg			Higher weight class: ≥45 kg		Lower weight class: 20 kg - <45 kg			Higher weight class: ≥45 kg		
			– Placebo			– Placebo		Started on Risperidone 0.125 mg /day on Day 1, increased to 0.25 mg on Day 4. Dose increments of 0.25 mg or 0.5 mg to a maximum of 1.25 mg/day were allowed every 2 weeks, if clinically indicated			Started on Risperidone 0.175 mg/day on Day 1, increased to 0.25 mg on Day 4. Dose increments of 0.25 mg or 0.5 mg to a maximum of 1.75 mg/day were allowed every 2 weeks, if clinically indicated		
			– Risperidone 0.125 mg/day (start: 0.05 mg on Day 1 and titrated up to 0.125 mg on Day 4)			– Risperidone 0.175 mg/day (start: 0.075 mg on Day 1 and titrated up to 0.175 mg on Day 4)							
			– Risperidone 1.25 mg/day (start: 0.5 mg on Day 1 and titrated up to 1.25 mg on Day 4)			– Risperidone 1.75 mg/day (start: 0.75 mg on Day 1 and titrated up to 1.75 mg on Day 4)							

EP=Endpoint
[a] End of double-blind phase: Week 6 or early withdrawal.
[b] Baseline of open-label extension phase.
[c] End-of-Study/End of open-label extension: open-label Week 26 or open-label early withdrawal.

Dosage and Administration: placebo or 1 of 2 dosages of risperidone once-daily in the morning (or evening, if sedation occurred). As the efficacious dose may vary by weight, 2 dose regimens were selected depending on 2 weight classes (20 to <45 kg and ≥45 kg).

The dosing regimens are shown in Figure 1 above. The dose levels of risperidone during the double-blind period were: 0.125 mg/day and 1.25 mg/day for subjects with a baseline weight of 20 kg to less than 45 kg; and 0.175 mg/day and 1.75 mg/day for subjects with a baseline weight of 45 kg or more.

The dosing during the extension period was "flexible" in that doses were titrated to acceptable tolerability and effectiveness. The initial starting dose of risperidone was 0.125 mg/day for subjects with a baseline weight of 20 kg to less than 45 kg or 0.175 mg/day for subjects with a baseline weight of 45 kg or more (the lower of the two doses from the double-blind phase) for three days. The dose was then increased to 0.25 mg for all subjects on Day 4. Thereafter, dose increments of 0.25 mg or 0.5 mg (upon the judgment of the investigator) were allowed every 2 weeks. The time of dosing could be changed from once-daily in the morning to once-daily in the evening, or in 2 divided doses daily, at the investigator's discretion.

Note that the purpose of the study was to determine if doses lower than those currently recommended are efficacious; the lower dose of 0.125 mg per day was chosen as recommended by the FDA.

Subjects: Male and female subjects age 5 to 17 years with a diagnosis of Autistic Disorder and associated irritability. Approximately 120 subjects were to be enrolled in this study to ensure that 93 subjects would be randomly assigned into the double-blind treatment phase (approximately 31 subjects per treatment group).

Key Inclusion criteria pertinent to the consult: body weight of at least 20 kg, good physical health with normal fasting glucose and no significant endocrine or metabolic disorder.

There were no exclusion criteria pertinent to the current consult.

Glucose metabolism assessments: Glucose metabolism-related adverse events were to be summarized using the standardized MedDRA query (SMQ) of hyperglycemia/new onset diabetes mellitus (broad). Glucose and insulin were obtained with subjects in a fasted state for at least 8 hours prior to collection of blood samples. This reviewer could not locate information about the particular assays used. Laboratory tests were analyzed by a central laboratory. Insulin resistance was quantitatively assessed by the homeostatic model assessment of insulin resistance (HOMA-IR), based on the fasting insulin and glucose values, and calculated using the formula (fasting insulin [μU/L] multiplied by fasting glucose [mmol/L] divided by 22.5). A value above 3 was considered abnormal.

Statistical Considerations:
Sample size: Sample size calculation was based on efficacy but the study report states that 29 subjects per group would have 80% power to detect a between group difference of approximately 1.7 to 2.2 in assessment of HOMA-IR based on the standard deviation of change from baseline observed in previous studies conducted by the Sponsor.

Randomization and blinding: these are described in the study report and appear adequate. Randomization was stratified by center and baseline weight (20 kg to <45 kg; or ≥45 kg).

Analysis sets: Glucose and insulin analyses used the intent-to-treat analysis set.

Safety Analysis Plan: Fasting glucose and insulin data were to be presented using descriptive statistics. HOMA-IR was to be analyzed in an ANCOVA model with dose level and baseline weight group as factors and baseline insulin resistance as a covariate. Possible prognostic factors such as age, sex, baseline weight group, weight gain, previous antipsychotic use (no previous use versus some previous use) and baseline Tanner stage were to be examined but no formal statistical analyses were planned.

Results:
Disposition of Patients
There were 96 subjects randomized into the trial. The majority of patients continued into the open-label period (placebo 86%, risperidone low dose 80%, risperidone high dose 81%). Note that patients who did not complete the double-blind phase were still eligible for the open-label phase as long as they had discontinued from the double-blind phase for reasons other than tolerability and had completed at least 3 weeks of the double-blind phase.

Overall completion rates for the double-blind phase across the treatment groups were comparable (placebo 77%, risperidone low dose 83%, risperidone high dose 81%) 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. There was one withdrawal for adverse event in the risperidone high dose group and none in the placebo and low dose groups.

Adverse Events

In the entire study period, there were no serious adverse events or adverse events leading to discontinuation related to glucose metabolism. In the double-blind study period, there were non-serious adverse events potentially related to glucose metabolism: increased appetite, weight increased and thirst that appeared to occur in a dose dependent manner (Table 1). Narratives were not available for these events. Further, adverse event reporting is often subjective and greater emphasis should be given to the objective glucose and insulin data. There were no reports of hyperglycemia, glucose increased, diabetes mellitus, ketoacidosis, hyperosmolar coma or other adverse events specifically related to hyperglycemia.

Table 1 – Adverse Events Potentially Related to Glucose Metabolism – Double-Blind Treatment Period

	Placebo N=34 n (%)	Risperidone Low Dose N=30 n (%)	Risperidone High Dose N=30 n (%)	Total Risperidone N=61 n (%)
Increased Appetite	2 (6)	5 (17)	11 (35)	16 (26)
Weight Increased	2 (6)	3 (10)	4 (13)	7 (11)
Thirst	0	0	2 (6)	2 (3)
Source: Attachment 4.20 Clinical Study Report RIS-AUT-4002				

Laboratory Results

This reviewer emphasized the double-blind treatment period since the extension period was uncontrolled and voluntary.

Analyses of central tendency:

At baseline mean fasting glucose was similar among treatment groups (Table 2). There was no apparent clinically relevant change in fasting glucose from baseline to the end of the double-blind treatment period either within or between treatment groups.

Table 2 – Mean Change in Glucose (mg/dL) and Insulin (µU/mL) – Double-Blind Treatment Period –ITT Population

	Placebo N=35	Risperidone Low Dose N=30	Risperidone High Dose N=31
Fasting glucose N Mean baseline	 22 88.0	 23 87.2	 23 92.0

Mean endpoint Change (SD)	87.5 -0.4 (8.2)	87.1 -0.1 (8.8)	91.7 -0.3 (9.74)
Fasting insulin N Mean baseline Mean endpoint Change (SD)	 22 8.6 8.6 (9.7) -0.04 (13.1)	 22 5.1 5.8 0.735 (3.0804)	 23 5.6 8.0 4.2 (3.5)
Source: Table 49 Clinical Study Report RIS-AUT-4002			

Fasting insulin (Table 2) was slightly higher in the placebo group than in the two risperidone groups at baseline. There was no apparent clinically relevant change in insulin level from baseline to the end of the double-blind treatment period in either the placebo or low dose risperidone group. The change in fasting insulin in the high dose risperidone group was 4.2 μU/mL (starting from 5.6 μU/mL and increasing to 8.0 μU/mL); this reviewer considers the clinical significance of this finding questionable in that an increase of 4.2 μU/mL is marginally significant, but the absolute value is still within the normal range. Further, since the mean fasting insulin value in the risperidone high dose group was similar to the placebo group at study endpoint, the increase seen in the risperidone high dose group could be due, in part, to the statistical phenomenon of regression to the mean.

Outlier analyses:
No subject shifted from normal glucose to abnormal glucose (>125 mg/dL), and no subject in the risperidone groups shifted from normal insulin level to high insulin level (>25 μU/mL) during the double-blind treatment phase.

HOMA-IR:
Between-group differences in mean HOMA-IR were analyzed using the ANCOVA model described above and results shown in Table 3. There was no significant difference in HOMA-IR between the placebo and low dose risperidone group, or between the placebo and high dose risperidone group.

Table 3 – ANCOVA of HOMA-IR – Double-Blind Treatment Period – ITT Population			
	Placebo N=35	Risperidone Low Dose N=30	Risperidone High Dose N=31
N Mean baseline Mean endpoint Change (SD)	22 1.92 1.86 0.04 (2.98)	22 1.13 1.31 0.14 (0.79)	22 1.26 1.91 0.55 (0.88)
p-value LS Mean Change from placebo 95% CI		0.34 -0.42 (0.4) (-1.29; 0.45)	0.86 0.08 (-0.79; 0.94)
Source: Table 50 Clinical Study Report RIS-AUT-4002			

For HOMA-IR, 2 subjects in the placebo group, 1 in the risperidone low dose group, and 3 in the risperidone high dose group, shifted from within normal limits at baseline, to above the abnormal limit during the double-blind period. Although small numbers of subjects limit conclusions, the shift from normal to abnormal HOMA-IR between treatment groups appears to be comparable. Examination of subgroups by the Sponsor did not suggest any prognostic factors. Note that while the current study set an upper limit of normal of 3, HOMA-IR cut off values for insulin resistance are generally higher in the pubertal period than in the prepubertal period, and at least one study suggests that oral glucose tolerance testing may be more sensitive than insulin resistance indexes derived from fasting samples in depicting the pubertal variations of insulin resistance (Guzzaloni, 2002).

The glucose, insulin, and HOMA-IR results were similar for the open-label study phase and data are not shown.

V. Discussion/Conclusions

DPP requested input from DMEP regarding metabolic and endocrine findings from a study in pediatric patients with Autism treated with risperidone entitled: Risperidone in the Treatment of Children and Adolescents With Autistic Disorder: A Double-Blind, Placebo-Controlled Study of Efficacy and Safety, Followed by an Open-Label Extension Study of Safety, whether any of the findings are potentially significant or would be useful to be included in labeling.

The findings from this study failed to show an overall relevant change in glucose metabolism between study groups over the double-blind study period. While there was a small increase in fasting insulin in the high dose risperidone group from baseline to the end of the double-blind study period, the entirety of the data suggest that risperidone does not result in a clinically meaningful adverse effect on glucose homeostasis in children and adolescents, at least over a 6-week time period. Limitations of the study include the short placebo-controlled study phase and the small sample size. Uncontrolled extension studies are difficult to interpret. Further, it remains possible that the study was underpowered to assess glucose metabolism.

The current risperidone label includes random glucose data from seven placebo-controlled, 3- to 8- week fixed- or flexible-dose studies in adult subjects with schizophrenia or bipolar mania (Table 1a) and change in fasting glucose from three placebo-controlled, 3- to 6-week, fixed dose studies in children and adolescents with schizophrenia, bipolar mania, or autistic disorder (Table 1b). These data suggest no clinically significant change in glucose metabolism with risperidone use at higher doses that those administered in the current study. The current study results are consistent with current labeling. Therefore, DMEP does not consider the data from the current study to be a useful addition to the label.

The current risperidone label does not include language about beta cell function. DMEP generally considers HOMA-IR and other estimations of insulin resistance that rely on calculated values to be surrogate markers of beta cell function, and we generally do not include this information in diabetes labels. Therefore, we do not recommend including HOMA-IR data in the risperidone label. In any case, in the current study, the HOMA-IR findings were unremarkable.

In summary, we conclude that the current study did not demonstrate a clinically meaningful negative effect on glucose homeostasis in children and adolescents. However, the study's short duration of assessment is a limitation and no conclusion can be made on the long-term effects of risperidone on glucose metabolism. The results from this study are similar to findings from previous studies already included in current labeling. Therefore, we do not recommend that these data related to glucose homeostasis be included in the risperidone label.

References:

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Conwell LS, Trost SG, Brown WJ, Batch JA. Indexes of insulin resistance and secretion in obese children and adolescents: a validation study. Diabetes Care. 2004 Feb;27(2):314-9.

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/s/

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