Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

NDA: 20-272/S-036
Drug: risperidone
Route: oral
Indication: irritability associated with (b) (4) children and adolescents
Materials reviewed: August 10, 2006 response to July 14, 2006 approvable letter; September 22 and September 28, 2006 responses to queries from Division
Sponsor: Johnson & Johnson
Reviewer: Alice T.D. Hughes, M.D.

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1 Background

The safety team was asked to review the data and proposed labeling pertaining to hyperprolactinemia in the sponsor's response[1] to the most recent approvable letter[2] for the use of risperidone for the treatment of irritability associated with autistic disorder. Changes to the labeling to more adequately address the available data pertaining to risperidone and hyperprolactinemia had been discussed with the sponsor during a teleconference on July 26, 2006.

The submitted data and proposed labeling are described in detail in the primary safety review by Dr. Lourdes Villalba dated September 28, 2006. (b) (4)

In this memorandum, I will address selected issues that require additional discussion and make labeling recommendations for the *Precautions; Hyperprolactinemia* and *Pediatric Use; Hyperprolactinemia, Growth, and Sexual Maturation* sections.

2 Hyperprolactinemia

All dopamine antagonists are associated with elevations in prolactin levels; this is due to the inhibitory effect of pituitary D_2 receptors on prolactin secretion. Risperidone has been shown in controlled studies to increase prolactin levels to a greater extent than the other atypical antipsychotics.[3,4]

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[1] August 10, 2006
[2] July 14, 2006
[3] Lieberman JA, Stroup TS, McEvoy JP et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353(12):1209-1223.

The available data from the application under review support the association between risperidone and hyperprolactinemia and indicate that risperidone is associated with hyperprolactinemia in children and adolescents.

In the safety database for the application under review, 43.9% (36/82) of risperidone-treated patients in placebo-controlled trials in children and adolescents developed elevated prolactin levels compared to 2.1% (2/95) of placebo-treated patients.[5] These data were provided in a September 22, 2006 response to a query from the Division. In this response, the sponsor also provided the percentages of patients who were reported to have the adverse event of "hyperprolactinemia." These data are less helpful given that hyperprolactinemia is frequently asymptomatic and may not have been reported.

In one short-term placebo-controlled study in children and adolescents with autistic disorder (USA-150), mean changes from baseline in prolactin levels were 29.70 ng/mL among risperidone-treated patients and 0.79 ng/mL among placebo-treated patients. In (b) (4)

The sponsor provided data regarding the percentage of children and adolescents treated with risperidone in clinical trials who experienced adverse events potentially related to hyperprolactinemia. 0.8% (16/1885) of (male and female) patients experienced galactorrhea ("lactation nonpuerperal"), 2.3% (44/1885) of patients experienced gynecomastia, and 0.6% (12.1885) of all patients experienced amenorrhea. 2.7% (7/264) of girls older than 12 were reported to have amenorrhea.

The sponsor's proposed modifications to the *Precautions; Hyperprolactinemia* sections are generally adequate. This section conveys the key information that risperidone increases prolactin levels more than do other atypical antipsychotics, and also conveys information regarding the known and potential consequences of supraphysiologic prolactin levels.

I agree with Dr. Villalba's recommendations regarding modifications to this section, (b) (4)

I agree with Dr. Villalba that including data from placebo-controlled trials in children and adolescents regarding the percentages of risperidone- and placebo-treated patients (b) (4)

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[4] Stroup TS, Lieberman JA, McEvoy JP et al. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. Am J Psychiatry 2006; 163(4):611-622.

[5] These percentages reflect the percentage of patients levels for whom both baseline and on-treatment prolactin levels were available who developed prolactin levels above the upper limit of normal.

(b) (4)

I support adding data regarding the percentages of children and adolescents who experienced galactorrhea and gynecomastia in clinical trials to the *Pediatric Use; Hyperprolactinemia, Growth, and Sexual Maturation section* of prescribing information. These events are likely to be related to hyperprolactinemia. (b) (4)

Although the data from the child and adolescent safety database provide strong support for an association between risperidone and hyperprolactinemia in this population, they do not shed light on the long-term consequences of this association, a particularly important question for children and adolescents that warrants further study.

3 Growth Hormone

In the pediatric and adolescent safety database, 12 patients treated with risperidone were reported to have had an adverse event of "growth hormone excess." All of these patients were in open-label trials (the majority of patients who underwent growth hormone measurements were in open-label trials). It is not possible, however, to conclude that risperidone is associated with increases in growth hormone levels based on the available data due to its substantial limitations. Growth hormone levels were only measured in selected trials, and not consistently measured within those trials. Baseline growth hormone measurements are available for 815 of the 1923 risperidone-treated patients (and 139 placebo-treated patients). Only 317 risperidone-treated patients and 54 placebo-treated patients had on-therapy growth hormone measurements. Measurement collection methodologies were not standardized within or between trials, which make the data particularly difficult to interpret because growth hormone is secreted in a pulsatile fashion and levels normally fluctuate throughout the day. Growth hormone levels are expected to be highest during sleep. For this reason, random blood sampling for determination of growth hormone levels is not very informative.[6] (b) (4) measurement of insulin-like growth factor-1 (IGF-1) may be more stable and more informative. Moreover, the laboratory reference ranges used for growth hormone (which were presumably the basis for patients being considered to have "growth hormone excess") were not age-adjusted. Children and adolescents have higher growth hormone

[6] Strasburger CJ and Bidlingmaier M. How robust are laboratory measurements of growth hormone status? Horm Res 2005; 64 suppl 2: 1—5.

levels than adults. The growth hormone elevations reported for the 12 patients with "growth hormone excess" were modest and well below levels reported in children with gigantism.[7,8]

None of the patients reported to have "growth hormone excess" had adverse events that can be directly attributed to increased growth hormone levels.

Hyperprolactinemia was present in 10 of the patients reported to have growth hormone excess, a notable finding. A true association between these two events cannot, however, be established based on the available data. Further study is warranted to assess whether risperidone increases the risk for pituitary tumors, some of which may secrete both growth hormone and prolactin.

The data in the current application pertaining to risperidone and growth hormone do not provide sufficient evidence of an effect of risperidone on growth hormone levels for us to mandate further study of the effect of long-term risperidone treatment on growth hormone levels and on the growth and development of children and adolescents treated with risperidone.

In order to understand whether risperidone does affect growth hormone levels, we will ask the sponsor to add growth hormone and IGF-1 assessments to the 6-week, fixed-dose, parallel-group, placebo-controlled clinical study that they have agreed to perform as a phase 4 commitment in autistic children and adolescents to determine the effect of risperidone treatment on fasting glucose, fasting insulin, and insulin resistance. Careful attention will need to be paid to appropriately and consistently collecting these hormone measurements. I recommend that we obtain Endocrinology input when we review the study protocol submitted by the sponsor.

In addition, IGF-1 and growth hormone level assessments will be added to the non-clinical (rat and dog) studies that the sponsor has agreed to as phase 4 commitments. In the dog study, we will also ask the sponsor to assess long bone growth in dogs. Any abnormalities detected would provide evidence that further study on growth in humans may be warranted.

We should also recommend to the sponsor that they consider studying the effect of long-term risperidone treatment on the growth and development of children and adolescents.

4 Sexual Maturation

No cases of precocious puberty were reported during clinical trials of risperidone in children. (b) (4) , cases of precocious puberty have been

[7] Zimmerman D et al. Congenital gigantism due to growth hormone-releasing hormone excess and pituitary hyperplasia with adenomatous transformation. J Clin Endocrinol Metab 1993; 76(1): 216-22.
[8] Minagawa et al. Effects of octreotide infusion, surgery and estrogen on suppression of height increase and 20K growth hormone ratio in a girl with gigantism due to a growth hormone-secreting macroadenoma. Horm Res 2000; 53 (3):157-60.

reported in the post-marketing setting. In the two most recent pediatric safety updates (together covering the period March 1, 2005 through February 28, 2006), I identified four cases of precocious puberty (two eight year-old boys, one of whom had elevated prolactin levels, a 5 year-old girl, and a 9 year-old girl). (b) (4)

Information regarding all of these cases is limited. We do not have evidence that risperidone was the cause of delayed or precocious puberty in these children. Many other etiologies are possible. Hyperprolactinemia itself is not known to be associated with precocious puberty. I do not think that the data currently available provide support for an association between risperidone treatment and either precocious or delayed puberty. I recommend adding precocious puberty to the post-marketing section of the risperidone prescribing information.

5 Labeling Recommendations

Published research has consistently indicated that risperidone is associated with increased prolactin levels and that this effect is more prominent than the effect observed with other atypical antipsychotics. The data from this safety database indicate that risperidone is associated with elevated prolactin levels in children and adolescents as well as in adults. The data from the child and adolescent safety database do not provide convincing evidence that risperidone is associated with changes in growth hormone levels, although further study of this area is warranted and will be requested as a phase 4 commitment.

I recommend the following labeling for the *Precautions; Hyperprolactinemia* and *Pediatric Use; Hyperprolactinemia, Growth, and Sexual Maturation sections*. (b) (4)

Precautions

Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. An increase in pituitary gland,

mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats (see PRECAUTIONS – Carcinogenesis, Mutagenesis, Impairment of Fertility). Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Hyperprolactinemia, Growth, and Sexual Maturation

Risperidone has been shown to elevate prolactin levels in children and adolescents as well as in adults (see PRECAUTIONS—Hyperprolactinemia). In double-blind, placebo-controlled studies of up to 8 weeks duration in children and adolescents (aged 5 to 17 years) (b) (4)

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/s/

Alice T. Hughes
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MEDICAL OFFICER