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

DATE: June 7, 2004

FROM: Paul J. Andreason, M.D.
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Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation of Approvable Action for Risperdal in the Treatment of the Symptoms of Irritability in Children Autistic Disorder

TO: File, NDA 20-272 Supplements SE1-036
[Note: This memo should be filed with the December 19, 2003 original submission of this NDA and likewise filed with 20-588/SE1-024 and 21-444/SE1-008.]

1.0 BACKGROUND

Autistic Disorder (autism) is a syndrome of mental retardation that begins in early childhood and persists throughout life. Its prevalence is estimated at from 2-20 per 10,000 individuals. The causes of autism are unknown. There are no approved treatments for autism and many current off-label treatments focus on relief of the irritability that is part of the autistic syndrome. Many of the atypical antipsychotics are used off-label to treat the irritability-like symptoms of autism; however, this is the first drug to present an application for the use of an atypical antipsychotic drug for the treatment of the irritability-like symptoms of autism.

There is no evidence that risperidone treats the mental retardation or pervasive disruption of childhood development that are the core features of Autistic Disorder. The focus of this application was on whether or not Risperdal was safe and effective for the relief of the irritability-like symptoms that are associated with autism. It is usually not the habit of the Division to approve drugs based on what might appear to be pseudo-specific effects of a drug on a disorder that is poorly understood; however, since there were no treatments for autism, the drug class was regularly used off-label for these symptoms, and there was little controlled trial data to support treatment for any part of autism, the Division decided to accept applications for the treatment of the irritability-like symptoms associated with autism based on the same logic that the Division (b) (4) We therefore decided not to take this particular supplement to the Psychopharmacological Drugs Advisory Committee (PDAC) at this time.

2.0 CHEMISTRY

As risperidone tablets are already approved, there were no CMC issues requiring review for this NDA.

3.0 PHARMACOLOGY

The Pharmacology-Toxicology Team review pointed out that sponsor had not performed juvenile animal studies in risperidone. The sponsor acknowledged this is and proposed outlines for juvenile rodent and non-rodent studies. The sponsor suggests that they perform these animal studies as a phase 4 commitment. The Pharmacology Toxicology Team recommends that these studies be completed prior to approval.

4.0 BIOPHARMACEUTICS

John Duan, PhD was the primary OCPB reviewer. A single dose PK study in 6 pediatric patients with autistic disorder was provided. Dr. Duan judged that the PK in general seemed to be consistent with that in adults. However, the sponsor concluded that the relative bioavailability of the active moiety is 3-fold higher than that in adults and other pediatrics. He noted that the sponsor collected PK samples in the pivotal trial RIS-USA-150 and a population analysis was planned. Requests for submitting the PK data were sent to the sponsor. However, he states that these data were not submitted to the Agency. I concur with Dr Duan that the sponsor should submit the analysis of this population PK data for review prior to approval of the Clinical Pharmacology section of labeling.

5.0 CLINICAL DATA

The primary clinical reviewers were June Cai, MD and Greg Dubitsky, MD.

The sponsor submitted two trials in support of this application. These studies were designated USA-150 and CAN-23. Both of these studies were double blind, placebo controlled, multi-center, randomized controlled trials. Both studies used the Irritability symptom subscale of the Aberrant Behavior Checklist (IS-ABC) as the primary efficacy variable.

5.1 Efficacy Data

Study USA 150

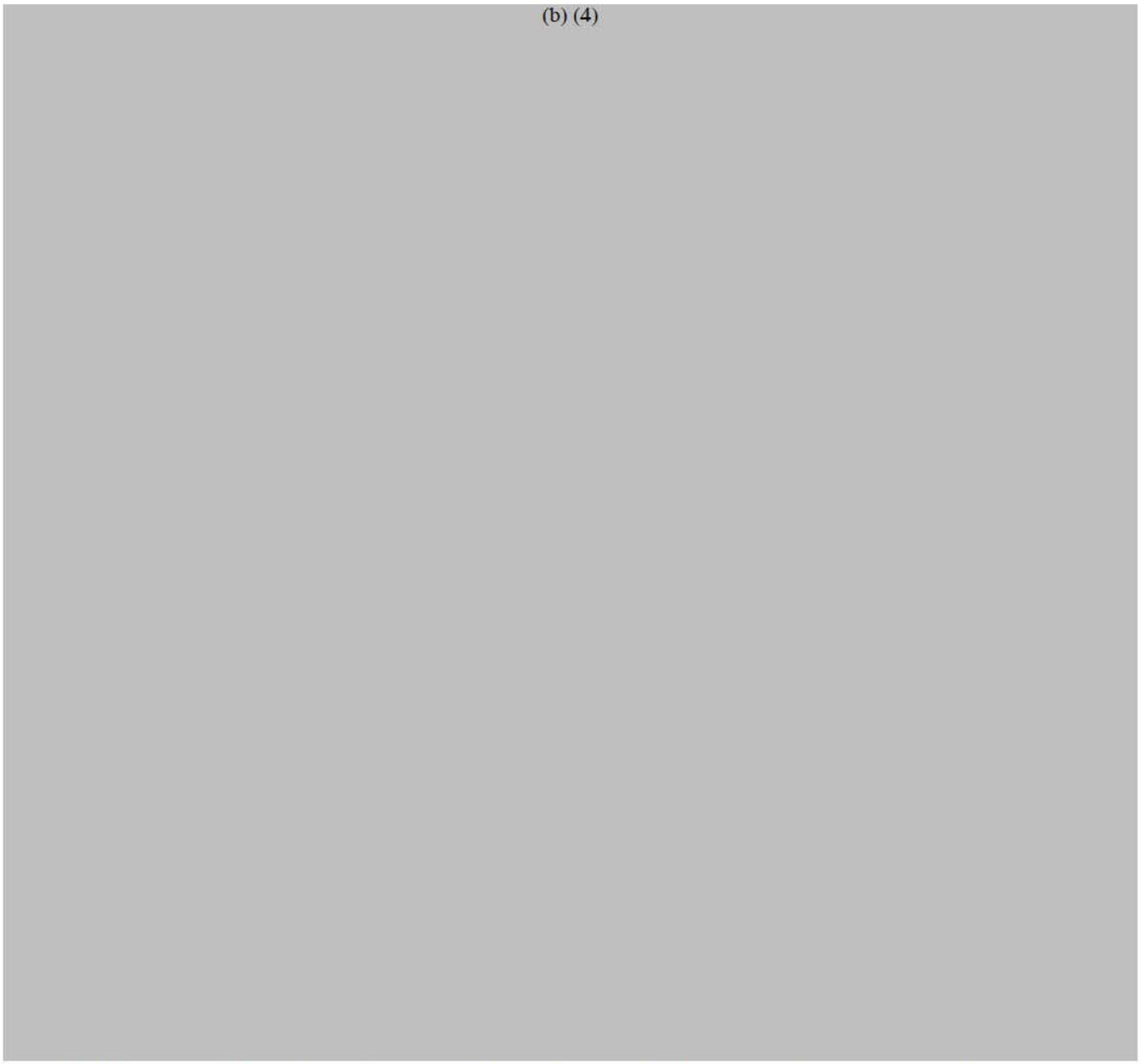
USA-150 had two controlled trial phases that can be considered as two separate clinical trials. Part I was a short term treatment phase and part III was a randomized withdrawal phase that was preceded by an open-label treatment phase of 4-months' duration.

USA-150-Part I was an 8-week, randomized, double-blind, parallel group, multi center trial. The study medication dosage was flexible, based on weight categories, ranging from 0.25mg to 2.5mg (for weight between 20kg and 45kg) or 0.5mg to 3.5 mg/day (for 45kg and over) of risperidone tablets versus placebo. This phase of the trial included 101 autistic children aging 5-16 years (Risperdal n=49; placebo n=52). The primary efficacy analysis was based on the change from baseline in the IS-ABC of the ITT population using LOCF to impute for missing data.

Results from part I of USA-150 showed that Risperdal was superior to placebo in reducing symptoms on the IS-ABC (treatment difference of -11.4 units in favor of Risperdal on a 45 point total possible scale, $p<0.001$). OC analysis produced similar results even with a third of the placebo patients

dropping out versus only 6% of the risperidone treated patients discontinuing from study. Based on these results, I believe that USA-150 part I represents a positive study in support of the claim that risperidone is effective in treating the irritability-like symptoms associated with Autistic Disorder.

(b) (4)



CAN-23 was an 8-week, randomized, double-blind, parallel group, multi-center trial. The study medication dosage was flexible (based on weight), ranging from 0.02 to 0.06 mg/kg/day of risperidone oral solution (concentration 1mg/ml) versus placebo. This study included patients with both Autistic and Pervasive Developmental Disorder (PDD). Enrollment included 79 total patients divided into the two treatment groups of placebo and risperidone (placebo n=39, risperidone n=40). The primary efficacy variable was the IS-ABC. The primary analysis was an ANCOVA using LOCF imputation of missing data in the ITT population.

Results from CAN-23 showed that risperidone was superior to placebo in the treatment of irritability-like symptoms associated with autism. The treatment effect difference between placebo and risperidone on the IS-ABC was -5.6 units ($p<0.001$). Sub-group analyses for autistic and PDD patients showed similar treatment effect sizes and both were statistically significant despite the small number of representative patients. I therefore believe that CAN-23 represents a second positive trial in support of the claim that risperidone is effective in the treatment of the irritability-like symptoms associated with autism.

Conclusions on Efficacy

The sponsor presents two positive 8-week trials that support a claim that risperidone is effective in the treatment of irritability -like symptoms associated with autism. (b) (4)

5.2 Safety Data

The safety review by Drs Cai and Dubitsky was based on data from 821 pediatric patients who received risperidone in completed Phase 2/3 studies: 83 of these patients were autistic and 738 had disruptive behavior disorders (DBD) or other PDD (Pervasive Developmental Disorders). A total of 331 patients were exposed for 13 months or longer and 565 were exposed for 7 months or longer. In all, 625 patients received modal doses of 1.0 mg/day or more and 217 received a modal dose of 2.0 mg/day or greater. Mean exposures to risperidone, on a mg/kg basis, were roughly two times higher in the non-autistic children, so conclusions drawn from the non-autistic group for autistic children will likely err on the side viewing adverse events occurring more frequently and severely than in reality might be expected.

Their safety review revealed no previously unrecognized, significant safety findings associated with risperidone therapy in pediatric patients that would preclude approval of this supplement or require a major revision to Risperdal labeling. There were no deaths or serious unlabeled/unexpected serious adverse events in the studies of autistic children. There was one case of "extrapyramidal disorder" that resulted from a 10-fold accidental overdose (2-mg instead of 0.2-mg in a 5-year-old) and was considered serious as he experienced an oculogyric crisis; however, acute dystonia is a recognized and labeled adverse event with risperidone. There was no evidence of drug related treatment emergent suicidality or aggression.

I concur with the primary reviewers that conclusions regarding growth and sexual maturation during 3 years of open-label treatment are difficult to reliably verify based on the data provided in this submission. Tanner Stage progression has to be interpreted in terms of expected progression, which varies with age and gender. I agree that height and weight increases must be interpreted within the context of percentile rankings based on age and gender (i.e., z-scores). The sponsor may not be aware of our current approach to doing this using historical growth data. The Drs Cai and Dubitsky suggested that the sponsor analyze height data by computing the changes from baseline to endpoint in z-scores for all patients who received risperidone for a certain continuous period of time (e.g.,3 months). I concur.

(b) (4)

They note that there appeared to be no glucose analytes drawn or reported in the studies of autism. I concur with their recommendation that the sponsor make a phase 4 commitment to study glucose metabolism in this population given the new warnings in the adult population.

6.0 World Literature

A world literature review and mid-cycle literature update were provided. This produced over 600 references. These references were reviewed by both the sponsor and Drs. Cai and Dubitsky who felt that they did not reveal any previously unreported serious adverse events likely to be causally associated with risperidone.

7.0 Foreign Regulatory Action

To my knowledge, risperidone is not approved for the treatment of children with autism anywhere at this time.

8.0 Psychopharmacological Drugs Advisory Committee (PDAC) Meeting

As noted above we did not take this supplement to PDAC.

9.0 DSI Inspections

The following sites were inspected by the Division of Scientific Investigations (DSI):

- RIS-USA-150: Dr. McDougle (Indiana) and Dr. Aman (Ohio).
- RIS-CAN-23: Drs. Fleisher (Winnipeg), Shea (Halifax) and Turgay (Scarborough).

The DSI inspection actions are not final at this time; however, DSI provided us with a preliminary clinical inspection summary. There were several record keeping inaccuracies that if they represent isolated occurrences appear to be minor.

At the McDougle site in Indiana, Dr Khin stated that they found that the study site has made several data entry errors while creating the data listing for patient 5090 from the CRF. Dr Khin stated that there were approximately 20 errors for subject's 5090 baseline ABC score. She suggests the review division check the SAS data sets in comparison with correct ABC score for subject 5090. Her report was not completely clear about her concerns over other patients' data but in an e-mail she explained that she was only concerned about the effect that patient 5090 might have on the study outcome and that the remainder of her audit was acceptable.

The cause of this error with patient 5090 remains unknown. A re-analysis of the data from USA-150 excluding patient 5090 is not necessary as excluding this particular patient could not possibly change the overall outcome of this study. Other inaccuracies in reporting adverse events by some of the audited investigators do not effect the overall action for this supplement.

10.0 Labeling and Approvable Action

10.1 Labeling for Approvable action Letter

Draft labeling for approvable claims along with imbedded recommendations to the sponsor for draft labeling modifications are attached to this action letter.

10.2 Foreign Labeling

To my knowledge, risperidone is not approved for the treatment of children with autism anywhere at this time.

11.0 Conclusions and Recommendations

I recommend that the Division take an approvable action for this supplement. I recommend that the following items must be addressed to reach final approval:

- Perform a re-analysis of part III of study USA-150 using a Kaplan-Meier survival analysis and the definition of relapse based only on the 25% worsening of ABC Irritability subscale change
- Height and weight increases must be interpreted within the context of percentile rankings based on age and gender (i.e., z-scores). This analysis of height and weight data is accomplished by computing the changes from baseline to endpoint in z-scores for all patients who received risperidone for a certain continuous period of time
- Four investigators from study USA-150 are listed as not having provided complete financial disclosure information and yet are certified as having no financial interests or arrangements to disclose ((b) (6) .). These discrepancies should be explained.
- The sponsor should provide a reanalysis of the effect of demographic variables on adverse event reporting rates, specifically a computation of the drug:placebo odds of each common, drug-related adverse event within each subgroup followed by a Breslow-Day Chi-Square test for the homogeneity of the odds between the subgroups.
- An analysis of quantitative ECG data from study CAN-23 should be submitted for our review.
- It was noted that the sponsor collected PK samples in the pivotal trial RIS-USA-150 and a population pharmacokinetic analysis was planned. Requests for submitting the PK data were sent however we can not find that these data were not submitted to the Agency. The sponsor should submit the analysis of this population PK data for review prior to approval of the Clinical Pharmacology section of labeling.
- The Pharmacology-Toxicology Team review points out that the sponsor had not performed juvenile animal studies in risperidone. The sponsor acknowledged this is and proposed outlines for a rodent and non-rodent study. The sponsor suggests that they perform these animal studies as a phase 4 commitment. The Pharmacology Toxicology Team recommends that these studies be completed prior to approval.
- Commit to performing a phase 4 study of glucose metabolism in children that includes substantial numbers of patients with Autistic Disorder
- Commit to performing a closely monitored phase 4 study of cognitive function in patients with Autistic Disorder who are treated with risperidone.
- Reach agreement on draft labeling with the Division.

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/s/

Paul Andreason
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MEDICAL OFFICER