

VARIATION ASSESSMENT REPORT

This report summarises the risk-benefit assessment made on the proposed new indication of the treatment of autism in children and adolescents.

Product: Risperdal - 0.25mg Tablets 0.5mg Tablets 1mg Tablets 2mg Tablets 3mg Tablets 4mg Tablets 1mg Liquid 0.5mg Quicklet 1mg Quicklet 2mg Quicklet	
MA numbers: PL 0242/0186-0189, 0199, 0346-0347, 0378-0380 MAH: Janssen-Cilag Ltd	Committee on Safety of Medicine (CSM) 24 February 2005 29 September 2005
Active constituent: Risperidone	Paediatric Medicines Working Group 8 February 2005
Therapeutic classification: Antipsychotic	Legal status: POM

Index	Page
Executive Summary	3
Introduction	5
Proposed Change	5
Background	6
Pharmacology	7
Pharmacokinetic Data	7
Evaluation of efficacy	11
Safety	27
Conclusion	41
Paediatric Working Group Advice	39
Recommendations	39

EXECUTIVE SUMMARY

This assessment report deals with a Type II Extended Complex variation proposing to add the indication of: 'Treatment of autism in children and adolescents'. In order to support this the company submitted the following data:

- i. pK data from 6 studies in children.
- ii. 2 efficacy trials for short-term treatment (8-weeks), one of which has 2 additional parts studying longer-term treatment (a further 4 months) and a withdrawal study
- iii. Safety data from the 2 pivotal trials plus data from an additional 7 studies in children. Post-marketing data from the company's safety database and a literature review were submitted.

pK Results

The blood levels of the active moiety of risperidone (active moiety = risperidone + 9-hydroxyrisperidone – the active metabolite) are very variable even when normalised for dose and taking into account CYP2D6 metabolic status. Dosing recommendations are based on weight with a low starting dose and an incremental dosing regimen which was used in the pivotal trials, combined with clinical monitoring.

Efficacy Results

Both pivotal trials showed an improvement in their primary end-points. The US Trial conducted in a pure population of autistic children, demonstrated efficacy in its 2 co-primary end-points; the Aberrant Behaviour Checklist – Irritability (ABC-I) and Clinical Global Impression - Change (CGI-C). RIS-CAN-23 was conducted in a mixed population of children but showed efficacy in that population and its autistic subgroup. The efficacy was less than that seen in The US Trial and may have been due to less severely affected children being recruited. Overall there were only 6 children aged over 12 years that were studied.

Safety

Two thirds of the children experienced somnolence at some stage and a small proportion (8%) continued to be drowsy. The somnolence did not appear to be related to dose or blood levels.

There are unresolved safety concerns in this population about long-term therapy causing extrapyramidal symptoms, weight gain and raised prolactin levels. The latter may affect growth and sexual maturation. Expert advice on this was sought from a Paediatric Endocrinologist.

Conclusion from CSM Meeting February 2005

Symptomatic treatment with risperidone appears to effectively reduce 'irritability' as measured by the Aberrant Behaviour Checklist in severely affected autistic children. This appears to be a clinically significant effect as demonstrated by the improvement in CGI-C scores. The children's views on taking the medication were not elicited but from the reports from their carers clearly demonstrate that the latter observed an improvement in the children. There are safety concerns with therapy. Somnolence occurs frequently but often resolves spontaneously and is reversible with stopping treatment. The potential long-term adverse events have not been adequately addressed.

In view of the unresolved safety concerns CSM advised that:

- i) The indication should be restricted to 'The short-term treatment of severe aggression and violence whether directed towards self or others in autistic children.' In addition it should be prescribed and supervised by a specialist and where possible non-pharmacological treatments to improve behaviour should have been tried first.

- ii) The views of children and carers should be sought on their experiences with antipsychotic therapy.
- iii) In addition a carer's organisation should be consulted over the restricted indication.
- iv) Centres of excellence in the treatment of autistic children should be consulted as to their methods on the management of violence and aggression in autistic children.
- v) The company should be asked to propose a risk management plan if the restricted indication is granted.

Consultation Results and Company's Risk Management Proposals

- i) Most of the carers expressed positive experiences with risperidone therapy. In all cases it had been used in response to severe behavioural problems. The National Autistic Society (NAS) was consulted and expressed similar concerns to those already identified in the regulators' assessment. The NAS supported the recommendations of CSM in their conditional approval.
- ii) Two experts in the treatment of autism sent their opinions, which were positive for a strictly limited indication as previously proposed. An additional concern of severe constipation was noted and a specific warning for the SPC proposed.
- iii) The Company's risk management plan was assessed as of limited benefit and not sufficient to address all the outstanding issues.

Conditional Approval

In considering the symptomatic improvement demonstrated in the clinical trials and the experience of children and their carers a conditional approval for risperidone was advised:

Risperidone is indicated for the short-term treatment of severe aggression and violence whether directed towards self or others in autistic children where available non-pharmacological methods have first been tried and failed.

Provided:

- i) The SPC and PIL were amended to include monitoring and safety information.
- ii) Risperidone should be monitored under black triangle status for this new indication.
- iii) The MAH submit a full risk management plan with defined milestones for data submission.

The approval would be conditional on all 3 elements being met.

Risk Management Plan and Registry

The Agency met with the company to give advice on the development of a robust risk management plan, which would include a registry of children on risperidone so that the effects of longer term risperidone therapy could be adequately monitored.

Company Withdrawal

The company withdrew their application in a letter dated 8th June 2006 stating that they were unable to agree with the wording advised by CSM for the licence (Summary of Product Characteristics) , which according to the Company is not in line with data submitted in support of this application, or specific registry proposals. However, the company had been seeking a wider indication which CSM had assessed as being inappropriate in view of the safety concerns with the use of this product in children and adolescents.

Publication of the Variation Assessment Report

The Agency has published the variation assessment report in order to provide the information on dosing, monitoring and safety based on independent expert advice. This information would otherwise not be available to health professionals, patients and carers as the

application was withdrawn. Publication is in line with the UK strategy on paediatric medicines and the forthcoming European legislation both aim to facilitate the availability of appropriately labelled medicines for paediatric use, supported by relevant information.

1. INTRODUCTION

This is a Type II Extended Complex variation proposing to add the indication of: ‘Treatment of autism in children and adolescents’.

The trial data consist of:

- i. pK data from 6 studies in children.
- ii. 2 efficacy trials for short-term treatment (8-weeks), one of which has 2 additional parts studying longer-term treatment (a further 4 months) and a withdrawal study. Due to company agreements the US study could not be named by protocol number and is henceforth referred to as the US trial.
- iii. Safety data from the 2 pivotal trials plus data from an additional 7 studies in children. Post-marketing data from the company’s safety database and a literature review were submitted.

The pK data and safety data are derived from trials in autistic children and adolescents but also include studies in children with other psychiatric diagnoses.

This is the first application for the treatment of autism and no regulatory guidelines are available on this indication. The above data along with the views from the experts in pharmacokinetics, paediatric endocrinology and the CSM Paediatric Working Group with a co-opted paediatric psychiatrist were considered by the CSM at a meeting on 24th February 2005. The efficacy of risperidone in decreasing irritability as measured by the Aberrant Behaviour Checklist was noted by the Committee but there were concerns about the safety of use outside a clinical trial. These concerns prompted the CSM to advise a wider consultation involving the National Autistic Society, carers of autistic children, Centres of Excellence in the treatment of autism and that the company should submit a risk/management plan to endeavour to clarify best practice and to establish appropriate safeguards for use.

2. PROPOSED CHANGE

The following proposed changes were made by the MAH after receiving comments from the MHRA in a request for supplementary information (RSI) letter. They address CSM comments on dosing.

Section 4.1. Therapeutic Indications

Risperdal is indicated for the treatment of autism in children and adolescents.

4.2.c Autism (children aged 5 or over and adolescents)

The dosage of RISPERDAL should be individualised according to the response of the patient.

Dosing should be initiated at 0.25mg per day for patients <20kg and 0.5mg per day for patients ≥20kg.

On Day 4, the dose may be increased by 0.25mg for patients <20kg and 0.5mg for patients ≥20kg.

This dose should be maintained and response should be assessed at approximately Day 14. Only in patients not achieving sufficient clinical response should additional dose increases be considered. Dose increases may proceed at 2-week intervals in increments of 0.25mg for patients <20kg or 0.5mg for patients ≥20kg.

In clinical studies, the maximum dose studied did not exceed a total daily dose of 1.5mg in patients <20kg, 2.5mg in patients ≥20kg, or 3.5mg in patients >45kg.

***Doses of RISPERDAL® in Paediatric Patients with Autistic Disorder
(by total mg/day)***

<i>Weight Categories</i>	<i>Days 1-3</i>	<i>Days 4-14+</i>	<i>Increments if Dose Increases are Needed</i>	<i>Dose Range</i>
<i><20kg</i>	<i>0.25mg</i>	<i>0.5mg</i>	<i>+0.25mg at ≥2 week intervals</i>	<i>0.5mg-1.5mg</i>
<i>≥20kg</i>	<i>0.5mg</i>	<i>1.0mg</i>	<i>+0.5mg at ≥2 week intervals</i>	<i>1.0mg-2.5mg*</i>

**Subjects weighing >45kg may require higher doses: maximum dose studied was 3.5mg/day*

For prescribers preferring to dose on a mg/kg/day basis the following guidance is provided.

***Doses of RISPERDAL® in Paediatric Patients with Autistic Disorder
(by mg/kg/day)***

<i>Weight Categories</i>	<i>Days 1-3</i>	<i>Days 4-14+</i>	<i>Increments if Dose Increases are Needed</i>	<i>Dose Range</i>
<i>All</i>	<i>0.01mg/kg/day</i>	<i>0.02mg/kg/day</i>	<i>+0.01mg/kg/day at ≥2 week intervals</i>	<i>0.2mg/kg/day- 0.06 mg/kg/day</i>

Risperdal can be administered once daily or twice daily.

Patients experiencing somnolence may benefit from a switch in dosing from once daily to either once daily at bedtime or twice daily.

Once sufficient clinical response has been achieved and maintained, consideration may be given to gradually lowering the dose to achieve the optimal balance of efficacy and safety. There is insufficient evidence from controlled trials to indicate how long the patient with Autistic disorder should be treated with Risperdal.

3. BACKGROUND ON AUTISM

According to the Diagnostic And Statistical Manual Of Mental Disorders 4th Edition, DSM IV the essential features of autistic disorder are the presence of markedly abnormal or impaired development in social interaction and communication and a remarkably restricted repertoire of activity and interests. Manifestations of the disorder vary greatly according to the developmental level and chronological age of the person. The 3 core areas of impairment that constitute Autistic Disorder according to DSM-IV criteria are qualitative impairments in social interaction (category A-1), qualitative impairments in verbal and nonverbal communication (category A-2), and restricted, repetitive, and stereotyped patterns of behaviour, interest, and activities (category A-3). A DSM-IV diagnosis of Autistic Disorder requires that all 3 core impairments be present in varying degrees.

Autistic Disorder affects children from all races and social backgrounds. Boys are affected 3-4x more commonly than girls. Symptoms may be noticed in the first year of life but diagnosis is usually not confirmed until early childhood.

There is some evidence that autistic children have a higher level of serotonin (blood 5-HT) levels than controls. This may be secondary to blunted neuroendocrine responses to 5-HT. There is some evidence, mainly from uncontrolled studies that Serotonin Reuptake Inhibitors are helpful in reducing aggression and repetitive behaviour. There is also evidence of dopamine dysregulation. There have been some published studies showing a decrease in aggressive behaviour with haloperidol and pimozide therapy.

4. PHARMACOLOGY

Risperidone is an atypical antipsychotic and is a benzisoxazole derivative. It antagonises 5-HT₂ and dopaminergic D₂ receptors. It also binds to alpha₁-adrenergic receptors and with lower affinity, to H₁-histaminergic and alpha₂-adrenergic receptors. It has no affinity for cholinergic receptors. Although risperidone is a potent D₂ antagonist, an activity which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extrapyramidal side effects (EPS) and extend the therapeutic activity to the negative and affective symptoms of schizophrenia. However, EPS-related adverse events are still clearly recognised with risperidone.

5. PHARMACOKINETIC DATA

5.1 Pharmacokinetic Background Information From Adult Data

Risperidone is primarily metabolised into 9-hydroxy-risperidone via CYP2D6. The metabolite has a similar receptor binding profile to risperidone and therefore the active moiety (the sum of risperidone and 9-hydroxy-risperidone) is relevant for the generation of the therapeutic effect. Hydroxylation is subject to debrisoquine-type genetic polymorphism but this does not affect antipsychotic fraction since this is a combination of risperidone and 9-hydroxy-risperidone. Although risperidone is primarily metabolised by CYP2D6, the active metabolite 9-hydroxy-risperidone is chiral. One enantiomer is further metabolised by CYP2D6 but the other largely through CYP3A4 to inactive species.

Based on adult data risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. The absorption is not affected by food.

Absolute oral bioavailability is 70%. For the active antipsychotic fraction, $t_{1/2}$ is 24 hours. From single dose studies higher active plasma concentrations and slow elimination were seen in the elderly, patients with renal insufficiency but not hepatic insufficiency. Risperidone and its metabolites are mainly renally excreted (70%). In the urine risperidone and 9-hydroxy-risperidone represent 35-45% of the dose and the remainder are inactive metabolites.

Fluoxetine and paroxetine, both CYP2D6 inhibitors, increase the plasma concentrations of the active moiety by 40-45%. Cimetidine and ranitidine increase the plasma concentrations of active moiety but probably not to a clinically relevant degree. Carbamazepine a known CYP450 inducer lowers levels of the active moiety by about 50%.

Risperidone has a volume of distribution of 1-2L/kg. Risperidone (90%) and 9-hydroxy-risperidone (77%) are bound to albumin and α -acid glycoprotein.

5.2 Analysis of Paediatric pK studies

5.2.1 pK studies in Autistic Disorder

There were 3 studies where pK data were measured in autistic children but only the first study provides sufficient data for review, since the data from the second study was very limited and the MAH did not have the data available from the third study.

RIS-BEL-21 This was a single dose open label study in 6 children (4-8 years) who had a diagnosis of Autistic Disorder by DSM III R. They were being admitted for brain imaging and received a single dose of risperidone. The first 3 children received 0.03mg/kg and showed excessive drowsiness and so the subsequent 3 children received 0.015 mg/kg. Risperidone, 9-hydroxyrisperidone and the active moiety were measured. There was a wide variation in results even when only the active moiety is considered. For the 3 children receiving 0.03 mg/kg Child 3 showed double the C_{max} and $AUC_{0-\infty}$ for the active moiety compared to Child 1. Similarly for the 0.015mg/kg/day dose Child 4 demonstrated an almost double C_{max} and $AUC_{0-\infty}$ of the active moiety compared to Children 5 and 6. In addition Child 2 demonstrated a greater $AUC_{0-\infty}$ compared to Child 1 due to a greatly prolonged $t_{1/2}$. The variations seen could not be adequately explained on this limited data.

RIS-BEL-22 Pilot study in 7 children, sparse data. This was an open-label, dose escalation pilot study in 7 children with Autistic Disorder. The mean daily dose increased from 0.019 mg/kg/day to 0.035 mg/kg/day on day 28. Trough levels approximately 16 hours post-dose were available on only 4 children. Plasma concentrations for the active moiety (2.32 – 4.57 ng/ml) were found to be lower than in other studies with b.d. dosing when normalised to a 0.04 mg/kg/day dose. The long sampling time after the last dose may be the explanation, in other studies this was only 12 hours, which is more consistent with b.d. dosing.

US Trial Part 1 The MAH state that the pK data from the US Trial Part 1 were not available, although blood levels of risperidone and 9-hydroxy-risperidone were taken on day one and week 8. The US Trial was conducted by another company and the MAH appear to have access to some but not all of the data.

5.2.2 pK studies in other psychiatric disorders

The main source of information on the pharmacokinetics of risperidone in children and adolescents comes from the first study with twice daily dosing.

RIS-USA-160 This is a phase 1 study in children (6-11 years) and adolescents (12-16 years) on risperidone maintenance therapy required for Pervasive Development Disorders, Attention Deficit or other Disruptive Behavioural Disorders or schizophrenia or other psychotic disorders. The subjects were stabilised on a twice-daily dose of risperidone between 0.01-0.08 mg/kg/day. The pK data were collected on day 7.

In this study most of the children and adolescents were genotyped for metaboliser status. There were 3 poor metabolisers, 19 extensive metabolisers and 2 untyped. However, 3 of the extensive metabolisers behaved as poor metabolisers. In 2 of these cases, the reason was thought to be due to drug interactions. One subject was taking perphenazine and another had taken fluoxetine up to the study start date (the latter has a long half-life 2-3 days for fluoxetine and 6-9 days for nor-fluoxetine).

Plasma protein binding of risperidone and 9-hydroxy-risperidone was slightly higher for children (88% and 85% respectively) than adolescents (75% and 71% respectively) and may be due to the higher α -acid glycoprotein levels in children. The plasma protein binding of risperidone and 9-hydroxy-risperidone in adults are in the order of 90% and 77% respectively.

RIS-CAN-19 and RIS-USA-93 were phase III studies in 110 and 118 children (5-12 yrs) respectively with borderline intellectual functioning or mild to moderate mental retardation and Conduct or other DBD in a 6-week double-blind study. They were both single dose studies and trough levels of risperidone, 9-hydroxyrisperidone and the active moiety were measured at week 6 in 35 and 21 of the children respectively. The timing of the measurements post-dose were variable especially for the first study (15-41 hours). The results were very variable but the information was used in the population pK analysis.

RIS-CAN-20 and RIS-INT-41 were follow-up studies to RIS-CAN-19. There were trough and peak levels of risperidone, 9-hydroxyrisperidone and the active moiety measured again with a wide range of post dose times (8-30 hours trough and 0-8 hours peak). The data were used in the population pK analysis.

RIS-USA-97 was a follow-up study for RIS-USA-93 but the timing of the specimens in relation to dose were not known and so the data were uninterpretable.

5.2.3 Population pK analysis

This was independently reviewed by a CSM expert.

Assessor's comments

Although there have been 3 studies in which pK parameters have been measured in autistic children, the only data available is from a single dose study in 6 children. The main source of pK data in children and adolescents is from RIS-USA-160, which was conducted in children and adolescents with other psychiatric diagnoses. In this study the subjects were genotyped and had their pK measurements taken at steady state. (According to the pharmacology summary extensive metabolisers are in a steady state at 1 day and poor metabolisers at 5 days. Both phenotypes should be at steady state at day 7 when the pK data were collected.)

Results were presented as measured for children and adolescents and then normalised for a 0.04mg/kg/day dose. Even when this attempt was made to take out the variation due to dose, a wide variation in risperidone, 9-hydroxy-risperidone and the active moiety measurements was seen.

Risperidone is stated to be completely absorbed after oral administration yet some subjects appear to have very poor absorption according to the levels of risperidone and 9-hydroxy-risperidone measured in RIS-USA-160 (or there was failure in compliance). Diarrhoea occurs more commonly in Autistic Disorder but the Expert does not think that this should affect absorption since risperidone is absorbed throughout the GI tract.

In conclusion there appears to be wide variation in the active moiety levels, which is unpredictable and is not explained by metaboliser status since the active moiety is a combination of parent and active metabolite. Apparently a similarly wide variation was seen in the adult data according to the MAH.

In their original submission the MAH proposed a flexible dosing regime based on body weight. Although there are problems noted with this approach it appears to be a reasonable compromise considering the complexities of the pharmacokinetics of risperidone. In addition this method based on weight is the one used in the clinical trials in autism although there appear to be some important variations in the regimen proposed compared to those used in the studies, which have not been adequately explained by the MAH.

In the US study the dosing was based on 3 weight bands 15-20kg, 20-45kg and >45kg (see section 6.8). No dose increment was greater than 0.5mg and a dose reduction of 0.25mg was permitted if AE were experienced. In trial RIS-CAN-23 a more rapid dosing regime was proposed on the basis of mg/kg/day. Slightly more somnolence was observed in the latter trial 72.5% versus 63% in the US study. It is not clear if the more rapid dose increases were responsible for this. The maximum dose proposed of 0.06 mg/kg/day is consistent with the mean dose (0.061 SD 0.0254) and the median dose (0.06 mg/kg/day) received in the US study.

The originally proposed dosing table was not consistent. The first line of the table recommends the maximum dose of risperidone based on mg/kg/day and the second line states the recommended maximum dose for various weights. It would appear if the total dose recommendations were followed for a particular weight band that children would receive higher doses than recommended than if calculated by the mg/kg/day method. For example, for a child weighing <20kg the starting dose should not exceed 0.25mg/day, which is not consistent with the 0.01 mg/kg/day recommendation which suggests a maximum dose of 0.2mg/day even for the heaviest child in this category.

The MAH amended the proposed dosing schedule and simplified it to 2 weight bands but they still did not address the following:

- | |
|--|
| <ul style="list-style-type: none">i) The lowest weight should be added to the <20kg statements (15kg).ii) A statement on dose reduction if adverse events are noted. |
|--|

6. EVALUATION OF EFFICACY

6.1 Data submitted

6.1.1 Short-term

There are 2 Phase III clinical studies which are both 8-week, randomised, double-blind, placebo-controlled trials:

- i) US Trial Part 1
- ii) RIS-CAN-23

The US Trial was sponsored by the National Institute of Mental Health (NIMH) and conducted by a consortium of academic investigators (Research Units on Pediatric Psychopharmacology, RUPP). RIS-CAN-23 was sponsored by J&JPRD.

6.1.2 Longer-term

The US Trial Part 2 was an open-label continuation study for a further 4 months. This included the risperidone responders (RIS-RIS) from Part 1 plus the placebo non-responders (PLA-RIS).

6.1.3 Withdrawal Study

The US Trial Part 3 was a double-blind, placebo-controlled, parallel group discontinuation study. Children from Part 2 who maintained an improved status during the open-label continuation were randomised to continued risperidone therapy or withdrawal of therapy. The objective was to study relapse prevention in a withdrawal design.

6.2 Scales used in the clinical studies

6.2.1 Diagnostic scales

The Autism Diagnostic Interview - Revised

A comprehensive structured parent interview probes for autistic symptoms (17-items) in the spheres of social relatedness, communication and ritualistic or preservative behaviours.

Childhood Autism Rating Scale

A 15-item structured interview and observation instrument, suitable for use >24 months. Each item has a 7-point scale to indicate how the child's behaviour deviates from the norm. It is designed to distinguish mild-moderate from severe autism.

6.2.2 Assessment scales

The Aberrant Behaviour Checklist (ABC)

The ABC is comprised of 5 subscales:

- i) **Lethargy/Social Withdrawal** (16 items, range: 0-48 points) relates to aspects of DSM-IV core symptom categories A-1 and A-2 for Autistic Disorder, and assesses features such as limited or poor communication, inactivity, and cold or unresponsive demeanor.
- ii) **Stereotypic Behaviour** (7 items, range: 0-21 points) assesses aspects of DSM-IV core symptom category A-3, primarily item A-3-c, “stereotyped and repetitive motor manifestations”.
- iii) **Inappropriate Speech** (4 items, range: 0-12 points) relates well to DSM-IV core symptom category A-2-c, “stereotyped and repetitive use of language”.
- iv) **Irritability** (15-items, range: 0-45 points) measures an array of disruptive symptoms that are listed as associated features and disorders for Autistic Disorder in DSM-IV, such as aggression, self-injurious behaviours, and tantrums.
- v) **Hyperactivity/Noncompliance** (16 items, range: 0-48 points) also assesses the behaviours that are associated features and disorders for Autistic Disorder in DSM-IV, including motor overactivity and high distractibility.

It was designed to assess the effect of medication in patients with developmental disorders. It was based on the common symptoms experienced by 400 individuals with mental retardation and then further refined in 500 further individuals. Interrater reliability is not high at a mean of 0.63.

It is stated in the MAH’s Clinical Expert Report that:

- i) 51 of 58 (87.9%) of the individual items of the ABC are relevant to DSM-IV manifestations of Autistic Disorder
- ii) 23 items (39.6%) are directly relevant to DSM-IV core manifestations (12 map to category A-1, an additional 4 to category A-2, and 7 to category A-3)
- iii) 28 items (48.3%) are related to associated features of Autistic Disorder.

ABC has been shown to be able to differentiate between active and placebo treatments in a published study involving haloperidol and clomipramine in subjects with Autistic Disorder.

Clinical studies with conventional antipsychotics suggested that the benefit of these agents for an autistic population was mainly in reducing severe behavioral disturbances associated with the disorder, such as tantrums, aggression, and self-injurious behaviour. For this reason, the clinical studies in Autistic Disorder with risperidone prespecified the change from baseline to the 8-week end point in the Irritability subscale score of the ABC as the primary efficacy variable and changes from baseline to end point in the other 4 subscales as secondary efficacy variables.

The Clinical Global Impression (CGI)

The CGI is a global rating scale used to assess the subject's overall condition in a variety of psychiatric indications and includes 3 global scales:

- i) Severity of illness
- ii) Improvement or change
- iii) Efficacy index

The CGI-Change (CGI-C) assesses the magnitude of the overall improvement or change in the subject's condition during treatment compared to baseline using a 7-point scale ranging from "very much improved" to "very much worse". The percentage of CGI-C responders (subjects with a "very much improved" or "much improved" rating) at the 8-week end point was calculated in both Phase 3 studies and was prespecified as a co-primary efficacy variable in the US Trial Part 1 and as a secondary efficacy variable in RIS-CAN-23.

Additional Assessment Scales

In addition the Vineland Adaptive Behaviour Scales - Maladaptive domains (VABS) and Nisonger Childhood Behavioural Rating (N-CBRF) were also used.

Assessor's comments

The ABC was devised to assess treatment effects in patients with developmental disabilities. A list of problem behaviours was drawn up from 418 individuals with mental retardation in a care centre. The items that were listed for fewer than 10% of residents were dropped and the remaining refined and grouped into the 5 categories above. The RUPP investigators chose the ABC instrument since it had some validation and ease of use. It was not specifically designed for use in autism and not all the items are relevant to the diagnosis of autism. Only 37.9% of items were deemed directly relevant to autism but an additional 20.7% were relevant to ADHD and 25.9% were related to irritability. The remaining 15.5% items were not linked. Of the 5 categories in the ABC the Lethargy and Social Withdrawal, Stereotypic Behaviour and to some extent Inappropriate Speech do sample the manifestations of autism.

The investigators for both pivotal trials have chosen the irritability subscale of the ABC as their primary endpoint. Although not a diagnostic feature of autism, aggression or tantrums/negative mood were listed by carers as the most troublesome symptom in almost half the cases in the VAS assessment in RIS-CAN-23.

6.3 Clinical endpoints

Study	Duration (weeks)	Placebo (n)	Risperidone (n)	Primary endpoints	Secondary endpoints
US Trial, Part 1	8	52	49	ABC-I, CGI-C	ABC, CGI-S, VABS
RIS-CAN-23	8	39	40	ABC-I	CGI-C, CGI-S, N-CBRF, VAS
US Trial Part 2	4 (months)	0	63	ABC-I, CGI-C	CGI-S, VABS
US Trial, Part 3	8	20	19	% patients who relapsed	ABC-I, CGI-C, CGI-S, VABS

ABC-I	Aberrant Behaviour Checklist – Irritability subscale
CGI-C	Clinical Global Impression of Change
ABC	Aberrant Behaviour Checklist – other subscales
CGI-S	Clinical Global Impression of Severity
VABS	Vineland Adaptive Behaviour Scales (Maladaptive domains)
N-CBRF	Nisonger Childhood Behavioural Rating
VAS	Visual Analogue Scale of worst symptom

US Trial

Two other secondary endpoints were measured but the data have not been sent:

- i) Compulsion score of Childs Yale Brown Obsessive Compulsive Scale, CY-BOCS
- ii) Ritvo-Freeman Real Life Rating Scale total score

Assessor's comments

The US Trial has 2 co-primary endpoints; the Irritability subscale score of the ABC (ABC-I) and the Clinical Global Impression – Change (CGI). RIS-CAN-23 used only one primary endpoint; the Irritability subscale score of the ABC. The former approach is to be preferred since the first co-primary endpoint gives a numerical measure of the improvement on the ABC irritability subscale, whereas the CGI gives an impression of the clinical impact of this change.

6.4 Inclusion and exclusion criteria

A DSM-IV diagnosis of Autistic Disorder, established by clinical assessment and corroborated by standard cutoff scores on:

The Autism Diagnostic Interview (US Trial Part 1)

Childhood Autism Rating Scale (RIS-CAN-23)

Differences in criteria are tabulated below:

Criteria	US Trial Part 1	RIS-CAN-23
Age	5-17 years 2 months	5-12 years
Weight	Weight = 15kg	
Type	Inpatients or outpatients	Outpatients
Seizures	Seizure free = 6 months Anticonvulsant dosage must be stable for 4 weeks	Seizure free = 3 months Not > 1 anticonvulsant
Severity	CGI = 4 ABC Irritability Score = 18	
Hx of tardive dyskinesia		Exclusion
Mental age	Not < 18 months	
Pervasive Developmental Disorder	Not Asperger's Disorder, Rett's, Childhood Disintegrative Disorder	

In both trials patients have to be physically healthy, not pregnant/sexually active if of child-bearing potential, not have a history of neuroleptic malignant syndrome, not allergic to risperidone, not to have been included in a previous risperidone trial, schizophrenia/psychosis or alcohol/drug abuse.

Assessor's comments

The mental age criteria was an exclusion criterion in the US Trial Part 1 since Autistic Disorder is very difficult to diagnose accurately in the profoundly retarded. This raises the possibility of misdiagnoses occurring in subjects with very low IQs in RIS-CAN-23. RIS-CAN-23 did not have minimum severity inclusion criteria and this may be one of the reasons that the results of this trial were not as marked as those of the US Trial due to less severely affected cases being included. In addition some of the children in RIS-CAN-23 may have been in a less stable condition since the exclusion criteria permitted the recruitment of children who had been seizure free for only 3 months rather than 6 months seizure free period required for inclusion to the US Trial. This may partly explain the higher placebo response rate seen in RIS-CAN-23.

6.5 Population

US Trial Part 1

Autistic Disorder 101

RIS-CAN-23

Autistic Disorder 55

Other diagnosis 24

(Asperger's Disorder 12, Pervasive Development Disorders Not Otherwise Specified 11, Childhood Disintegrative Disorder 1).

6.6 Demographics

Most children's normal place of residence was with their parents (86-91%).

The majority of children had mild or moderate cognitive impairment.

	US Trial	RIS-CAN-23
Mean age (years)	8.3	7.3
Male	81%	77%
Median IQ	63	60
Caucasian	66%	62%
Black	10%	18%
On an anticonvulsant (n)	4 (2 risperidone)	1 (risperidone)

6.7 Severity

CGI-S Scores

Severity	US Trial (n=96)	RIS-CAN-23 (n=79)
Very mild	0	1
Mild	0	8
Moderate	17	30
Marked	52	18
Severe	26	21
Extremely Severe	1	1

Mean ABC values at baseline (approx.)

	Irritability	Social withdrawal	Stereotypic behaviour	Hyperactivity	Speech
USA-150	26	16	10	32	6
CAN-23	20	14	8	29	5
CAN-23 A	21	14	9	31	5

Assessor's comments

Comparison of the baseline severity as measured by CGI-S reveals that the US Trial included more severely affected children. Almost a half of the children in RIS-CAN-23 were only moderately affected or less, whereas less than a quarter were moderately affected in the US Trial and none were classified as very mild or mild. The baseline values on the ABC subgroups for the 2 trials also demonstrate that the children in RIS-CAN-23 are less severely affected, especially for the irritability subscale.

The MAH when asked to justify the lack of severity inclusion criteria for RIS-CAN-23 state that over 50% of the subjects for this study were in the severe autism category when measured by CARS. This does not alter the comparative data seen above.

The MAH were asked how many children in RIS-CAN-23 would not have reached the severity criteria for the US Trial. The response stated that there were 14/28 in the placebo Autistic subset and 15/27 in the risperidone subset. The MAH were then asked to produce a subgroup analysis comparing the milder group, who would not have met the entry criteria, to the severer group. The further analysis did not reveal a difference in treatment effect above that seen with placebo. However, this masks the fact that the improvement from baseline was much greater for those children with an irritability score of over 18 but due to a greater placebo response effect (approximately an 11 point improvement) the net improvement over placebo was no greater than in the milder group. This is in contrast to the results in the US Trial where a much smaller placebo response rate is seen (of the order of 3 points improvement). This suggests the population included in RIS-CAN-23 may have been less stable.

6.8 Dose

The dosing schedules were based on information from clinical pilot studies and expert opinion. It had been previously noted that there were more adverse events, including EPS, when higher initial doses were used with a faster dose escalation.

Study RIS-CAN-23

Time	Dose	Criteria
Starting dose	0.01 mg/kg/day	
Day 3	0.02 mg/kg/day	
Day 8	0.04 mg/kg/day (max.)	On therapeutic response
Day 15 onwards*	0.06 mg/kg/day (max.)	On therapeutic response

*Weekly increases or decreases of up to 0.02 mg/kg/day

Study US Trial (Part 1)

Time	Dose (20-45kg)	Dose (=45kg)	Average Dose
Starting dose (nocte)*	0.5mg/day	0.5mg/day	0.01mg/kg/day
Day 4	0.5mg b.d.	0.5mg b.d.	
0.5mg to a Max. Dose on Tx response	2.5mg/day (20-45kg)	3.5mg/day (=45kg)	0.05mg/kg/day

* 15-20kg started on 0.25mg/day

No further increases after day 29 were permitted but decreases to manage adverse events were allowed.

Doses were not increased if adverse events limited therapy or if the individual achieved at least a ‘much improved’ therapeutic response.

Compliance

Measured by tablet counting. In the US Trial Part 1 carers were warned if compliance fell to < 70% and were excluded from the study if this occurred a second time, although if there were extenuating circumstances they might be reprieved.

Discontinuations

	US Trial		RIS-CAN-23	
Trial	Risperidone	Placebo	Risperidone	Placebo
8-week trials	6.1% (3/46)	34.6% (18/34)	5% (2/38)	13% (5/34)
Part 2	27% (17/63)	N/A		
Part 3	47% (9/19)	75% (15/20)		

Parts 2/3

Reason	Part 2	Part 3	
	Risperidone	Risperidone	Placebo
Insufficient response	3	3	5
Relapse	1	3	7
Other	13	3	3
Total	17	9	15

Assessor’s comments

In both the US Trial Part 1 and RIS-CAN-23 1 subject in each group discontinued due to adverse events. The commonest reason for withdrawal was lack of response, this is particularly noticeable in the placebo group in the US Trial Part 1. The high withdrawal rate (17/63) in the US Trial Part 2 was largely due to withdrawal of consent or insufficient response (9 and 3 subjects respectively). The remaining subjects were withdrawn due to a variety of reasons including 1 loss to follow up, 1 adverse event, 1 non-compliance, 1 relapse, 1 ineligible to continue. The withdrawal rates did not differ in reason or frequency as to whether the subject was a risperidone responder or a placebo non-responder at trial entry. In Part 3 the commonest reason for withdrawal in the placebo group was relapse or lack of response as expected but there was a high withdrawal rate in the risperidone group as well.

6.9 Efficacy Results

The intention to treat (ITT) population was defined as all subjects who took at least one dose of medication. Efficacy was analysed using 4 analysis sets: the ITT populations from the US Trial Part 1 and RIS-CAN-23, the Autistic Disorder subset from RIS-CAN-23 (n=55), and combined Autistic Disorder subset from the US Trial Part 1 and RIS-CAN-23 (n=156).

6.9.1 Primary End Point

Primary Endpoint Results

ABC-I

Analysis of 5 ABC Subscales – Irritability = 1° Endpoint

	Lethargy/Social Withdrawal	Stereotypic Behaviour	Inappropriate Speech	Irritability	Hyperactivity/Noncompliance
US Trial Part 1					
N (RIS:Placebo)	101 (49:52)	101 (49:52)	101 (49:52)	101 (49:52)	101 (49:52)
Diff LS Means Change	-3.2	-2.5	-1.8	-10.6	-10.4
(95% CI)	(-5.6, -0.8)	(-3.9, -1.1)	(-2.7, -0.9)	(-13.8, -7.5)	(-13.8, -7.1)
p value	0.009	<0.001	<0.001	<0.001	<0.001
RIS-CAN-23					
N (RIS:Placebo)	77 (39:38)	76 (38:38)	77 (39:38)	75 (37:38)	75 (37:38)
Diff LS Means Change	-3.3	-1.9	-1.3	-6.3	-8.1
(95% CI)	(-5.8, -0.8)	(-3.6, -0.2)	(-2.3, -0.2)	(-9.4, -3.2)	(-12.0, -4.2)
p value	0.010	0.030	0.016	<0.001	<0.001
RIS-CAN-23 Autistic Disorder Subset					
N (RIS:Placebo)	54 (26:28)	53 (25:28)	54 (26:28)	52 (24:28)	52 (24:28)
Diff LS Means Change	-3.9	-2.2	-1.3	-5.8	-8.8
(95% CI)	(-7.1, -0.6)	(-4.4, 0.0)	(-2.6, 0.0)	(-9.5, -2.2)	(-13.8, -3.9)
p value	0.020	0.053	0.058	0.002	<0.001
Pooled Autistic Disorder Subset					
N (RIS:Placebo)	155 (75:80)	154 (74:80)	155 (75:80)	153 (73:80)	153 (74:79)
Diff LS Means Change	-3.4	-2.5	-1.6	-9.4	-10.4
(95% CI)	(-5.2, -1.5)	(-3.7, -1.3)	(-2.4, -0.9)	(-11.8, -6.9)	(-13.2, -7.6)
p value	<0.001	<0.001	<0.001	<0.001	<0.001

Diff LS Means Change = LS Means change in risperidone group minus LS Means change in placebo group based on ANCOVA model.

p value: Comparison with placebo based on ANCOVA model with treatment, investigator (or study for pooled) as factors, and baseline value as a covariate.

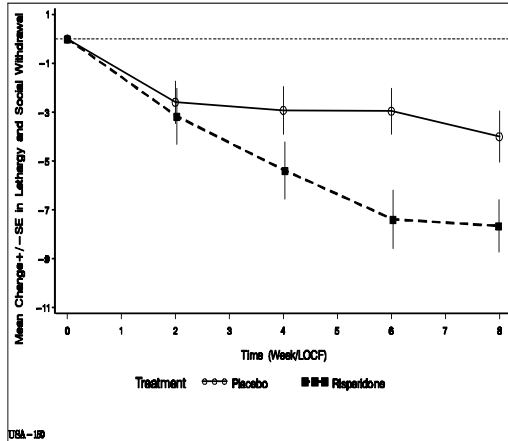
Statistical Comment

The clinical studies used to support this application have been fully described in the Medical Assessment Report. There is clear evidence of an effect on the primary end-points in both pivotal studies. The statistical methods used to analyse these studies are appropriate and there are no methodological flaws with the approach taken. The clinical relevance of the effects seen in the autistic subjects remains to be established.

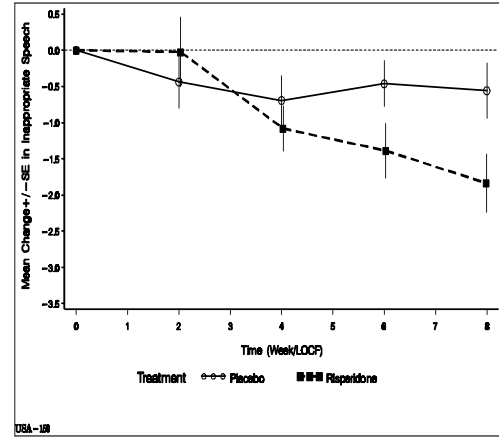
ABC Results over Time

Mean (\pm SE) of Change From Baseline in 5 Subscales of the ABC by Treatment Group Over Time (LOCF) (US Trial Part 1)

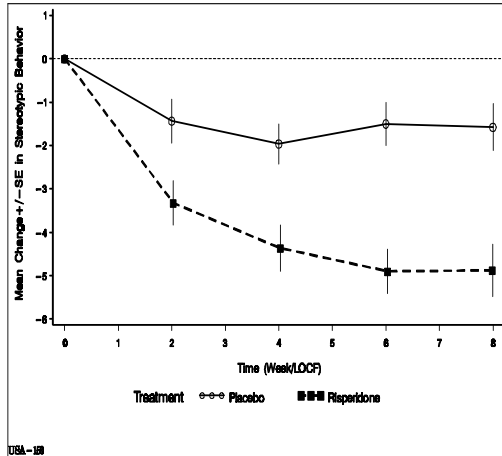
Lethargy and Social Withdrawal Subscale



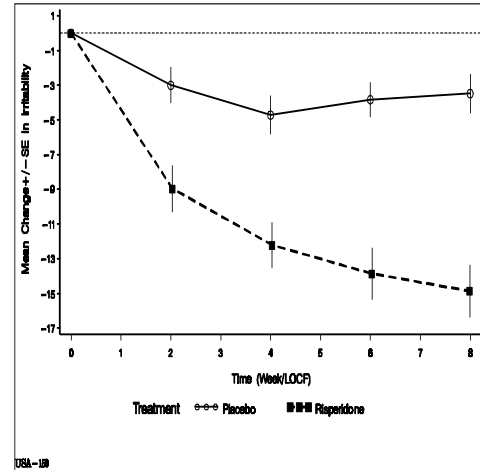
Inappropriate Speech Subscale



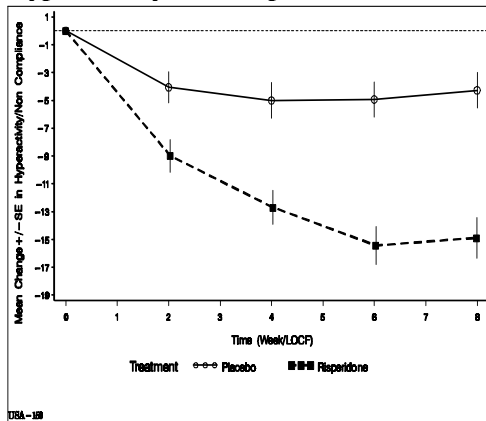
Stereotypic Behavior Subscale



Irritability Subscale



Hyperactivity/Noncompliance Subscale



Assessor's comments

The improvement in the irritability subscale was statistically significant for all groups analysed and the degree of improvement was likely to be clinically significant with the US Trial risperidone group showing an improvement of -10.6 (95% CI -13.8 to -7.5) over placebo (their baseline score being 26 out of a possible maximum of 45). The RIS-CAN-23 autistic group demonstrating a smaller but still significant effect over placebo -5.8 (95% CI -9.5 to -2.2). The US Trial had an inclusion criterion which stipulated that the disease severity as measured on the ABC Irritability Scale and CGI had to meet a certain severity of disturbance (CGI = 4 and ABC Irritability Score = 18). No such criteria were stated for RIS-CAN-23 thus children with less severe symptoms were included. This raises the possibility that children with milder symptoms obtain smaller benefit from risperidone therapy. Limiting the population of use to children with CGI = 4 and ABC Irritability Score = 18 may be appropriate in view of the adverse events of risperidone.

The improvement in irritability commenced almost immediately and appeared to plateau at 6 weeks, which is consistent with the gradual introduction of risperidone and no dose increase being permitted after week 4.

The different scales used on the y axes of the different ABC subscale graphs above should be noted. The only scales to demonstrate a substantial change were irritability and hyperactivity/noncompliance. The other 3 subscales demonstrated a statistically significant change in the US Trial but 2/3 failed to demonstrate significance at the 0.05 level in the RIS-CAN-23 Autistic subset. It is also difficult to assess whether changes of the order of 3 on a scale 0-48 for lethargy/social withdrawal, 2.5 on a scale of 0-21 for stereotypic behaviour and 2 on a scale of 0-12 for inappropriate speech in the US Trial are clinically meaningful. However, it can be stated that the improvement in irritability does not appear to be a trade off for deterioration in other elements of the ABC.

6.9.2 Clinical Global Impression CGI-C

The clinical global impression of the investigator who is blinded to the assigned treatment attempts to provide an estimation of the clinical relevance of observed treatment effect. The table below presents the results for the analysis of CGI-C responders at the 8-week end point.

CGI-C Responders at End Point				
Study Treatment	Total N	Responders N (%)	Comparison with Placebo	
			Tx Diff in % (95% CI)	p value ^a
US Trial Part 1				
Placebo	52	6 (11.5)	—	—
Risperidone	49	37 (75.5)	64.0 (49.1, 78.8)	<0.001
RIS-CAN-23				
Placebo	38	7 (18.4)	—	—
Risperidone	39	21 (53.8)	35.4 (15.5, 55.3)	0.001
RIS-CAN-23 Autistic Disorder Subset				
Placebo	28	6 (21.4)	—	—
Risperidone	26	14 (53.8)	32.4 (8.0, 56.9)	0.015
US Trial + RIS-CAN-23 Autistic Disorder Subset				
Placebo	80	12 (15.0)	—	—
Risperidone	75	51 (68.0)	53.0 (39.9, 66.1)	<0.001

^a p value: CMH test for association between risperidone treatment and CGI-C response controlling for investigator (or study for pooled).

Assessor's comments

When the CGI-C responder definition is applied to both trials a major difference in response rates is observed between the active group and placebo. In the US Trial a difference in CGI-C response rate of 64% (95%CI 49-79%) is seen and in RIS-CAN-23 a difference in CGI-C response rate of only 35.4% (95%CI 8-57%) is observed with an even lower CGI-C response rate in the autistic subgroup. However, due to the small numbers of subjects the confidence intervals are wide.

6.9.3 Responder Rates

Responder Definition

There were 2 different responder definitions since the definition was different in the 2 trials.

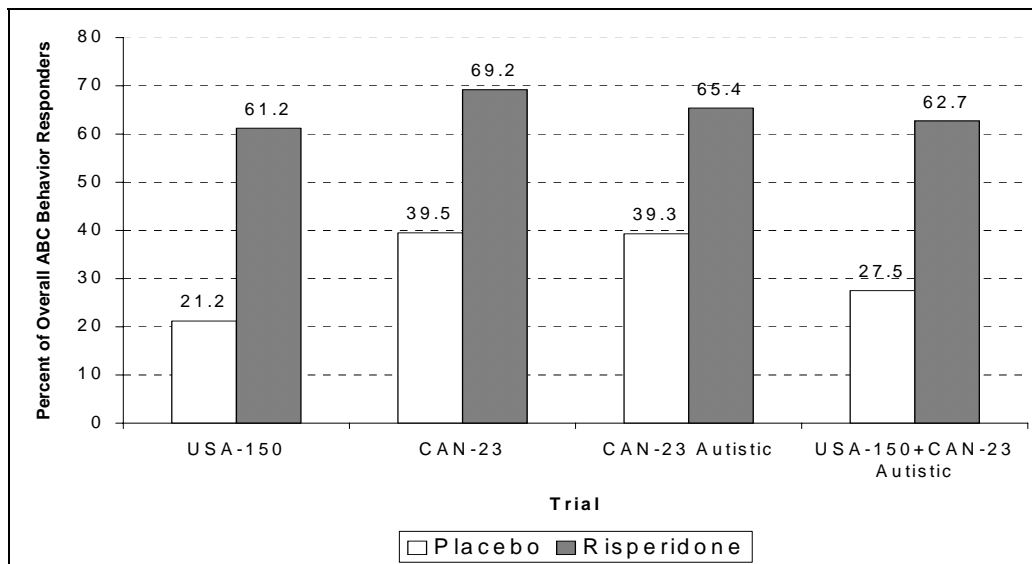
- i) The percentage of responders, using other criteria established a priori, was also analysed. The overall ABC response (defined a priori in RIS-CAN-23), based upon the change from baseline for the 5 ABC subscale scores, was computed; an ABC responder was defined as a subject demonstrating a $\geq 50\%$ decrease (improvement) at end point in at least 2 of the 5 ABC subscales, with none of the remaining subscales showing a 10% or larger increase (worsening).
- ii) Response based on both the change from baseline in the Irritability subscale of the ABC and the CGI-C rating (defined a priori in the US Trial) was also examined. For this analysis, an ABC/CGI-C responder was defined as a subject demonstrating a $\geq 25\%$ decrease (improvement) in the Irritability subscale score at end point and a rating of "very much improved" or "much improved" on the CGI-C.

For both definitions of response, the percent of responders in the 2 treatment groups was compared using a Cochran-Mantel-Haenszel (CMH) test controlling for centre (or study for pooled analysis).

ABC- Irritability/CGI-C = Definition Used In the US Trial

	Placebo	Risperidone	Response over placebo
USA-150	11.5	69.4	57.9
CAN-23	15.8	51.3	35.5
CAN-23 Autistic A	21.4	53.8	32.4
USA-150+CAN-23A	15	64	49

Responder analysis on ABC = Definition Used In RIS-CAN-23



Response was defined a 50% or greater decrease (improvement) from baseline in at least 2 ABC subscales and no ABC subscale showed a 10% or greater increase (worsening).

Assessor's comments

The definitions of responder in the US Trial and RIS-CAN-23 were different. The responder rate the MAH presented was the definition used for RIS-CAN-23 trial. The bar chart above, by emphasizing the risperidone responders by hatching makes it appear that the results of the Canadian trial were superior for this definition. However, it is the responder rate above placebo that is important to consider. This reveals that the US Trial had a responder rate of 40% above placebo whereas RIS-CAN-23 had only a 30% response rate above placebo. The Canadian definition of response rate is also likely to be less clinically relevant in the assessor's view. It used as its definition at least a 50% improvement in any 2 of the ABC subscales. This increases the likelihood of clinically meaningless changes being included. The only 2 subscales, which demonstrated reasonably large absolute change, were irritability and hyperactivity / non-compliance. It is possible that minor changes in for example

inappropriate speech could result in the threshold of 50% improvement being reached, whereas in reality the actual change was very small. The responder rate definition for the US Trial included a percentage change in the most relevant parameter irritability plus a ‘much improved’ or ‘very much improved’ result on CGI-C. This revealed a marked difference between the 2 studies again the US Trial having a 58% responder rate above placebo, whereas RIS-CAN-23 had only 32% responder rate above placebo in autistic subsection.

The MAH were also asked to perform a further analysis on dose, plasma levels and response (defined as a $\geq 25\%$ improvement in the Irritability subscale score at end point and a rating of “very much improved” or “much improved” on the CGI-C). In the US Trial Part 1 there was a higher mean and median dose with higher mean active moiety plasma levels ($25.0 \pm 8.5 \text{ ng/mL}$) in responders versus non-responders ($18.5 \pm 9.5 \text{ ng/mL}$). This difference in dose between responders and non-responders was not seen in RIS-CAN-23 and children received lower doses of risperidone, with a mean dose in the order of 1.4 mg/day, whereas in the US Trial the mean dose in responders was $1.91 \pm 0.68 \text{ mg/day}$ and non-responders $1.75 \pm 0.59 \text{ mg/day}$. Since the responder rate was lower in RIS-Can-23 the response in some children may well be determined by whether they can tolerate the adverse events such as somnolence in order to receive an effective dose of risperidone.

6.9.4 Subgroup analyses

Severity

The MAH was asked to conduct a subgroup analysis for RIS-CAN-23 based on dividing the autistic subgroup into those who would have met the entry criteria for the US Trial (severer group) and those who would not (milder group) to investigate further whether this was the reason for the smaller improvement seen in the RIS-CAN-23 study.

Age

There were only 6 children >12 years, thus it was not possible to perform this sub-group analysis. There were 3 children on risperidone and 3 on placebo. Numerically the children on risperidone improved on the ABC-I but to a lesser extent than the younger group aged 5-12. However, it is not possible to be sure this is a real effect in view of the very small numbers involved.

Assessor’s comments

Since the planned analysis of children younger than 12 vs. those older than 12 could not be conducted the MAH was asked to conduct a similar analysis with a different age divide to ensure the older children responded as well as the younger. The age chosen by the MAH was 7, which placed approximately equal numbers in both groups. There was no evidence that there was any change in the ABC Irritability response between the 2 age groups although interestingly the younger children experienced a slightly greater placebo improvement.

Sexual Maturation

For the US Trial there was also a subgroup analysis based on puberty (Tanner stage I or II vs. III, IV, V). There were 87 patients in the pre-pubertal group and 13 in the post-pubertal group and in both groups the risperidone showed a numerical advantage compared to placebo in change from baseline in ABC-I. The between difference in LS mean was -11.5 (-15.0 to -8.0) compared to -6.0 (-11.8 to -0.3) for the post-pubertal group.

Sex

The least square mean change in Irritability subscale was -7.3 for females (31, 20%) and -9.6 for males (124, 80%).

Race

In a pooled analysis there was no difference seen between the effects on the subscale measures of ABC in the Caucasian population (100, 64.5%), Black (20, 12.9%) or other (35, 22.6%).

Baseline Diagnosis

This subgroup analysis was performed for the RIS-CAN-23 only. Approximately the same reduction in LS mean was seen in the Irritability subscale but only half the benefit was seen on the hyperactivity /non-compliance subscale. There were only 23 patients with other PDD studied (13 on risperidone and 10 on placebo).

IQ Score

In a pooled analysis of Autistic Disorder there were 155 subjects 84 (54%) had an IQ ≤ 84 and 13 (8%) had an IQ > 84 , the remainder were missing. Only 3 of the subjects who had IQ scores > 84 were on risperidone. Thus the comparison is not very meaningful. The changes in the Irritability subscore were similar. There were a large number of baseline IQ measurements missing.

Assessor's comments

The diagnosis of autism in the profoundly retarded is difficult and the US Trial excluded children with a mental age of < 18 months. Out of the 43 subjects with Autistic Disorder in RIS-CAN-23, 4 were profoundly retarded with IQs ≤ 25 and 11 children had not had their IQ estimated. This raises the possibility that the diagnosis of autism may not be as accurate in RIS-CAN-23 as compared to the US Trial.

Somnolence

Somnolence was reported in 69 subjects, of whom 51 were on risperidone. For all ABC subscales the improvements were greater for subjects who did not suffer somnolence. However, there was still a numerical improvement in all 5 items of the ABC in somnolent children on risperidone compared to somnolent children on placebo. In the somnolent group 42.5% were CGI-I responders, whereas 62.1% of the non-somnolent group were CGI-I responders. (See section 7 for full analysis of somnolence as an adverse event.)

6.9.5 Other secondary endpoints

Vineland Adaptive Behaviour Scales (VABS)

This is a measure of personal and social sufficiency. It is designed to measure communication, daily living skills, socialisation and motor skills. This showed significant improvement with risperidone therapy. Maladaptive behaviour-I improved by LS means -7.3 (95% CI -9.9 to -4.6) over placebo and Maladaptive behaviour-I and II improved by -9.3 (95% CI -12.8 to -5.8).

Nisonger Childhood Behavioural Rating

Positive behaviours

This scale measures the positive social aspects of the individual and increase in the measurements indicates improvement. It was measured for RIS-CAN-23 only and showed a significant difference in change from baseline for risperidone vs. placebo for the compliant/calm subscale (LS mean change of 1.4 95% CI 1.0-2.7 p=0.04) but not for adaptive social, although this showed a positive trend. It is not clear what a change of this magnitude means for the patient or carer.

Negative behaviours

This measured conduct problems, insecurity, hyperactivity, self-injury, self-isolation/ritualistic and over sensitivity. There was a marked baseline imbalance for conduct disorders with the risperidone group being less affected. All groups showed significant improvement from baseline over placebo except self-isolated behaviour which just missed the 0.05 level and self-injury/stereotypical behaviour, which showed a slightly positive trend. Again there has been no discussion as to which changes reflect a clinically important one for the individual or their carer.

Visual analogue change of the most troublesome symptom

Using a 0-100 point scale there was a decrease in the placebo group of -26.2 (SD = 29.17) and -38.4 (SD = 28.91) in the risperidone VAS (p=0.036).

Assessor's comments

The VAS scale indicates a modest improvement in the worst symptom of about 10% over placebo for risperidone therapy. For the individual symptom subgroups there are insufficient numbers to achieve a statistically significant change, even for the commonest subgroup, aggression there were only 18 subjects. It should be noted that when aggression is not the most troublesome symptom risperidone is not always numerically superior to placebo e.g. defiance/disorientation but there were only 9 children in this group. This is a reminder that the indication should be for the symptomatic improvement of aggression and therapy may not be indicated if aggression is not the main feature of the illness.

6.10 RIS-USA-Part 2

Subjects who responded to risperidone in the US Trial Part 1 (RIS-RIS, n=33), along with subjects who were placebo non-responders in Part 1, and were subsequently shown to respond to risperidone during an 8-week open-label treatment period that followed Part 1 (PLA-RIS, n=30) entered an open-label treatment phase (the US Trial Part 2) during which they received flexible dosages of risperidone for up to 4 months. The median duration of treatment with open-label risperidone in the US Trial Part 2 was 113.0 days (3.8 months) for both groups of paediatric subjects (RIS-RIS and PLA-RIS). The modal dose of risperidone during open-label treatment was 0.066 mg/kg/day for those in the RIS-RIS group and 0.054 mg/kg/day for those in the PLA-RIS group.

The effectiveness of risperidone was sustained over the 4-month open-label treatment period. Throughout the US Trial Part 2, improvements in each of the 5 ABC subscale scores were maintained, and 81.0% of subjects were CGI-C responders (relative to the double-blind baseline) at the 4-month end point (i.e. ratings of “very much improved” or “much improved”). The improvement in ABC-I was -14.9 (SD 8.10) in the PLA-RIS group and -15.2 (SD 7.85) in the RIS-RIS group.

Assessor's comments

Despite the above results, it should be noted that there was a 27% discontinuation rate (17/63), see tables in section 6.8. So even in the trial where a greater benefit was seen with risperidone treatment nearly one third of the population felt that continuing with therapy was not beneficial to them.

6.11 RIS-USA-Part 3

At the end of the 4-month open-label treatment period, children and adolescents who maintained a significantly improved status while on risperidone entered an 8-week, randomized withdrawal study and were randomized to continued risperidone therapy or gradual placebo substitution over 3 weeks. They continued on their assigned medication for a further 5 weeks.

The efficacy was judged on the relapse rates of the first 32 patients to be entered to this phase of the trial. Relapse was defined as = 25% deterioration on the most recent ABC irritability scale from baseline and a 'much worse' or 'very much worse' rating on the CBG-C in 2 categories. Only 12.5% of children and adolescents with Autistic Disorder who continued treatment with risperidone in the US Trial Part 3 relapsed. By comparison, 68.8% of subjects previously shown to be responders to risperidone relapsed after being switched gradually to placebo. The between treatment group difference of 56.3% in the rate of relapse at 8 weeks was significant, and the odds ratio of 15.4 [95% CI: (2.50, 95.05)] indicated that subjects who remained on risperidone were 15 times less likely to experience a worsening in their ABC Irritability subscale score and CGI-C ratings than those gradually switched from risperidone to placebo after 6 months of successful therapy. The odds ratio analysis was confirmed by an analysis of time to relapse. Based on Kaplan Meier estimates, continued treatment with risperidone for 8 weeks in the US Trial Part 3 was associated with an 84.0% reduction in the relapse rate relative to gradually switching to placebo, and the between treatment group difference in time to relapse was statistically significant (p=0.001).

Assessor's Comments

Medication was withdrawn in the placebo arm over 3 weeks to attempt minimisation of any adverse effects from abrupt discontinuation. It was therefore assumed that any deterioration observed at the end of the study could be attributed to the absence of risperidone rather than a withdrawal reaction. It is also possible to observe any withdrawal effects such as dyskinesias during the initial 3 weeks (section 7.7).

7. SAFETY**7.1 Safety database:**

- i) Safety data from autistic patients in the US Trial (Parts 1-3) and RIS-CAN-23.
- ii) Supported by safety data from seven additional clinical trials in a paediatric patient population suffering from conduct and other disruptive behaviour disorders (DBD) in children and adolescents with sub average intellectual functioning or mental retardation in whom destructive behaviours (e.g. aggression, impulsivity and self-injurious behaviours) are prominent. This includes pooled data from RIS-CAN-19; RIS-USA-93; RIS-CAN-20; RIS-USA-97; RIS-INT-41; RIS-INT-70 and RIS-HUN-

4. The first 3 studies were 6-week, randomised, doubleblind studies and the other studies were open-label extension studies. A total of approximately 710 paediatric patient years of risperidone exposure is included.
- iii) Post-marketing data from the company's safety database and literature review.

Assessor's Comments

Three safety populations are considered:

- i) Autistic Double-Blind Subgroup – the most relevant to the present variation. This includes all children from the US Trial and the autistic subset from RIS-CAN-23. Separate references are made to the AE rate in the US Trial since some AE were directly asked for using a check list and thus a more accurate incidence rate is obtained.
- ii) Double-Blind Analysis Set – providing a larger population of children on risperidone with a placebo comparative group.
- iii) All Subjects Analysis Set – within this group are included the children in open-label long-term studies and comparison can be made as to whether some AE increase over time.

7.2 Autistic Double-blind Subgroup

Exposure

Dose (mg/kg/day) of Study Medication and Duration of Exposure
(Studies US Trial Part 1 and RIS-CAN-23; Intent-to-Treat Analysis Set)

	US Trial		RIS-CAN-23	
	Placebo (N=52)	Risperidone (N=49)	Placebo (N=39)	Risperidone (N=40)
Mode dose (including days off drug)				
Mean (SD)	0.057 (0.0431)	0.049 (0.0341)	0.051 (0.0145)	0.044 (0.0147)
Median (Range)	0.055 (0.00-0.15)	0.05 (0.00-0.12)	0.060 (0.02-0.07)	0.05 (0.02-0.06)
Total duration, days				
Mean (SD)	48.8 (13.50)	57.0 (6.51)	49.9 (14.82)	53.0 (9.71)
Median (Range)	56.0 (8-64)	57.0 (33-72)	56.0 (7-63)	55.5 (2-62)

In the double-blind Autistic Disorder Analysis Set, the incidence of adverse events was higher in the risperidone group than in the placebo group (98.7% vs. 82.5%). The table below lists those adverse events in the risperidone group that occurred with an incidence of $\geq 5\%$ and at a rate at least twice that seen in the placebo group. In the US Trial Part 1 (comprising 65% of Autistic Disorder Analysis Set), investigators completed a Side Effect Review form in addition to collecting information on spontaneous adverse events. On this form, investigators rated the absence or presence and the severity of 29 specific adverse events for each subject at all visits.

Incidence of Common Treatment-Emergent Adverse Events
in Double-Blind Studies in Pediatric Subjects With Autistic Disorder

Organ Class Preferred Term	Placebo (N=80) N (%)	Risperidone (N=76) N (%)
Any adverse event	66 (82.5)	75 (98.7)
Psychiatric disorders	43 (53.8)	70 (92.1)
Somnolence*	18 (22.5)	51 (67.1)
Appetite increased*	15 (18.8)	37 (48.7)
Confusion	0 (0.0)	4 (5.3)
Gastro-intestinal system disorders	38 (47.5)	47 (61.8)
Saliva increased*	5 (6.3)	17 (22.4)
Constipation*	6 (7.5)	16 (21.1)
Mouth dry*	5 (6.3)	10 (13.2)
Body as a whole – general disorders	27 (33.8)	47 (61.8)
Fatigue	10 (12.5)	32 (42.1)
Central & peripheral nervous system disorders	20 (25.0)	36 (47.4)
Tremor*	1 (1.3)	9 (11.8)
Dizziness	2 (2.5)	7 (9.2)
Automatism	1 (1.3)	5 (6.6)
Extrapyramidal disorder	0 (0.0)	5 (6.6)
Respiratory system disorders	32 (40.0)	48 (63.2)
Upper respiratory tract infection	12 (15.0)	26 (34.2)
Metabolic and nutritional disorders	5 (6.3)	10 (13.2)
Weight increase	0 (0.0)	4 (5.3)
Heart rate and rhythm disorders	0 (0.0)	7 (9.2)
Tachycardia*	0 (0.0)	5 (6.6)

Note: Adverse events reported during treatment or within 4 days of end of treatment are included. Incidence is based on the number of subjects, not the number of events.

* Reflects spontaneous + elicited reports.

7.3 Double-Blind Analysis Set

The types of adverse events and their relative frequencies in the risperidone group versus placebo group were generally similar to those for the Double-Blind Autistic Disorder Analysis Set. However, the overall incidence rate, as well as the incidence rate for certain individual adverse events, was higher among subjects with Autistic Disorder, for example fatigue and increased appetite.

7.4 All Subjects Analysis Set

Exposure

There were 821 children and adolescents in this data set who received a median dose of risperidone of 0.05mg/kg/day.

Duration	Number (n=821)
>3/12	621
>6/12	565

>12/12	331
>24/12	62

The most frequently reported adverse events for all pediatric subjects treated with risperidone were somnolence (38.5%), rhinitis (29.0%), and headache (25.5%). EPS-related adverse events of tremor and hypertonia were reported at rates of 5.5% and 5.4%, which were similar to those seen with double-blind risperidone treatment (6.8% and 5.0%, respectively, for in Double-Blind Analysis Set). By comparison, incidence rates for hyperprolactinemia and weight increase in the All Subjects Analysis Set (11.2% and 18.9%, respectively) were higher than those seen during double-blind treatment (5.9% and 7.2%, respectively).

In the All Subjects Analysis Set, the incidence of most adverse events was highest during the first 3 months of risperidone treatment, and decreased substantially after that. By months 10-12, most adverse events occurred in 3% or fewer pediatric subjects. Furthermore, there were no late-occurring adverse events and no evidence that any adverse event increased in incidence over time.

Children and adolescents with at least one TEAE

	Risperidone	Placebo
Autistic double-blind	98.7%	82.5%
Other dx double-blind	89.0%	66.9%
All risperidone open + double-blind	92.4%	N/a

Assessor's Comments

The higher rate of adverse events seen during double-blind risperidone treatment in the Autistic Disorder subgroup may be related to the fact that some of the adverse events were elicited by a checklist in one of the Phase 3 studies in Autistic Disorder. In addition to the adverse events discussed below there was also an increase in upper respiratory tract infections which is not of particular concern and is unlikely to be attributable to risperidone and tachycardia with 5 (6.6%) of children on risperidone noting this and none in the placebo group. In 4 cases this appeared to be associated with an infection, so causation is not clear. For the US Trial the mean pulse rate in both groups at baseline were equivalent (96.3±19.08 for placebo and 97.2±19.60 for risperidone). The rate in the placebo group decreased slightly (-0.9 ±23.96) whereas in the risperidone group it increased by 6.6±18.02 bpm), this was not associated with a change in baseline BP. Similar changes are noted in RIS-CAN-23. Tachycardia is noted as an adverse event in the SPC.

7.5 Any serious adverse event.

There were no deaths or cases of neuroleptic malignant syndrome.

In the double-blind studies 3 children on risperidone vs. 4 on placebo had serious adverse events. In the former group 1 had an extrapyramidal reaction in response to an accidental overdose, one had appendicitis and 1 had an aggressive reaction but recovered and continued on medication. In the total risperidone dataset (n=821) serious adverse events occurred in approximately 11% but there appeared to be no specific pattern in the adverse events. The events occurring at >1% included aggressive reaction (1.3%) and condition aggravated (2.2%). There were 4 cases of suicide attempt, none of whom had autism. They had all received risperidone for some months (86 days, 193 days, 246 days, 376 days). In the second case the attempt was made 6 days after a dose reduction but this was a very minor adjustment (3.4mg to 3mg).

7.6 Adverse events leading to withdrawal

Only 1 child on risperidone with autism in the double-blind studies withdrew due to adverse events, as did 1 child on placebo. In total including all open-label studies 64/821 withdrew due to adverse events. There were 18 cases of extrapyramidal disorder, dyskinesias, hyperkinesias, dystonia, hypokinesia or hypertonia. There were 4 cases of increased appetite and 12 of weight gain or obesity. There were 5 cases of gynaecomastia.

7.7 Extrapyramidal Adverse Events

Extrapyramidal Symptom Rating Scale

These were assessed at each visit and before anticholinergic therapy and consisted of:

- i) Questionnaire and Behaviour Scale (12 items)
- ii) Parkinsons (8 items)
- iii) Dystonia (2 items)
- iv) Dyskinetic Movements (7 items)

Clinical Global Impression (CGI) overall severity (absent, borderline, very mild, mild, moderate, moderately severe, marked, severe and extremely severe).

In the Autistic subgroup there were 22/76 (28.9%) children with EPS-related adverse events vs. 8/80 (10.0%) on placebo. Most of the EPS-related events in the risperidone group were mild (13) or moderate (7) in severity and only 2 events (hyperkinesia and extrapyramidal disorder) were rated as severe.

Incidence of EPS-Related Adverse Events by Grouped Term
and by Diagnosis for Double-Blind Placebo-Controlled Studies
(Double-Blind Analysis Set; Double-Blind Autistic Disorder Analysis Set)

Grouped Term	Placebo			Risperidone		
	Total (N=237) n (%)	Autistic Disorder (N=80) n (%)	Other PDD/ DBD (N=157) n (%)	Total (N=222) n (%)	Autistic Disorder (N=76) n (%)	Other PDD/ DBD (N=146) n (%)
Dystonia ^a	8 (3.4)	5 (6.3)	3 (1.9)	15 (6.8)	9 (11.8)	6 (4.1)
Tremor	2 (0.8)	1 (1.3)	1 (0.6)	15 (6.8)	9 (11.8)	6 (4.1)
Parkinsonism ^b	0	0	0	8 (3.6)	6 (7.9)	2 (1.4)
Dyskinesia	2 (0.8)	0	2 (1.3)	5 (2.3)	5 (6.6)	0
Akathisia ^c	3 (1.3)	1 (1.3)	2 (1.3)	3 (1.4)	1 (1.3)	2 (1.4)
Tardive dyskinesia	1 (0.4)	1(1.3)	0	0	0	0

Note: Adverse events reported during treatment or within 4 days of end of treatment are included. Incidence is based on the number of subjects, not the number of events.

^a WHO-preferred terms of dystonia, hypertonia, oculogyric crisis, involuntary muscle contractions, tetany, and tongue paralysis

^b WHO preferred terms of extrapyramidal disorder, hypokinesia, bradykinesia.

^c WHO-preferred term hyperkinesia renamed

Assessor's comments

The combined figures appear to underestimate EPS-related adverse events. In the US Trial these were specifically asked for by questionnaire. In this study 16/49 (32.7%) of children on risperidone suffered with EPS symptoms vs. 6/52 (11.5%) that were on placebo. The incidence of EPS-related symptoms appears to treble on active treatment when measured in this fashion, whereas in the table above they appear only to double, although children in the US Trial also tended to receive higher mg/kg doses of risperidone. Please see table below for the EPS-related events for the US Trial. There were approximately twice as many children started on anti-Parkinsonian medication in the risperidone group (9/76 children who were started on anti-Parkinsonian medication in the risperidone group and 4/80 in the placebo group).

These adverse events may worsen over time but it is difficult to assess from the US Trial Part 2 since this was a selected group of risperidone responders who opted to continue into the 4 month open-label phase and may not reflect a general pool of autistic children. Only 9/63 (14.3%) exhibited EPS-related AE.

EPS-related AE the US Trial

AE	Placebo (n=52)	Risperidone (n=49)
Total	6 (11.5)	16 (32.7)
Tremor	1 (1.9)	7 (14.3)
Hypertonia	4 (7.7)	6 (12.2)
Dyskinesia	0	4 (8.2)
Extrapyramidal disorder	0	3 (3.1)
Ataxia	0	2 (4.1)
Involuntary muscle contractions	0	2 (4.1)
Hyperkinesia	1 (1.9)	0

Withdrawal reactions the US Trial Part III

The rate of EPS-related adverse events was higher in the risperidone continuation group than the placebo substitution group (21.1% vs. 15.0% respectively). In the group withdrawn from risperidone treatment there was a higher incidence of anxiety (6/30; 30% placebo vs. 3/19; 15.8% risperidone), anorexia (2 vs. 1 case) and nausea (4 vs. 0 cases).

Assessor's comments

There appears to be a higher incidence of EPS-related adverse events in the children treated with risperidone with autism compared to those with other diagnoses. The company expert argues that the reason for this is that the adverse event questionnaire used in the US Trial, included EPS adverse events. This was not the case in trials in other conditions. However, in RIS-CAN-23 where a questionnaire is not used 11/40 (27.5%) experienced an EPS-related adverse event. This is still much higher than the event rate seen in the other treated conditions. There was no evidence that EPS-related adverse events increased over time when AE were reviewed for all trials at 3 monthly intervals.

There is no evidence of a withdrawal reaction causing EPS in the US Trial but there did appear to be an increase in anxiety and nausea. The small numbers in this part of the study should be noted.

Prolactin Related Adverse Events

Among all subjects who received at least 1 dose of risperidone (All Subjects Analysis Set), potentially prolactin-related adverse events occurred at a rate of 14.3%, and consisted of hyperprolactinemia (11.2%), gynaecomastia (3.4%), dysmenorrhoea (0.2%), and lactation - nonpuerperal (0.1%). Amenorrhoea was reported in 6 (0.7%) paediatric subjects receiving risperidone. None of the potentially prolactin-related adverse events occurring in risperidone-treated children or adolescents was considered serious, although 5 (0.6%) subjects were withdrawn from therapy for gynaecomastia.

For the Double-Blind Analysis Set, overall mean prolactin levels increased during treatment with risperidone from 8.107 ng/mL at baseline to 29.330 ng/mL at end point. Prolactin levels at double-blind study end point were above laboratory limits for 2 of 98 (2.0%) placebo subjects and for 36 of 83 (43.4%) risperidone subjects with normal prolactin at baseline.

In the long-term open-label studies in DBD (RIS-INT-41, RIS-INT-70, and RIS-HUN-4), the mean value for prolactin increased from 7.917 ng/mL at baseline to 29.90 ng/mL at Week 4, which was the highest value recorded during the up to 3 years of treatment. The mean values decreased toward the normal range during the course of treatment and were 16.01 ng/mL at Month 12, 16.37 ng/mL at Month 24, and 12.82 ng/mL at Month 36.

Weight Gain

In the US Trial there was a greater weight gain in the risperidone group ($2.7 \pm 4.27\text{kg}$) compared to placebo ($0.7 \pm 1.77\text{kg}$). An increase in appetite was noted in 69.4% of risperidone treated patients compared to 26.9% in the placebo group.

Glucose related adverse events

In all double-blind trials only 18 cases had BS measured at baseline and end-point. There appeared to be no difference between measurements in this small group with mean values of 5mmol/l. There were no glucose related adverse events and all urine sugars were negative.

Assessor's comments

The endocrine aspects of the safety data on prolactin, growth, sexual maturation and weight gain were reviewed by a CSM expert on Paediatric Endocrinology.

The main points were:

- i) Prolactin levels were raised to levels of 29ng/ml. At this level prolactin would be expected to interfere with the hypothalamic-pituitary-gonadal axis.
- ii) The company's model for growth is too simplistic and height measurements have not been validated.
- iii) The Tanner scale for sexual maturation has been misapplied and erroneous conclusions drawn. The assessment of sexual maturation in the trial is dubious; since there are cases of regression, a phenomenon yet to be described by endocrinologists.
- iv) Weight gain occurred in children on risperidone therapy. It appears from Z score analysis that from USA standards there was a marked increase in weight resulting in a shift of 0.5 standard deviations. This is then maintained whilst on risperidone therapy i.e. the child is shift onto a higher percentile of weight but then gains weight at a normal rate subsequently.
- v) The duration of follow-up is too short to ascertain effects on sexual maturation (a process which takes approximately 4 years in girls and 3 years in boys) or growth.

It is not possible to establish the effect of risperidone on blood glucose from these data but obviously the weight gain described above means there is still a concern about a possible increase in blood glucose with long-term therapy.

Gastrointestinal events

It has been reported that gastrointestinal disorders may be more common in Autistic Disorder. A somewhat higher rate of gastrointestinal adverse events was seen among subjects with Autistic Disorder compared to DBD/other PDDs in the double-blind studies, and this was true in the risperidone (61.8% vs. 39.0%) and placebo (47.5% vs. 18.5%) groups.

Common gastrointestinal events that occurred with at least a 2-fold higher rate in the risperidone group compared with placebo for the Double-Blind Analysis Set were saliva increased (11.7% on risperidone vs. 2.5% on placebo), constipation (9.9% vs. 3.4%), abdominal pain (5.9% vs. 2.5%), and mouth dry (5.4% vs. 2.5%). Gastrointestinal adverse events were rarely treatment-limiting in children and adolescents receiving risperidone; only 8 of the 821 subjects (1.0%) were withdrawn for a gastrointestinal adverse event.

Somnolence

RIS-CAN-23 29/40 (72.5%) risperidone subjects experienced somnolence with a median duration of 14 days. The onset was within the first 20 days of treatment in virtually all cases. Of the 29 cases 20 changed to b.d. or nocte dosing and 18 resolved, 2 had dose decreases and 7 continued or had their dose increase, 5/7 somnolence had resolved by the end of the study.

Assessor's comments

The company expert in his clinical overview focuses on the overall double-blind population where the incidence of somnolence was not so high (49.5% risperidone vs. 13.5% placebo). The company was asked to perform a further analysis in the autistic sub-group. Again looking at the US Trial where adverse event data were more carefully collected twice as many children experienced somnolence on active treatment 31/49 vs. 16/52. The median number of days with somnolence was 18.0 vs. 5.5 days respectively. It would appear that the incidence of somnolence is very common at treatment outset and 2/3 of children may experience an increase. During the double-blind studies the median duration of somnolence was 14 days (range 1-57) with some children being affected for longer (mean duration 18.7 SD 15 days).

The MAH were asked if there was any relationship between the pK data and somnolence. From the US Trial of the children receiving risperidone 31 were somnolent and 18 not. The mean and modal doses for risperidone were lower in the somnolent subgroup as were the steady state active moiety levels. The MAH explained that the likely reason for the lower dose in the somnolent individuals was due to a decision in delaying upward dose titration in those affected by somnolence. In addition, there is evidence from a trial in children with Disruptive Behavioural Disorders reviewed previously by the MHRA. In this study 143 children experienced somnolence and had 326 plasma samples analysed and compared to the 326 children without somnolence who had 820 plasma samples taken. According to the MAH the mean plasma concentrations of the active moiety were 9.75 ± 9.15 ng/mL in somnolent individuals compared to 12.5 ± 10.9 ng/mL in the unaffected children. In conclusion there appears to be no consistent relationship detectable between the pK data and the adverse event of somnolence.

The incidence of somnolence was related to time and peaked at week 2 of treatment (34.7% risperidone and 2.5% placebo) in the autistic subgroup. This reduced to 16.0 vs. 8.1% respectively at week 4 and between weeks 5-8 ran at similar levels to the placebo group. It would appear that 6/76 (7.9%) subjects had persistent somnolence as defined as longer than 2 weeks and not resolved at end point vs. 2/80 (2.5%) in the placebo group. There were a few subjects who once they became somnolent were somnolent for the duration of the study.

The company was asked to further define the severity of the somnolence seen. Of a total number of 316 subjects in the all subjects analysis group who had somnolence, there were 11 cases where somnolence was characterised as severe in patients on risperidone, 1 ceased treatment and 5 temporarily stopped but successfully restarted, usually at a lower dose. A further 4 subjects had a dose reduction and 1 subject had no alteration but in all the adverse event resolved. In addition a further 4 risperidone treated subjects stopped due to mild/moderate somnolence.

Convulsions

There were no cases of convulsions in children on risperidone in the double-blind sub-group. There was an incidence of 0.6% in the risperidone safety population overall. In 1 case it led to treatment withdrawal and 2 cases it was considered serious.

Assessor's comments

Convulsions are not noted as an adverse event in section 4.8 but there is no evidence from the double-blind population that it needs to be added.

Cognition

A battery of cognitive tests was selected for the US Trial but only a very small proportion of the children completed these. It is therefore not possible to draw firm conclusions from these. Cognition was not assessed in RIS-CAN-23. There are some assessments of attention, concentration, and/or verbal memory in other PDDs/DBD. The expert states 'In double-blind studies RIS-USA-93 and RIS-CAN-19, the mean changes from baseline to end point in the items of the easy Continuous Performance Task (CPT), hard CPT, and Modified Verbal Learning Test (MVL) – Children's Version were generally small and similar for risperidone and placebo treatment groups. While there was an indication that risperidone increased reaction time, this effect was most pronounced in subjects who experienced somnolence. In the combined, long-term, open-label studies, mean changes in cognitive function tests were small and did not change over time.'

Assessor's comments

There is no discussion of whether these scales have been validated in children with PDD/DBD.

8. CONCLUSION

Symptomatic treatment with risperidone appears to effectively reduce irritability in severely affected autistic children in both 8-week efficacy trials. This is reflected in the improvement in ABC-I and CGI-C scores. However, the benefit appears less in the autistic subgroup of RIS-CAN-23, possibly due to less severe cases being included or possibly less stable cases being included. Therefore a limitation on severity has been advised and a precaution has been proposed not to commence children on risperidone within 6 months of having a seizure, which is based on the entry for the US Trial. There are no data collected directly from the children on how they feel on risperidone but the carers clearly see an improvement. The justification for treatment is therefore based on improvement observed by carers.

There are safety concerns with therapy in this population. Despite titrating the dose, somnolence occurs in approximately 2/3 of the children but often resolves spontaneously. It would appear that 6/76 (7.9%) subjects had persistent somnolence defined as longer than 2 weeks and not resolved at end point vs. 2/80 (2.5%) in the placebo group. There were a few subjects who, once they became somnolent, were somnolent for the duration of the study. However, somnolence can be addressed by nocturnal dosing, reducing therapy or stopping treatment. It should also be noted that the improvement seen in the irritability subscale of the ABC is not at the expense of deterioration in the other subscales, this give some reassurance that the somnolence is not impacting negatively on other functions.

The long-term adverse events have not been adequately assessed, in particular the effects of weight gain and raised prolactin levels. The latter may affect growth and sexual maturation and the attempts to assess these in the trials have been inadequate. In addition approximately 20% of children on risperidone experience extrapyramidal adverse events.

In the assessor's view this makes the risk/benefit analysis negative for long-term treatment despite the behavioural improvements seen. Therefore it is proposed to limit any indication to symptomatic short-term use in a clearly defined population of moderately to severely affected autistic children. The indication should clearly be for the symptomatic improvement of irritability and if irritability is not the main feature of the illness, therapy is not indicated.

Only 6 children aged over 12 have been studied. In this group, there was still a numerical benefit seen for risperidone treatment but this appeared less than for the younger age group. This may well be due to the small numbers treated. In view of this it may be considered appropriate to limit the population of use to children aged 5-12 years.

There have not been sufficient numbers of other Pervasive Developmental Disorder patients to recommend licensing of risperidone outside the diagnosis of Autistic Disorder.

10. PAEDIATRIC WORKING GROUP ADVICE

This paper was discussed at the Paediatric Working Group on the 8/02/05 and the Working Group advised that:

The efficacy and safety of risperidone were assessed as positive to grant a variation to its Marketing Authorisation for the short-term symptomatic treatment of irritability in children with autism. However, it was considered that there were concerns about the risk of inappropriate sedation of autistic children and it was proposed that this should be addressed by limiting initiation of the prescription and supervision of therapy to a specialist in the field. It was also recommended that it should be made clear that pharmacological treatment is considered second line to non-pharmacological methods when dealing with the problem of irritability in autistic children.

The Working Group decided that there is insufficient evidence of efficacy and safety in adolescents due to the small numbers studied and the indication should be limited to children of 12 years and under. They also advised that the safety of long-term therapy has not been adequately demonstrated and that the potential risks of long-term therapy should be clearly stated in the SPC.

The incremental dosing schedule is in accordance with the pivotal trials. The MAH should describe how they propose to accurately give the smallest doses from the currently licensed formulations. The company were asked to provide this information before the CSM meeting on the 24th February.

11. RESULTS OF CSM CONSULTATION

The CSM considered the variation application on 2 occasions. Following the first discussion in February 2005, the Committee advised that various bodies should be consulted in relation to the use of risperidone in autism. In addition the MAH was asked to submit a detailed risk management plan to address the unresolved safety issues. This was done and the outcome presented at the second CSM review in September 2005. The results for the consultation and a summary of the risk management plan are detailed below.

11.1 Views of the National Autistic Society

These are summarised as follows:

Risperidone should only be licensed only for specific behavioural problems in autism and its use should not be long-term. They also stated they had particular concerns around the use in children aged less than 8 years of age, although these were not specified. In addition the following points were made:

- i) Risperidone may be used as a first rather than a last resort in the management of anxiety or aggression.
- ii) Clear guidance should be given on starting on very low doses with full information on adverse events, in particular EPS related adverse events.
- iii) Adverse events noted by users included panic, loss of control, increased agitation, arousal and restlessness. The possibility that these adverse events could be confused with the symptoms of autism and the medication erroneously increased rather than stopped.
- iv) Long-term safety concerns including weight gain and amenorrhoea. The reported increase in strokes from studies in adults (mainly trials in dementia).
- v) They do not feel any drug can be licensed for 'ASD' in terms of treating the core deficits.

11.2 Views of the carers of autistic children

A number of carers were contacted via one of the centres of excellence and the National Autistic Society. In most cases the children had a diagnosis of autism but some children suffered from Asperger's syndrome. In almost all the case histories risperidone had only been prescribed for severe behavioural problems after other measures had been tried and failed. In almost all cases the medication was found to be helpful, for example in permitting a child to participate in schooling again and to be taken out of the house where this had been previously impossible. In general the children were reported to be calmer and this was confirmed by the direct report of the child in one case. Interestingly there were several cases of weight gain reported which had been of concern in this assessment of the data. However, two carers viewed this as a benefit since due to the symptoms of autism it had been previously very difficult to get adequate nutrition into their children. There was one case history of a teenager with Asperger's syndrome which reported use of extremely high doses of risperidone (according to her mother up to 200mg twice daily) which made her aggressive behaviour worse. Her behaviour improved on stopping the risperidone.

11.3 Centres of Excellence

Many centres were contacted but most of the experts had been consultants to Janssen-Cilag rendering them ineligible to give advice. The independent views of 2 experts with extensive experience of the use of risperidone in autistic children have been obtained.

In summary, both experts state that aggression in autistic children whether directed at themselves or others, is a devastating problem. The first expert estimates approximately 5% of his caseload is taking risperidone and the second expert 25%. The second expert considered his caseload as a whole, not just the two thirds who were estimated to have autism. This might explain some of the disparity but it would appear there is variation in the

frequency of use. Although it should be noted that it is not known whether the severity of their patients' behavioural problems is similar for the 2 experts.

Both experts consider that the use of risperidone should be limited to severely aggressive behaviour in autism.

They consider that the behaviour should be identified and precipitating or aggravating factors investigated and addressed initially by non-pharmacological means whenever possible. There may be emergency situations of extreme patient and family distress where first line short-term drug therapy may be appropriate. It would be difficult to add appropriate wording to cover this eventuality without increasing the risk of inappropriate usage. In addition the data did not extend to emergency usage so it is not proposed to add specific wording to the SPC to address this point.

They considered that treatment should not exceed 6 months unless careful review indicates value in continuing therapy. The second expert recommended that attempts at withdrawal of therapy should be made at 3 months and then at least annually. This should be done with the involvement of the carers, including teachers of the child. Reduction should take place gradually over several weeks in an attempt to avoid withdrawal dyskinesias. Drug therapy should not be used in isolation without other behavioural interventions

Treatment with risperidone is likely to be made safer in the more controlled environment of a licensed indication with a clear indication and guidance on dosing and monitoring of efficacy and safety.

Monitoring should include:

- i) Pre-treatment physical examination for endocrine or cardiac problems
- ii) Height and weight measured at least twice a year
- iii) Developmental status
- iv) Bowel habit monitored due to severe constipation having occurred in association with risperidone therapy
- v) Periodic neurological examination for extra-pyramidal and motor complications
- vi) Blood pressure in early treatment
- vii) Blood chemistry (glucose, lipids and prolactin) if the dose of risperidone exceeds 2mg daily or a child gains more than 2kg of weight above the expected growth curve. Venesection must be considered in context since in certain cases any safety gains would be out-weighed by the intervention in terms of distress caused to the child.

Carers should be educated about signs of rare but serious adverse events such as neuroleptic malignant syndrome, liver failure, and priapism.

11.4 Risk-Management Plan

The MAH was asked to write a risk management plan in order to address the deficiencies in the safety data. The plan included the following points:

- i) The new indication is given black triangle status. Drugs in this category should have any adverse events reported, even if they are known adverse events, for a minimum of 2 years.

- ii) Post-approval commitment to provide a periodic review of the world-wide safety database for adverse reactions involving children and adolescents aged 5-17 years old. These reports would be 6-monthly for the first 2 years and then annually for the next 2 years and then 5-yearly. Adverse events, which would be reviewed in detail, would include tardive dyskinesias, weight gain, glucose intolerance and prolactin-related adverse events.
- iii) SPC changes which are presented in the proposed MAH wording in section 2 of this paper.
- iv) A communication and education plan to be carried out by the MAH targeting child and adolescent psychiatrists, learning disability consultants and community & developmental paediatricians.

12. CONCLUSION

12.1 Risk/Benefit Analysis of Submitted Data

Symptomatic treatment with risperidone appears to effectively reduce moderate to severe irritability in autistic children in both 8-week efficacy trials. This is reflected in the improvement in ABC-I and CGI-C scores. However, the benefit appears less in the autistic subgroup of RIS-CAN-23, this may be due to the differences in inclusion criteria which permitted less severe cases being included in the latter trial in addition it is possible that less stable cases were also included. Therefore the indication has been restricted to severe symptoms and a precaution has been proposed not to commence children on risperidone within 6 months of having a seizure, which are based on the entry for the US Trial. There is no data collected directly from the children on how they feel on risperidone but the carers clearly see an improvement. The justification for treatment is therefore based on improvement observed by carers.

There are safety concerns with therapy. Despite titrating the dose, somnolence occurs in approximately 2/3 of the children but often resolves spontaneously. It would appear that 6/76 (7.9%) subjects had persistent somnolence (> 2 weeks or not resolved at end point) vs. 2/80 (2.5%) in the placebo group. There were a few subjects who once they became somnolent were somnolent for the duration of the study. However, somnolence can be addressed by nocturnal dosing, reducing therapy and if necessary stopping treatment. Appropriate wording will be added in the SPC. It should also be noted that the improvement seen in the irritability subscale of the ABC is not at the price of deterioration in the other subscales, which is reassuring that in most cases somnolence does not appear to be causing deterioration in other functions.

The potential long-term adverse events have not been adequately studied. In particular the effects of weight gain and raised prolactin levels. The latter may affect growth and sexual maturation and the attempts to assess these in the trials have been inadequate. In addition approximately 20% of children on risperidone experience extrapyramidal adverse events.

There have only been 6 children studied aged over 12. In this group, there was still a numerical benefit seen for risperidone treatment but this appeared less than for the younger age group. This may well be due to the small numbers treated. In view of this it is considered appropriate to limit the population of use to children aged 5-12 years. The MAH have appealed against this limitation in their response document citing need for therapy continuation into adolescence. It is unfortunate that the MAH did not identify this need when

planning their clinical trials and include more adolescents in their studies since this argument does not address the lack of evidence submitted.

12.2 Views from Consultation

The National Autistic society has expressed 5 specific concerns. Four of these concerns had been identified in the previous CSM paper and actions to address these via amendments to the SPC had been previously advised. These were:

- i) Non-pharmacological treatments should be tried before drug therapy.
- ii) Instructions in the posology should give guidance for low doses, gradual increases, monitoring adverse events with advice on dose reduction, alteration in timing of dose and cessation of therapy when appropriate.
- iii) Identification of the adverse effects of therapy both short and long-term. The occurrence of these will be identified by increased post-marketing surveillance in the form of clinical monitoring and black triangle status of the drug.
- iv) It is not proposed to indicate risperidone for the treatment of autism per se but only very specific severe symptoms of the illness.

Additional SPC wording has now been proposed to ensure that deterioration in behaviour is not assumed to be just due to inadequate dosing and that a drug adverse event should be considered. This addresses their fifth concern.

Following the advice from the experts in autism clear guidance on baseline examination, monitoring height, weight, BP (after initiation), bowel habit and neurological signs should be given in the SPC. If excess weight gain is noted and the medication is unable to be stopped more intensive monitoring is required including biochemical monitoring, provided this can be done without undue stress to the child. Both experts refer to autistic children being severely affected by aggressive behaviour. The indication should be tightened to reflect this.

13. CSM ADVICE

On the evidence before them, the Committee on Safety of Medicines advised that:

The efficacy and safety of risperidone has been assessed as positive to grant a variation to its Marketing Authorisation for the symptomatic treatment of severe aggression or violence, whether directed towards self or others, in children with autism provided:

- iv) The SPC and PIL are amended as detailed below.
- v) Risperidone should be monitored under black triangle status for this new indication.
- vi) The MAH submit a full risk management plan with defined milestones for data submission.

The approval is conditional on that all 3 elements are met.

SPC Points

Section 4.1 Indications

Risperidone is indicated for the short-term treatment of severe aggression and violence whether directed towards self or others in Autistic children where available non-pharmacological methods have first been tried and failed.

~~Risperdal is indicated for the treatment of moderate to severe emotional and behavioural signs and symptoms of autism such as deliberate self-injuriousness, poor frustration tolerance, irritability, quickly changing moods and aggression towards others in children and adolescents.~~

Section 4.2. Posology

~~Autism (children aged 5-12 years or over and adolescents)~~

For the symptomatic treatment of aggression and violence in autistic children risperidone therapy should be initiated and supervised by a consultant specialist. The dosage of risperidone should be individualised according to the weight of the patient, their response to therapy and the incidence of adverse events.

~~Use of Risperdal for patients with Autism should be on specialist advice, e.g. paediatric neurologists, paediatricians, child and adolescent psychiatrists or physicians conversant with treatment of autistic disorders in children and adolescents.~~

~~The dosage of RISPERDAL should be individualised according to the response of the patient.~~

~~Dosing should be initiated at 0.25mg per day for patients <20kg 15-20kg and 0.5mg per day for patients ≥20kg.~~

~~On Day 4, the dose may be increased by 0.25mg for patients <20kg 15-20kg and 0.5mg for patients ≥20kg.~~

~~This dose should be maintained and response should be assessed at approximately Day 14. Only in patients not achieving sufficient clinical response should additional dose increases be considered. Dose increases may proceed at 2-week intervals in increments of 0.25mg for patients <20kg 15-20kg or 0.5mg for patients ≥20kg.~~

~~In clinical studies, the maximum dose studied did not exceed a total daily dose of 1.5mg in patients <20kg 15-20kg, 2.5mg in patients ≥20kg, or 3.5mg in patients >45kg.~~

Doses of RISPERDAL® in Paediatric Patients with Autistic Disorder (by total mg/day)

Weight Categories	Days 1-3	Days 4-14+	Increments if Dose Increases are Needed	Dose Range
<20kg <u>15-20kg</u>	0.25mg	0.5mg	+0.25mg at ≥2 week intervals	0.5mg-1.5mg
≥20kg	0.5mg	1.0mg	+0.5mg at ≥2 week intervals	1.0mg-2.5mg*

*Subjects weighing >45kg may require higher doses: maximum dose studied was 3.5mg/day

For prescribers preferring to dose on a mg/kg/day basis the following guidance is provided.

**Doses of RISPERDAL® in Paediatric Patients with Autistic Disorder
(by mg/kg/day)**

<i>Weight Categories</i>	<i>Days 1-3</i>	<i>Days 4-14+</i>	<i>Increments if Dose Increases are Needed</i>	<i>Dose Range</i>
<i>All</i>	<i>0.01mg/kg/day</i>	<i>0.02mg/kg/day</i>	<i>+0.01mg/kg/day at ≥2 week intervals</i>	<i>0.02mg/kg/day-0.06 mg/kg/day</i>

Risperidone can be administered once daily or twice daily.

Patients experiencing somnolence may benefit from a switch in dosing from once daily to either once daily at bedtime or twice daily or by a dose reduction.

Once sufficient clinical response has been achieved and maintained, consideration may be given to gradually lowering the dose to try and achieve the optimal balance of efficacy and safety. There is insufficient evidence from controlled trials to ~~indicate how long the patient with Autistic disorder should be treated with Risperdal.~~ establish the safety of risperidone therapy for long-term treatment. An attempt to gradually withdraw risperidone should be made after a maximum of 8 weeks treatment. Therapy should not be continued beyond 6 months unless gradual, supported withdrawal has resulted in a severe relapse of aggression, which is not manageable by other means.

~~There is limited clinical experience with risperidone in adolescents with autism. The risk-benefit should be reassessed at adolescence.~~

Section 4.4 Special Warnings and Precautions of Use

Special precautions of use of risperidone in ~~patients~~ children with autism

Before risperidone is prescribed the child must be fully assessed for physical, psychological and social causes of the aggressive behaviour such as pain, Attention Deficit Hyperactivity Disorder (ADHD), inappropriate environmental demands. Non-pharmacological methods should be tried before medication is resorted to.

Pre-treatment assessment and regular clinical monitoring should be performed. ~~arranged,~~ including This should include:

- i) Measurement of height, weight and developmental status including sexual maturation.*
- ii) Bowel habit should be monitored to avoid constipation.*
- iii) Somnolence and other behavioural changes.**
- iv) Neurological examination for movement disorders, including tardive dyskinesia or motor complications.***
- v) Cardiovascular assessment and initially blood pressure monitoring*

**Deterioration in behaviour on risperidone should be carefully assessed as to whether this is due to a drug adverse event rather than a sign of inadequate dosage.*

*****Movements disorders, abnormal posturing and disorders of muscle tone can be present as an integral part of autistic disorder. Hence, a thorough baseline assessment of muscle tone and movement disorders should be conducted prior to initiation of risperidone treatment in order to distinguish movement and muscle tone disorders present in autistic disorder from those induced by medication. Caregivers and patients should be alerted to both movement disorders associated with underlying autism and extrapyramidal symptoms that may emerge in the course of treatment with risperidone. Screening for symptoms of acute movement disorders, as well as tardive dyskinesia, should be part of clinical assessments at each follow-up visit.***

~~In addition to the monitoring of tolerability of treatment, a re-evaluation of the indication for treatment must be made by the specialist at each consultation.~~

A re-evaluation of the indication for treatment must be made by the specialist at each consultation in light of the tolerability and the results of the monitoring detailed above.

The effect of long-term risperidone therapy in autistic children has not been fully assessed. Double-blind control trials have only been conducted for up to 8 weeks with an open label continuation of one of the studies for a further 4 months. Therefore, it is not known what the long-term consequences of weight gain are for these children or what effect the raised prolactin levels will have on growth and sexual maturation. If a child's weight increases by more than 10 percentile points above the expected growth curve fasting blood glucose, lipids and prolactin should be monitored where possible. The need for invasive monitoring must be balanced against any distress caused to the child.

Particular care should be taken if the child is taking fluoxetine (see section 4.5 Interaction with other medicinal products).

In autistic children who have epilepsy, treatment with risperidone should not be initiated for at least 6 months after the last seizure.

Patient Information Leaflet

All the information advised for the SPC needs to be clearly conveyed to the carer of the child receiving medication. The MAH will be asked to develop a PIL specifically for this patient group which will state the indication, dosing, assessment, monitoring and adverse events.

14. RISK MANAGEMENT PLAN AND REGISTRY

The MAH provided an outline for a registry of autistic children on risperidone. It was proposed that the data should be collected from 6 centres of excellence in order to obtain reliable data. This proposal was assessed as being acceptable provided adequate numbers were recruited. The main shortfall was in the duration of the proposed registry of only 3 years, which in view of the nature of the safety problems to be monitored was deemed inadequate. Due to the uncertainty of numbers to be recruited to the registry the agency proposed that the registry remain open until sufficient data had been collected.

15. WITHDRAWAL OF APPLICATION

The company withdrew their application in a letter dated 8th June 2006 stating that they were unable to agree with the wording advised by CSM for the licence (Summary of Product Characteristics) , which according to the Company is not in line with data submitted in support of this application, or specific registry proposals. However, the company had been seeking a wider indication which CSM had assessed as being inappropriate in view of the safety concerns with the use of this product in children and adolescents.

The trial data and expert review has resulted in extensive recommendations which would improve the safety of the prescribing of risperidone. These will not be incorporated into the summary of product characteristics due to the withdrawal of the application by the MAH. The UK paediatric strategy aims to improve the information available on the paediatric use of medicines. This is achieved, in part, by the publication of paediatric assessment reports, irrespective of whether the assessment of data leads to a change in the summary of product characteristics.

DATE :- 12/10/06

RISPERDAL