Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

(Risperidone)
Risperdal

IS/W/0001/pdWS/001

Rapporteur:	Iceland
Finalisation procedure (day 120):	4 November 2012
Date of finalisation of PAR	6 December 2012

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Risperdal (also known as Risperdal Oral)
INN (or common name) of the active substance(s):	Risperidone
MAH (s):	Jansen-Cilag AB
Pharmaco-therapeutic group (ATC Code):	N05AX08
Pharmaceutical form(s) and strength(s):	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 6 mg tablets. Oral solution 1 mg/ml. 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg, oro-dispersible tablets.

I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in sections 4.4 and 2.

Summary of outcome

☐ No change

☒ Change

- ☐ New study data: <section(s) xxxx, xxxx>
- ☐ New safety information: <section(s) xxxx, xxxx>
- ☒ Paediatric information clarified: section(s) SmPC 4.4, PIL 2.
- ☐ New indication: <section(s) xxxx, xxxx>

II. RECOMMENDATION[1]

The rapporteur is of the opinion that the changes in the SmPC and PIL, as proposed by the applicant (see chapter V) are acceptable and Type IB variation is requested from the MAH within 60 days of this report.

III. INTRODUCTION

Only one marketing authorisation holder (MAH), Jansen-Cilag AB, submitted data for Risperidone, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use. The Company currently has risperidone products approved as Risperdal (also known as Risperdal Oral, whose presentations include tablets, orodispersible tablets and an oral solution) and Risperdal CONSTA (a long-acting injectable form). No paediatric indications have been sought for Risperdal CONSTA as this formulation is not considered suitable for paediatric patients. The studies included in this submission relate to the oral presentations of risperidone.

The aim of this EU Worksharing project is the assessment of the clinically relevant information on efficacy and safety data relative to the use of Risperidone in children and adolescents.

The supportive documentation available for from the MAH for this purpose was the following:

1. Use and Safety of Risperidone in Children in Published Literature. A Review of All Sources up to 25 May 2000. Final Version 16 October 2000. Janssen Research Foundation

2. Review of Spontaneous Adverse Events in Children and Adolescents
Receiving RISPERDAL® (Risperidone). From 01 September 2010 to 28 February 2011. Author: Michelle Busch, RN, BSN

Risperidone is approved for the following therapeutic indications:
• for the treatment of schizophrenia.
• for the treatment of moderate to severe manic episodes associated with bipolar disorders.
• for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.
• for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with sub-average intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviors require pharmacologic treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment program, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of conduct disorder of children and adolescents.

After the Article 30 harmonisation, the following statements are in Section 4.2 Posology and Method of Administration of the SmPC:

[1] *The recommendation from section V can be copied in this section*.

"Risperidone is not recommended for use in children/ adolescents under 18 years of age with bipolar mania due to a lack of clinical data."

and

"Risperidone is not recommended for use in children/ adolescents under 18 years of age with schizophrenia due to a lack of clinical data."

Therefore the MAH did not apply for the indication of use of Risperidon for children in the EU in the following conditions: Scizophrenia and Bipolar disoders.

Conduct Disorder and DBD

A number of studies are available in relation to conduct disorder and DBD. Although many of these have formed part of earlier submissions, the following studies were listed on at least 1 country's original Article 45 line listing submission:
RIS-INT-47, PK-7, PK-8, PK-9, PK-11, PK-12, RIS-INT-39, CL-12, N152164,
De Smedt et al, CL-13, CL-14, RIS-CAN-19, RIS-USA-93, RIS-INT-79, RIS-CAN-20,
RIS-USA-97, RIS-INT-41, RIS-INT-70, RIS-HUN-4, RIS-INT-84, RIS-BEL-24,
RIS-NED-9 and RIS-INT-160
The indication resulting from the Article 30 referral review was:

• RISPERDAL is indicated for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviors require pharmacologic treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment program, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of conduct disorder of children and adolescents.

An extensive overview of how this indication was reached is provided in the CHMP assessment report available on the risperidone Article 30 referral on the EMA website.

Autism

The following studies were included as part of an application to register a paediatric indication in Autism in several countries in Europe:
RIS-USA-150, RIS-CAN-23, RIS-BEL-22 and RIS-BEL-21
Prior to MRP harmonisation, an autism indication was approved in a number of member states. However, during the recent Article 30 referral the autism indication was removed.

The following text is taken from the CHMP assessment report on the risperidone Article 30 referral and explains the removal of the autism indication in the post-referral SmPC.

"The CHMP further discussed efficacy in Children and Adolescents with Autistic Disorder, a Pervasive Developmental Disorder that is different from Conduct Disorder which is a Disruptive Behaviour Disorder. As a consequence, children with autistic disorders are not included in the proposed indication. This exclusion is supported by the fact that the primary symptoms of the autism disorder cannot successfully be treated with Risperdal because the target symptoms in autism for which Risperdal has demonstrated its most robust efficacy are associated symptoms rather than a broad spectrum of symptoms of the disease. Because of the lack of specificity and the availability of other treatment options, the CHMP did not consider the indication in Autistic Disorder as

supported."

The MAH stated that the submitted paediatric studies do not influence the benefit risk for RISPERIDONE and that there is no consequential regulatory action.

The MAH does not propose any changes to the SmPC or Patient Information Leaflet (PIL) on the basis of data presented in this submission.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

No quality data was submitted in this application because all studies were conducted with the currently approved formulations. This is acceptable in the context of Article 45.

Rapporteur's comment: Several pharmaceutical forms are marketed for Risperidone, tablets in different dosage and mixture. No specific formulation exists for paediatric usage but dosage range available is convenient in accordance with recommended daily dosage. Long acting formulation is not used in treatment of children and adolescence.
RISPERDAL orodispersible tablets and oral solution are bio-equivalent to RISPERDAL film-coated tablets.

IV.2 Non-clinical aspects

1. Introduction

The MAH did not submit any non-clinical study or data but presented with an overview of preclinical safety data:
In (sub)chronic toxicity studies, in which dosing was started in sexually immature rats and dogs, dose-dependent effects were present in male and female genital tract and mammary gland. These effects were related to the increased serum prolactin levels, resulting from the dopamine D2-receptor blocking activity of risperidone. In addition, tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Risperidone was not teratogenic in rat and rabbit. In rat reproduction studies with risperidone, adverse effects were seen on mating behaviour of the parents, and on the birth weight and survival of the offspring. In rats, intrauterine exposure to risperidone was associated with cognitive deficits in adulthood. Other dopamine antagonists, when administered to pregnant animals, have caused negative effects on learning and motor development in the offspring. Risperidone was not genotoxic in a battery of tests. In oral carcinogenicity studies of risperidone in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were seen. These tumours can be related to prolonged dopamine D2 antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown. In vitro and in vivo, animal models show that at high doses risperidone may cause QT interval prolongation, which has been associated with a theoretically increased risk of torsade de pointes in patients.

Pharmacokinetic properties
The MAH submitted an overview of pharmacokinetic properties:
Risperidone is metabolised to 9-hydroxy-risperidone, which has a similar pharmacological activity to risperidone.

Absorption
Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) compared with a solution. The absorption is not affected by food and thus risperidone can be given with or without meals. Steady-state of risperidone is reached within 1 day in most patients. Steady-state of 9-hydroxy-risperidone is reached within 4-5 days of dosing.

Distribution
Risperidone is rapidly distributed. The volume of distribution is 1-2 l/kg. In plasma, risperidone is bound to albumin and alpha1-acid glycoprotein. The plasma protein binding of risperidone is 90%, that of 9-hydroxy-risperidone is 77%.

Biotransformation and elimination
Risperidone is metabolised by CYP 2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxy-risperidone form the active antipsychotic fraction. CYP 2D6 is subject to genetic polymorphism. Extensive CYP 2D6 metabolisers convert risperidone rapidly into 9-hydroxy-risperidone, whereas poor CYP 2D6 metabolisers convert it much more slowly.
Although extensive metabolisers have lower risperidone and higher 9-hydroxy-risperidone concentrations than poor metabolisers, the pharmacokinetics of risperidone and 9-hydroxy-risperidone combined (i.e., the active antipsychotic fraction), after single and multiple doses, are similar in extensive and poor metabolisers of CYP 2D6.

Another metabolic pathway of risperidone is N-dealkylation. In vitro studies in human liver microsomes showed that risperidone at clinically relevant concentration does not substantially inhibit the metabolism of medicines metabolised by cytochrome P450 isozymes, including CYP 1A2, CYP 2A6, CYP 2C8/9/10,CYP 2D6, CYP 2E1, CYP 3A4, and CYP 3A5. One week after administration, 70% of the dose is excreted in the urine and 14% in the faeces. In urine, risperidone plus 9-hydroxy-risperidone represent 35-45% of the dose. The remainder is inactive metabolites. After oral administration to psychotic patients, risperidone is eliminated with a half-life of about 3 hours. The elimination half-life of 9-hydroxy-risperidone and of the active antipsychotic fraction is 24 hours.

Linearity
Risperidone plasma concentrations are dose-proportional within the therapeutic dose-range.

Paediatric patients
The pharmacokinetics of risperidone, 9-hydroxy-risperidone and the active antipsychotic fraction in children are similar to those in adults.

2. Non clinical study(ies)

None.

IV.3 Clinical aspects

1. Introduction

The MAH, presented an extensive summary on published literature on the use of risperidone (Risperdal) in children and adolescents. The literature search was conducted on 25 May 2000. The search included all available clinical published data up to this date. The JRF database was searched for articles relating to the use of risperidone in children and adolescents. In addition, the Medline database was searched to check the completeness of the data.

In this literature search, after extraction of irrelevant studies, 114 articles were found containing original clinical data, specifically on populations of children and adolescents up to the age of 17 years.
The doses administered ranged from 0.25 to 10 mg/day, and the duration of treatment was up to 3 years.

2. Clinical study(ies)

The following is a list of these relevant studies:

1. Acri AA, Henretig FM: Effects of risperidone in overdose. Am J Emerg Med 16/5: 498-501, 1998.
2. Anderson J, Souire JH: Risperidone in the management of psychotic adolescents - An open trial.
150th Annual Meeting of the American Psychiatric Association, San Diego, California, USA, May 17-22, 1997 (Abstr No. 25): 11-12, 1997
3. Armenteros JL, Whitaker AH, Welikson M, Stedge DJ, Gorman J: Risperidone in adolescents with schizophrenia - An open pilot study. J Am Acad Child Adolesc Psychiatry 36/5: 694-700, 1997.
4. Bhadrinath BR: Olanzapine in Tourette syndrome. Br J Psychiatr 172: 366, 1998
5. Bramble DJ, Cosgrove PVF: Risperidone augmentation therapy in children and young adults. J
Psychopharmacol (Abstr P35) 13/3/Suppl/A: A 18, 1999.
6. Calhoun J, Barry G, Guskin K, Calhoun D: Use of risperidone in adolescents - A retrospective chart review. Schizophr Res 36: 272-273, 1999
7. Carroll NB, Boehm KE, Strickland RT: Chorea and tardive dyskinesia in a patient taking risperidone (Letter). J Clin Psychiatry 60/7: 485-487, 1999
8. Cheslik TA, Erramouspe J: Extrapyramidal symptoms following accidental ingestion of risperidone in a child. Ann Pharmacother 30: 360-363, 1996
9. Cosgrove F: Recent advances in paediatric psychopharmacology (Letter). Hum Psychopharmacol 9: 381-382, 1994
10. Cosgrove PVF: Risperidone added to methylphenidate in attention deficit hyperactivity disorder.
Eur Neuropsychopharmacol (Abstr O-6-5) 6/Suppl/3: 11-12, 1996
11. Cozza SJ, Edison DL: Risperidone in adolescents (Letter). J Am Acad Child Adolesc Psychiatry
33/8: 1211, 1994
12. Crockford DN, Fisher G, Barker P: Risperidone, weight gain, and bulimia nervosa (Letter). Can

J Psychiatry 42/3: 326-327, 1997
13. Daigneault S, Braun CMJ, Bouffard R, Villeneuve L: Pseudoakathisia from an acquired lesion.
Neuropsychiatry Neuropsychocol Behav Neurol 11/3: 164-170, 1998
14. Demb HB, Nguyen KT: Movement disorders in children with developmental disabilities taking risperidone (Letter). J Am Acad Child Adolesc Psychiatry 38/2: 56, 1999
15. Demb HB: Risperidone in young children with pervasive developmental disorders and other developmental disabilities (Letter). J Child Adolesc Psychopharmacol 6/1: 79-80, 1996
16. Dhossche DM, Bouman NH: Catatonia in an adolescent with Prader-Willi syndrome. Ann Clin
Psychiatr 9/4: 247-253, 1997
17. Diaz-Atienza J, Blanquez-Rodriguez MP: Behavioral and neuropsychological phenotype of the
48XXYY syndrome - A longitudinal study of a case. Rev Neurol 29/10: 926-929, 1999
18. Dicker R, Solis S: Risperidone treatment of a psychotic adolescent (Letter). Am J Psychiatry 153/3; 441-442, 1996
19. Doan RJ: Risperidone for insomnia in PDDs (Letter). Can J Psychiatry 43/10: 1050-1051, 199820. Drtílková I: Predbezné zkusenosti s risperidonem u detí s pervazivními vývojovými poruchami
(Preliminary experience with resperidone in children with pervasive developmental disorders). C S Psychiat 95/Suppl/2: 18-21, 1999a
21. Drtílková I: Risperidon u detí a adolescentu se schizofrenními poruchami (Risperidone in children and adolescents with psychotic disorders of the schizophrenic type). C S Psychiat 95/Suppl/2: 22-29, 1999b
22. Dryden-Edwards RC, Reiss AL: Differential response of psychotic and obsessive symptoms to
risperidone in an adolescent. J Child Adolesc Psychopharmacol 6/2: 139-145, 1996
23. Edleman RJ: Risperidone side effects (Letter). J Am Acad Child Adolesc Psychiatry 35/1: 4-5,
1996
24. Feeney DJ, Klykylo W: Risperidone and tardive dyskinesia (Letter). J Am Acad Child Adolesc
Psychiatry 35/11: 1421-1422, 1996
25. Ferrari MC, Elkis H: A six month trial of risperidone versus conventional neuroleptics in young
patients with early onset schizophrenia. Schizophr Res 24/1/2: 194, 1997
26. Findling RL, Maxwell K, Wiznitzer M: An open clinical trial of risperidone monotherapy in young children with autistic disorder. Psychopharmacol Bull 33/1: 155-159, 1997
27. Findling RL, McNamara NK, Branicky LA, Schluchter MD, Lemon E, Blumer JL: A double-blind pilot study of risperidone in the treatment of conduct disorder. J Am Acad Child Adolesc Psychiatry 39/4: 509-516, 2000
28. Fisman S, Steele M: Use of risperidone in pervasive developmental disorders - A case series. J
Child Adolesc Psychopharmacol 6/3: 177-190, 1996
29. Fitzgerald KD, Stewart CM, Tawile V, Rosenberg DR: Risperidone augmentation of serotonin
reuptake inhibitor treatment of pediatric obsessive compulsive disorder. J Child Adolesc Psychopharmacol 9/2: 115-123, 1999
30. Fras I, Major LF: Clinical experience with risperidone (Letter). J Am Acad Child Adolesc Psychiatry 34/7: 833, 1995
31. Frazier JA, Meyer MC, Biederman J, Wozniak J, Wilens TE, Spencer TJ, Kim GS, Shapiro S: Risperidone treatment for juvenile bipolar disorder - A retrospective chart review. J Am Acad Child Adolesc Psychiatry 38/8: 960-965, 1999

32. Frischauf E: Drug therapy in autism (Letter). J Am Acad Child Adolesc Psychiatry 36/5: 577, 1997
33. Gesell LB, Stephen M: Toxicity following a single dose of risperidone for pediatric attention deficit hyperactivity disorder (AHDH). J Toxicol Clin Toxicol 35/5: 549, 1997
34. Gool DA van, Igodt PM: Risperdone in child psychiatry. 151st Annual Meeting of the American
Psychiatric Association, Toronto, Canada, May 30-June 4, 1998 (Abstr NR178): 115, 1998
35. Gram LF: Malignt neuroleptikasyndrom ved behandling med de nye, atypiske antipsykotika, risperidon og olanzapin (Translation – Neuroleptic malignant syndrome associated with risperidone and olanzapine - New atypical antipsychotic agents). Ugeskr Laeger 162/13: 1914-1915, 2000
36. Hanna GL, Fluent TE, Fischer DJ: Separation anxiety in children and adolescents treated with
risperidone. J Child Adolesc Psychopharmacol 9/4: 277-283, 1999
37. Hardan A, Johnson K, Johnson C, Hrecznyj B: Case study - Risperidone treatment of children
and adolescents with developmental disorders. J Am Acad Child Adolesc Psychiatry 35/11: 1551-1556, 1996
38. Healy E, Subotsky F, Pipe R: Quetiapine in adolescent psychosis (Letter): J Am Acad Child Adolesc Psychiatry 38/11: 1329, 1999
39. Heimann SW: High-dose olanzapine in an adolescent (Letter). J Am Acad Child Adolesc Psychiatry 38/5: 496-497, 1999
40. Himstreet JE, Daya M: Hypotension and orthostasis following a risperidone overdose (Letter).
Ann Pharmacother 32: 267, 1998
41. Horrigan J, Sikich L: Diet and the atypical neuroleptics (Letter). J Am Acad Child Adolesc Psychiatry 37/11: 1126-1127, 1998
42. Hrdlicka M, Propper L, Vinar O, Bares M, Lorenc J, Koutek J, Pánková I: Risperidon v akutní lécbe schizofrenie v adolescenci. C S Psychiat 94/3: 131-136, 1998
43. Hudson RG, Cain MP: Risperidone associated haemorrhagic cystitis. J Urol 160/159: 1, 1998
44. Jefferson AM, Markowitz JS, Brewerton TD: Atypical antipsychotics (Letter). J Am Acad Child
Adolesc Psychiatry 37/12: 1243-1244, 1998
45. Kelly DL, Conley RR, Love RC, Horn DS, Ushchak CM: Weight gain in adolescents treated with risperidone and conventional antipsychotics over six months. J Child Adolesc Psychopharmacol 8/3: 151-159, 1998
46. Kleinsasser BJ, Misra LK, Bhatara VS, Sanchez JD: Risperidone in the treatment of choreiform
movements and aggressiveness in a child with "PANDAS". S D J Med 52/9: 345-347, 1999
47. Kotadama S, Morioka H, Fukuzako H, Takigawa M, Kobae H, Oobo Y: A case of idiopathic basal ganglia calcification with schizophrenia-like symptoms (+Translation). Clin Psychiatry 40/11: 1238-1239, 1998
48. Kotsopoulos S, Anderson M, Beggs K, Boyd W, Hiebert A: Risperidone in childhood schizophrenia - A two case report. J Psychopharmacol (Abstr 291) 11/3: A 73, 1997
49. Kramer TM, Cottingham EM: Risperidone in the treatment of steroid-induced psychosis (Letter). J Child Adolesc Psychopharmacol 9/4: 315-316, 1999
50. Kumra S, Herion D, Jacobsen LK, Briguglia C, Grothe D: Case study - Risperidone-induced hepatotoxicity in pediatric patients. J Am Acad Child Adolesc Psychiatry 36/5: 701-705, 1997
51. Landau J, Martin A: Is liver function monitoring warranted during risperidone treatment? (Letter). J Am Acad Child Adolesc Psychiatry 37/10: 1007-1008, 1998
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54. Lombroso PJ, Scahill L, King RA, Lynch KA, Chappell PB, Peterson BS, McDougle CJ, Leckman JF: Risperidone treatment of children and adolescents with chronic tic disorders - A preliminary report. J Am Acad Child Adolesc Psychiatry 34/9: 1147-1152, 1995
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developmental disorder. Psychopharmacol Bull 33/3: 553, 1997
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60. Mandoki MW: Risperidone treatment of children and adolescents with schizophrenic disorder (Abstr 305). Biol Psychiatry 37: 678, 1995b
61. Mandoki MW: Side effects profile of risperidone in the treatment of children and adolescents (Abstr 210). Biol Psychiatry 37: 651, 1995c
62. Mandoki MW: Risperidone in the treatment of children and adolescents with Tourette's disorder
(Abstr 94). Biol Psychiatry 37: 618, 1995d
63. Martin A, Landau J, Leebens P, Ulizio K, Scahill L, Leckman JF: Board 128 - Naturalistic course of risperidone-associated weight gain in hospitalized children and adolescents - A systematic chart review. 38th Annual Meeting of the American College of Neuropsychopharmacology, Acapulco, Mexico, December 12-16, 1999
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65. McDougle CJ, Holmes JP, Bronson MR, Anderson GM, Volkmar FR, Price LH, Cohen DJ: Risperidone treatment of children and adolescents with pervasive developmental disorders - A prospective, open-label study. J Am Acad Child Adolesc Psychiatry 36/5: 685-693, 1997
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72. Okumura K: Puberty schizophrenia and schizophreniform disorder for which risperidone was used. Meeting of the Japanese Society of Clinical Neuropsychopharmacology, Sapporo, Japan, September 17-18, 1998: 78, 1998 (+Translation)
73. Penn JV, Martini J, Radka D: Weight gain associated with risperidone (Letter). J Clin Psychopharmacol 16/3: 259-260, 1996

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38/3: 230, 1999
81. Rowan AB, Malone RP: TICS with risperidone withdrawal (Letter). J Am Acad Child Adolesc Psychiatry 36/2: 162-163, 1997
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by risperidone and pimozide combination (+Translation). Jpn J Clin Psychiatry 27/9: 1149-1155, 1998
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conduct disorder and attention deficit hyperactivity disorder. Int J Neuropsychopharmacol (Abstr PT07038) 2/Suppl/1: S 103, 1998
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Adolesc Psychiatry 38/2: 112-113, 1999a
87. Schaller JL, Behar D: Quetiapine for refracAdolesc Psychiatry 38/5: 498-499, 1999b
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89. Schreier HA: Risperidone for young children with mood disorders and aggressive behavior. J Child Adolesc Psychopharmacol 8/1: 49-59, 1998
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Efficacy results were reported in 92 of the 114 articles containing original data. In 3 of the 22 articles reporting no efficacy results, risperidone was taken in a suicide attempt or accidentally. Of the 92 articles reporting efficacy, 75 articles assessed the treatment with risperidone clearly positive. 11 of the articles reported only some and/or transient improvement or the efficacy results were not definite. In 6 articles the treatment with risperidone resulted in no or only minimal improvement. The only double-blind placebo-controlled study reported a significant difference in the RAAPP score in patients with conduct disorder in favor of risperidone. Furthermore risperidone was superior to placebo in ameliorating aggression. In the only reference-controlled study, the effect of risperidone in patients with schizophrenia was compared to conventional neuroleptics. Significant improvement of the CGI in the risperidone group was observed, and 7 of 8 patients had more than 20% improvement on negative symptoms. Positive results concerning the effectiveness of risperidone were also noted in 22 of 23 open studies. In one open study no efficacy results were reported. The open studies included patients with various psychiatric disorders.

Results of the safety of risperidone were reported in 94 articles in this report. Of these, 8 articles reported that no adverse events had been observed during the treatment with risperidone. Two articles mentioned only the discontinuation because of adverse events (in a total of 4 patients, Anderson & Sourie 1997, Lloyd et al. 1998), and another article only noted that minimal adverse events occurred without further explanation (Cosgrove et al. 1996). A further article stated that adverse events leading to termination of risperidone treatment were low (Bramble & Cosgrove 1999). There is a great variation in reporting adverse events. In some of the articles the frequency of the individual adverse events is noted, in others only the adverse events were reported. Furthermore, some authors report only the main or special adverse events. For that reason, it is not possible to give the overall frequencies of the individual side effects referred to the patients treated with risperidone. On this basis the most frequent adverse events reported were weight gain (27 articles), EPS (21 articles) and sedation (21 articles). Concerning the occurrence of EPS it is important notice that some authors reported only EPS as the sum of the individual symptoms (eg, rigidity, drooling, bradykinesia), other report of parkinsonian symptoms and yet other the individual symptoms.

QTc/QRS abnormalities were reported by Tolbert et al. (1998) and Nasrallah et al. (1997). Tolbert et al. (1998) stated only that these AEs were rare in 15 preadolescents. Nasrallah et al. (1997) reported that QTc/QRS abnormalities occurred in 1 of 15 patients without giving further details. Posey et al. (1999) described one case of QTc prolongation in a 23-month-old boy. The treatment of the patient was complicated by persistent tachycardia. Two initial ECGs done prior to starting risperidone showed normal sinus rhythm with heart rates of 126-147 bpm and a QTc interval of 385-394 msec. An ECG done 1 month after the initiation of risperidone (0.5 mg/day) found a ventricular rate of 187 bpm along with a QTc of 444 msec. Risperidone was reduced to 0.25/day. A subsequent ECG revealed sinus tachycardia at 166 bpm and a QTc of 418 msec. Months later, the dose of risperidone was increased to 0.5 mg/day, with no resultant problems with tachycardia. At last follow-up, the rest heart rate was 110 bpm. QT intervals were corrected for heart rate using Bazett's correction formula. It should be noted that because of the higher heart rates, Fridericia's correction formula is considered more appropriate for correcting the QTc interval than Bazett's formula. However, this information is lacking (Funck-Brentano & Jaillon 1993).

Discontinuation because of adverse events was reported in 31 articles. In three of these articles only the frequency of discontinuation was given, but not the concrete number. Bramble &

Cosgrove (1999) reported that adverse events leading to cessation of risperidone were low (8% of 168 patients), Calhoun et al. (1999) noted a discontinuation rate because of AE of 4% (in 191 patients), and Tolbert et al. (1998) observed a discontinuation rate of 21% (of 39 patients). Excluding these articles, 53 patients stopped treatment with risperidone because of adverse events. Furthermore, Diaz-Atienza & Blánquez-Rodriguez (1999) reported that risperidone had to be withdrawn periodically because of the decompensation that it produced in compulsive eating. The pattern followed consisted in administration of risperidone during the periods of anorexia or normalised appetite and those where hyperphagia was not especially severe. In an additional article it was reported that risperidone, haloperidol and pimozide were discontinued due to either poor control or side effects with no further information (Bhadrinath 1998). Furthermore, Robb et al. (1997) reported NMS in one patient, but the authors did not report discontinuation of therapy.

Furthermore the MAH presented a review of spontaneous adverse events in children and adolescents receiving Risperdal from 01 september 2010 through to 28 february 2011:
This assessment represents the thirteenth 6-month review prepared for Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) as a post-approval commitment to evaluate spontaneous reports from worldwide post-marketing surveillance involving paediatric use of RISPERDAL® (risperidone) for any indication. In 2008, as part of the European Union Risk Management Plan submitted during the Article 30 referral procedure for RISPERDAL® oral formulations, the Company committed to perform this review for an additional 2 years following the completion of the referral and harmonisation of the European Summary of Product Characteristics, which was completed on 07October 2008. The current 6-month paediatric review (data lock 28February 2011) is prepared for submission to AFSSAPS due to lack of confirmation from AFSSAPS whether or not the 6-month paediatric review should be discontinued after fulfilling the 2 year commitment.

Predefined areas of special interest are reviewed in detail, including those outlined by AFSSAPS (tardive dyskinesia, sedative effects, weight gain, endocrine effects, cardiac effects, and metabolic effects) and other areas of special interest under scrutiny for the antipsychotic class of drugs (extrapyramidal symptoms, suicidality, and prolactin-related events). Additional case review was also performed on selected topics based on a review of a frequency tabulation of all events reported in children and adolescents during the 6-month review period (Cytolytic hepatitis, Hepatic failure, Neuroleptic malignant syndrome, Pulmonary embolism, and Pituitary tumour benign) and based on topics of potential medical significance(cases reporting events with a fatal outcome, medication errors, overdose, and drug abuse/misuse). All spontaneous cases received from 01 September 2010 to 28February 2011 in SCEPTRE, the Global Medical Safety (GMS) Safety Database, were compared by age group (5 to 17 years versus all other age groups, i.e., those patients ≥18 years of age and <5 years of age) using proportional reporting ratios (PRR) for each Preferred Term (PT) reported in 3 or more paediatric cases, select PTs, and groups of PTs of interest. The term “disproportionality” is applied in this review to PTs reported in 3 or more cases with a PRR of 2 or more. PTs of interest are identified if disproportionality was present among children and adolescents both during the current review period and in the cumulative data through 28 February 2011. There were 223 medically confirmed cases involving children or adolescents (ages 5 to 17 years) received during the current review period, of which approximately 49% were serious.
The patterns of disproportionately reported PTs observed during this review period were generally consistent with those identified during the prior review periods. The 6 PTs that demonstrated disproportionality for both the current and the cumulative reporting periods are Abnormal behaviour, Aggression, Gynaecomastia, Impulsive behaviour, Type 1 diabetes mellitus, and Off label use. Based on an estimated 2,318,590 person-years of exposure in children or adolescents (ages 5 to 17 years) cumulatively, the 6 events that showed

disporportionality for the current and cumulative period were very rarely reported based on CIOMS criteria.
The PTs Abnormal behaviour, Aggression, and Impulsive behaviour are unlisted in the current risperidone CCDS (January 2011). Causal assessments of these events were limited because of: confounding of cases by concurrent conditions/medical history and/or concomitant medications; implausible latencies (i.e., time from exposure to onset of event); or insufficient information.
These events could also be manifestations of the underlying conditions for which risperidone was prescribed. The most frequently reported off label uses of risperidone during the review period were treatment of ADHD (8 cases) and administration of the long-acting injectable formulation (microspheres) to patients under the age of 18 years (5 cases). No new safety issues were identified from these off label uses.

The predefined areas of special interest did not show disproportionality of reporting for children and adolescents when compared to all other age groups for this review period, except for ocular manifestations of EPS and sedation-related events and the PTs Gynaecomastia and Type 1 diabetes mellitus, which are all known ADRs listed in the current risperidone CCDS. AEs reported in association with the predefined areas of special interest were consistent with the known safety profile for risperidone. No new safety issues were identified. Of the 3 fatal cases reviewed, assessment of 2 cases reporting fatal drug toxicity was confounded by ingestion of an overdose of multiple drugs with risperidone. Minimal details were provided in both of these cases. The role of the IV administration of risperidone in the third case involving NMS with multiple complications is unclear as risperidone dosage and blood levels were not reported. The IV administration of risperidone is not an approved route of administration in the current risperidone CCDS. Review of the fatal cases did not reveal any new safety issues.
Additional case review of Cytolytic hepatitis/Hepatic failure and NMS revealed underlying conditions that confounded the assessment of the cases. Assessment of the single case reporting the PT Pulmonary embolism was confounded by multiple risk factors that are known to be associated with venous thromboembolism(VTE). The Company is conducting a safety assessment to determine if VTEis an ADR associated with risperidone. The outcome of the ongoing assessment of VTE will be included in the next annual Periodic Safety Update Report for risperidone (data lock of 31 May 2011). The single case reporting the PT Pituitary tumour benign provided insufficient information for a meaningful assessment. Based on the review of cases reporting overdose, medication error or intentional drug misuse/abuse, no new safety issues or consistent patterns were identified. Overall, no new safety issues were identified in children and adolescents treated with risperidone during this review period. The current CCDS regarding paediatric safety remains adequate.

Based on the estimated paediatric exposure, AEs were reported uncommonly (<1%) in children and adolescents treated with risperidone duringthe 6-month review interval from 01 September 2010 to 28 February 2011. The majority of the events in children and adolescents over the life of the product through 28February 2011 have been nonserious. In general, the pattern of AEs is consistent with the known safety profile for risperidone as reflected in the product's current CCDS. No new safety concerns specifically occurring in children and adolescents receiving risperidone were identified during this review interval. The current CCDS regarding paediatric safety remains adequate.

The report from the MAH includes comprehensive tables listing AEs. They are very informative.

The MAH report summarizes original clinical safety data related to risperidone use in children and adolescents as reported in 114 articles identified in literature searches covering the period up to the 25 May 2000. Most of the articles are case reports or chart reviews. There is only one

double-blind, placebo-controlled and one comparative, reference-controlled study in children and adolescents in this search. Additionally, there are 23 open studies.
There is a great variation in the way information was presented in the articles. In some of the articles, number of patients, diagnoses, dosage, duration of treatment, efficacy results, and/or adverse events are not reported. A large number of diagnoses were present in the case reports and studies reported in the articles. Furthermore, a great number of patients was treated with risperidone in combination with other medications. This resulted in a great heterogeneity of data which made it difficult to draw specific conclusions.
Overall, data were reported for more than 1,442 subjects. Efficacy results were reported in 92 articles. The majority of articles assessed the effectiveness of risperidone positively.
Results of the safety of risperidone were reported in 94 articles. There is a great variation in reporting adverse events. In some articles, only general statements on the safety of risperidone were made. Some of the articles reported the frequency of the individual adverse events, in others only the adverse events were noted. Furthermore, some authors report only the main or specific side effects. For that reason, it is not possible to give the overall frequencies of the individual adverse events referred to the patients treated with risperidone. The most frequent adverse events reported were weight gain (27 articles), EPS (21 articles) and sedation (21 articles). Serious adverse events were reported in 7 cases. NMS was noted in 4 patients, and tardive dyskinesia in 2 patients. Toxic carbamazepine level after initiation of risperidone was observed in one case. A trial on pharmacokinetic interaction performed by JRF, however, does not indicate that risperidone would increase carbamazepine level (see Tittelboom 1998).
All of the adverse events reported in these articles are already known and no new adverse event was reported.
An overdose of risperidone (accidentally or in a suicide attempt) was described in four cases. No deaths were reported in children and adolescents.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Comments from Rapporteur and Member States**

1. Update of chapter 4.4 in SmPC with regard to attention and follow up on weight gain is recommended.

COMPANY RESPONSE: To address the Rapporteur's comments on weight, the Company proposes to include the following statement in the third paragraph of the 'Children and Adolescent' subsection of Section 4.4 of the Summary of Product Characteristics (SmPC), after the first sentence: 'Baseline weight measurement prior to treatment and regular weight monitoring are recommended.'
In addition, the Company proposes to include the following wording in the 'Children and Adolescent' subsection of Section 2 of the Patient Information Leaflet (PIL):'Before treatment is started your, or your child's body weight may be measured and it may be regularly monitored during treatment.'
The Company believes that the following, current wording, in the 'Children and Adolescents' subsection of Section 4.4 of the SmPC, adequately addresses the Rapporteur's concerns with regard to the assessment of extrapyramidal symptoms: 'During treatment with risperidone regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.' The proposed changes to the SmPC and PIL are annotated in the current versions of the SmPC and PIL, which are provided with this response document.

2. In section 4.4 of the SmPC already contains a statement that 'Weight should be monitored regularly', however, this is not under the 'Children and adolescents' subheading.

COMPANY RESPONSE: The Company proposes to amend the SmPC (Section 4.4, Children and Adolescents) and the PIL (Section 2, Children and Adolescents) as described above in Section 1 of this response.

3. The member state would also like to note that the company's conclusion that 'AEs were reported uncommonly (<1%) in children and adolescents during the 6 month review period' is inadmissible, as the denominator is not known and underreporting cannot be excluded.

COMPANY RESPONSE: The Company acknowledges the comment regarding adverse event (AE) frequency based on estimated paediatric exposure. Nevertheless, the conclusion of the review of spontaneous AEs in children and adolescents receiving RISPERDAL from 01 September 2010 through to 28 February 2011 remains that the majority of the events in children and adolescents over the life of the product through 28 February 2011 have been nonserious. In general, the pattern of the AEs is consistent with the known safety profile for risperidone as reflected in the product's current Company Core Data Sheet. No new safety concerns specifically occurring in children and adolescents receiving risperidone were identified during this review interval.

4. The company was asked to provide the actual state of the paediatric study RIS-NAP-4022 (Post-Marketing Commitment after Art. 30 Referral on Risperdal).

COMPANY RESPONSE: The paediatric study **RIS-NAP-4022** (Post-Marketing Commitment after Article 30 Referral of RISPERDAL) was terminated early due to recruitment issues. The early termination was agreed with the Reference Member State (BfArM) and European Medicines Agency and the final study report was submitted to all Concerned Member States on 29 December 2011.

- **Overall conclusion**

Risperidone has proven efficacious in the paediatric population from age 5 and has been in clinical use in this age group for a long time. The most frequent AEs in children and adolescence are sedation, weight gain and EPS. These AEs are clinically well known and these aspects are already mentioned in the SmPC. However this assessment lead to recommendations for clarifications of the SmPC, especially in regards to monitoring of weight gain. The company has responded well to recommendations from Assessor and Member states with changes in the text of SmPC increasing awareness of possible weight gain and of clarification and focus on monitoring of weight.

- **Recommendation**

The rapporteur is of the opinion that the changes in the SmPC and PIL, as proposed by the applicant (see chapter V) are acceptable and Type IB variation is requested from the MAH within 60 days of this report.

SmPC
4.4 Special warnings and special precautions for use
include the following statement in the third paragraph of the 'Children and Adolescent' subsection, after the first sentence: 'Baseline weight measurement prior to treatment and regular weight monitoring are recommended.'

PIL
2. What you need to know before you /../ is given to you:
Warnings and precautions
include the following wording in the 'Children and Adolescent' subsection:'Before treatment is started your, or your child's body weight may be measured and it may be regularly monitored during treatment.'

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

The list can be taken from the spreadsheet compiled from the EMA