East London NHS
NHS Foundation Trust

| Document control summary | |
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| Title | **Guidelines for the use of ORAL RISPERIDONE in the short-term management of severe behavioural disturbance in AUTISTIC CHILDREN and ADOLESCENTS (aged 5 to 18 years)** |
| Purpose of document | To present the evidence for and offer guidelines on the prescribing & monitoring of oral risperidone in the short-term management of severe behavioural disturbance in autistic children and adolescents aged 5 to 18 years |
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# INDEX

# 1. Introduction

### Autism Spectrum Disorders (ASD)

Autism is defined by three core features: abnormal interaction, communication impairment and stereotyped behaviours with limited activities and interests[1]. ASD sufferers present a particular challenge in relation to challenging behaviour, hyperactivity and other behaviour disorders. Individuals with autism often have difficulty in expressing emotion and may indulge in repetitive stereotypical behaviours, rocking movements or repetitive self-injury as part of an autistic habit or obsession and similarly may have a very different potential for the localisation and appreciation of pain compared to the general population. Similarly people with autism can be almost catastrophically upset by relatively minor changes in their environment.

### Antipsychotics and Autism Spectrum Disorders (ASD)

Antipsychotics are the most frequently used psychotropic agents used in autism. Typical antipsychotics were traditionally used, and haloperidol has been shown to reduce motor stereotypies, hyperactivity, temper tantrums, and improve social relatedness[2]. Limiting their use however has been the extrapyramidal side effects (EPSE) seen with these older drugs. The risk of EPSE may be greater in young patients anyway, because the number of striatal dopamine $D_2$ receptors declines after childhood[1]. Since the introduction of the atypical antipsychotics, a new opportunity has arisen for the use of these drugs in ASD, as they carry a lower risk of causing EPSE and possibly tardive dyskinesia. There are however other side effects such as weight gain which can compromise the safe and effective use of these drugs in this patient population. The use of antipsychotics in paediatric populations for all indications has been largely guided by evidence and experience in adults, and is not based on paediatric dosing studies. It is important to bear in mind that the pharmacokinetics of these drugs may be different in children and adolescents compared to adults.

### Risperidone

Risperidone has been the most widely used atypical antipsychotic in autism. It was introduced in the early 1990s as the second atypical antipsychotic drug after clozapine in 1959. It was first synthesized and developed by Janssen Pharmaceuticals in Belgium. It is a potent blocker of central 5-HT2a receptors and dopamine D2 receptors.

**Licenses for Risperidone –** note changes in license from December 2008 & changes to SPC following pan-European harmonisation of indications.

The licensed indications in the UK for risperidone (as of December 2008) include the treatment of –

1 - schizophrenia,

2 - the treatment of moderate to severe manic episodes associated with bipolar disorders,

3 - 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 and

4 - 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 behaviours require pharmacological treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment programme, 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. (UK Summary of the Product Characteristics (SPC)).

The use of Risperidone is not recommended in the UK for use in children under 18 years of age for either schizophrenia or bipolar disorders.
The licensed indications in the USA for children and adolescents for risperidone include treatment of schizophrenia in adolescents, aged 13 to 17 years, and for the short term treatment of manic or mixed episodes of bipolar 1 disorder in children and adolescents aged 10 to 17 years (since August 2007). In October 2006 the US FDA approved risperidone for the treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years.

**Application to the UK licensing authority: Medicines & healthcare Regulatory Agency (MHRA)**

The license holder for risperidone, Janssen-Cilag, applied to the MHRA for a license to be used for 'irritability in autism'. Efficacy for this indication has been demonstrated in two double blind placebo controlled studies with risperidone[4,5]. Janssen-Cilag withdrew the application however because the MHRA offered only a conditional approval limiting the use of risperidone and placing certain conditions on the license including safety monitoring.

# 2. UK Summary of the product characteristics (SPC)

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| **1.** NAME OF THE MEDICINAL PRODUCT | RISPERDAL▼* 0.5,1, 2, 3, 4 and 6 mg film-coated tablets<br>RISPERDAL▼* 1mg/ml oral solution<br>RISPERDAL Quicklet▼* 0.5,1, 2, 3 & 4 mg orodispersible tablets<br>**Intensive monitoring is requested only when used for the recently licensed indications of short-term treatment of persistent aggression in Alzheimer's dementia and conduct disorder in children* |
| **2.** QUALITATIVE AND QUANTITATIVE COMPOSITION | *Film-coated Tablets:*<br>Each film-coated tablet contains 0.5,1, 2, 3, 4 or 6 mg of risperidone<br>Excipients: Each 0.5 mg film-coated tablet contains 91 mg lactose<br>Each 1 mg film-coated tablet contains 131 mg lactose<br>Each 2 mg film-coated tablet contains 130 mg lactose and 0.05 mg orange yellow S aluminium lake (E110)<br>Each 3 mg film-coated tablet contains 195 mg lactose<br>Each 4 mg film-coated tablet contains 260 mg lactose<br>Each 6 mg film-coated tablet contains 115 mg lactose and 0.01 mg orange yellow S aluminium lake (E110)<br>*Oral Solution:*1 ml oral solution contains 1 mg of risperidone<br>*Orodispersible Tablets:* Each orodispersible tablet contains 0.5,1,2,3 or 4 mg of risperidone<br>Excipients: Each 0.5 mg orodispersible tablet contains 0.25 mg aspartame (E951)<br>Each 1 mg orodispersible tablet contains 0.5 mg aspartame (E951)<br>Each 2 mg orodispersible tablet contains 0.75 mg aspartame (E951)<br>Each 3 mg orodispersible tablet contains 1.125 mg aspartame (E951)<br>Each 4 mg orodispersible tablet contains 1.5 mg aspartame (E951)<br>For a full list of excipients, see section 6.1. |
| **3.** PHARMACEUTICAL FORM | *Film-coated Tablets:*<br>Film-coated tablet<br>0.5 mg risperidone as brownish-red half-scored oblong biconvex tablets.<br>1 mg risperidone as white half-scored oblong tablets.<br>2 mg risperidone as orange half-scored oblong tablets.<br>3 mg risperidone as yellow half-scored oblong tablets<br>4 mg risperidone as green half-scored oblong tablets.<br>6 mg risperidone as yellow circular biconvex tablets.<br>The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.<br>*Oral Solution:*<br>Oral solution.<br>The solution is clear and colourless<br>*Orodispersible Tablets:*<br>Orodispersible tablet<br>0.5 mg risperidone as light coral, round, biconvex tablets<br>1 mg risperidone as light coral, square, biconvex tablets<br>2 mg risperidone as coral, square, biconvex tablets<br>3 mg risperidone as coral, round, biconvex tablets<br>4 mg risperidone as coral, round, biconvex tablets<br>Oro-dispersible tablets are etched on one side with R 0.5, R1, R2, R3, and R4 respectively. |
| **4. CLINICAL PARTICULARS** | |
| **4.1 Therapeutic indications** | RISPERDAL is indicated for the treatment of schizophrenia.<br>RISPERDAL is indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders.<br>RISPERDAL is indicated 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.<br>RISPERDAL is indicated for the short-term 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 behaviours require pharmacologic treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment programme, 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. |
| **4.2 Posology and method of administration** | Schizophrenia *Adults* RISPERDAL may be given once daily or twice daily.<br>Patients should start with 2 mg/day risperidone. The dosage may be increased on the second day to 4 mg. Subsequently, the dosage can be maintained unchanged, or further individualised, if |

needed. Most patients will benefit from daily doses between 4 and 6 mg. In some patients, a slower titration phase and a lower starting and maintenance dose may be appropriate.
Doses above 10 mg/day have not demonstrated superior efficacy to lower doses and may cause increased incidence of extrapyramidal symptoms. Safety of doses above 16 mg/day has not been evaluated, and are therefore not recommended.
*Elderly*
A starting dose of 0.5 mg twice daily is recommended. This dosage can be individually adjusted with 0.5 mg twice daily increments to 1 to 2 mg twice daily.
*Paediatric population*
Risperidone is not recommended for use in children below age 18 with schizophrenia due to a lack of data on efficacy.
Manic episodes in bipolar disorder
*Adults*
RISPERDAL should be administered on a once daily schedule, starting with 2 mg risperidone. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. Risperidone can be administered in flexible doses over a range of 1 to 6 mg per day to optimize each patient's level of efficacy and tolerability. Daily doses over 6 mg risperidone have not been investigated in patients with manic episodes.
As with all symptomatic treatments, the continued use of RISPERDAL must be evaluated and justified on an ongoing basis.
Elderly
A starting dose of 0.5 mg twice daily is recommended. This dosage can be individually adjusted with 0.5 mg twice daily increments to 1 to 2 mg twice daily. Since clinical experience in elderly is limited, caution should be exercised.
*Paediatric population*
Risperidone is not recommended for use in children below age 18 with bipolar mania due to a lack of data on efficacy.
Persistent aggression in patients with moderate to severe Alzheimer's dementia
A starting dose of 0.25 mg twice daily is recommended. This dosage can be individually adjusted by increments of 0.25 mg twice daily, not more frequently than every other day, if needed. The optimum dose is 0.5 mg twice daily for most patients. Some patients, however, may benefit from doses up to 1 mg twice daily.
RISPERDAL should not be used more than 6 weeks in patients with persistent aggression in Alzheimer's dementia. During treatment, patients must be evaluated frequently and regularly, and the need for continuing treatment reassessed.
Conduct disorder
*Children and adolescents from 5 to 18 years of age*
For subjects ≥50 kg, a starting dose of 0.5 mg once daily is recommended. This dosage can be individually adjusted by increments of 0.5 mg once daily not more frequently than every other day, if needed. The optimum dose is 1 mg once daily for most patients. Some patients, however, may benefit from 0.5 mg once daily while others may require 1.5 mg once daily. For subjects <50 kg, a starting dose of 0.25 mg once daily is recommended. This dosage can be individually adjusted by increments of 0.25 mg once daily not more frequently than every other day, if needed. The optimum dose is 0.5 mg once daily for most patients. Some patients, however, may benefit from 0.25 mg once daily while others may require 0.75 mg once daily.
As with all symptomatic treatments, the continued use of RISPERDAL must be evaluated and justified on an ongoing basis.
RISPERDAL is not recommended in children less than 5 years of age, as there is no experience in children less than 5 years of age with this disorder.
Renal and hepatic impairment
Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than in adults with normal renal function. Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone.
Irrespective of the indication, starting and consecutive dosing should be halved, and dose titration should be slower for patients with renal or hepatic impairment.
RISPERDAL should be used with caution in these groups of patients.
Method of administration
RISPERDAL is for oral use. Food does not affect the absorption of RISPERDAL.
Upon discontinuation, gradual withdrawal is advised. Acute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotic medicines (see section 4.8). Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported.
*Switching from other antipsychotics.*
When medically appropriate, gradual discontinuation of the previous treatment while RISPERDAL therapy is initiated is recommended. Also, if medically appropriate, when switching patients from

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| | depot antipsychotics, initiate RISPERDAL therapy in place of the next scheduled injection. The need for continuing existing anti-Parkinson medicines should be re-evaluated periodically.<br>*RISPERDAL oral solution:* For instructions on handling RISPERDAL oral solution see section 6.6.<br>*RISPERDAL orodispersible tablets:* Do not open the blister until ready to administer. Peel open the blister to expose the tablet. Do not push the tablet through the foil because it may break. Remove the tablet from the blister with dry hands. Immediately place the tablet on the tongue. The tablet will begin disintegrating within seconds. Water may be used if desired. |
| **4.3 Contraindications** | Hypersensitivity to the active substance or to any of the excipients. |
| **4.4 Special warnings and precautions for use** | Elderly patients with dementia<br>*Overall mortality*<br>Elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotics, including RISPERDAL. In placebo-controlled trials with RISPERDAL in this population, the incidence of mortality was 4.0% for RISPERDAL-treated patients compared to 3.1% for placebo-treated patients. The odds ratio (95% exact confidence interval) was 1.21 (0.7, 2.1). The mean age (range) of patients who died was 86 years (range 67-100).<br>*Concomitant use with furosemide*<br>In the RISPERDAL placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.<br>No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination or co-treatment with other potent diuretics should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.<br>Cerebrovascular Adverse Events (CVAE)<br>In placebo-controlled trials in elderly patients with dementia there was a significantly higher incidence (approximately 3-fold increased) of CVAEs, such as stroke (including fatalities) and transient ischaemic attack in patients treated with RISPERDAL compared with patients treated with placebo (mean age 85 years; range 73 to 97). The pooled data from six placebo-controlled studies in mainly elderly patients (>65 years of age) with dementia showed that CVAEs (serious and non-serious, combined) occurred in 3.3% (33/1009) of patients treated with risperidone and 1.2% (8/712) of patients treated with placebo. The odds ratio (95% exact confidence interval) was 2.96 (1.34, 7.50). The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. RISPERDAL should be used with caution in patients with risk factors for stroke.<br>The risk of CVAEs was significantly higher in patients with mixed or vascular type of dementia when compared to Alzheimer's dementia. Therefore, patients with other types of dementias than Alzheimer's should not be treated with risperidone.<br>Physicians are advised to assess the risks and benefits of the use of RISPERDAL in elderly patients with dementia, taking into account risk predictors for stroke in the individual patient.<br>Patients/caregivers should be cautioned to immediately report signs and symptoms of potential CVAEs such as sudden weakness or numbness in the face, arms or legs, and speech or vision problems. All treatment options should be considered without delay, including discontinuation of risperidone.<br>RISPERDAL should only be used short term for persistent aggression in patients with moderate to severe Alzheimer's dementia to supplement non-pharmacological approaches which have had limited or no efficacy and when there is potential risk of harm to self or others.<br>Patients should be reassessed regularly, and the need for continuing treatment reassessed.<br>Orthostatic hypotension<br>Due to the alpha-blocking activity of risperidone, (orthostatic) hypotension can occur, especially during the initial dose-titration period. Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment. RISPERDAL should be used with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended (see section 4.2). A dose reduction should be considered if hypotension occurs.<br>Tardive dyskinesia/extrapyramidal symptoms (TD/EPS)<br>Medicines with dopamine receptor antagonistic properties have been associated with the |

induction of tardive dyskinesia characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. The onset of extrapyramidal symptoms is a risk factor for tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics should be considered.

Neuroleptic malignant syndrome (NMS)

Neuroleptic Malignant Syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels has been reported to occur with antipsychotics. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, all antipsychotics, including RISPERDAL, should be discontinued.

Parkinson's disease and dementia with Lewy bodies

Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including RISPERDAL, to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB). Parkinson's Disease may worsen with risperidone. Both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medicinal products; these patients were excluded from clinical trials. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Hyperglycemia

Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with RISPERDAL. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Hyperprolactinaemia

Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. RISPERDAL should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours.

QT prolongation

QT prolongation has very rarely been reported postmarketing. As with other antipsychotics, caution should be exercised when risperidone is prescribed in patients with known cardiovascular disease, family history of QT prolongation, bradycardia, or electrolyte disturbances (hypokalaemia, hypomagnesaemia), as it may increase the risk of arrhythmogenic effects, and in concomitant use with medicines known to prolong the QT interval.

Seizures

RISPERDAL should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Priapism

Priapism may occur with RISPERDAL treatment due to its alpha-adrenergic blocking effects.

Body temperature regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines. Appropriate care is advised when prescribing RISPERDAL to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g. exercising strenuously, exposure to extreme heat, receiving concomitant treatment with anticholinergic activity, or being subject to dehydration.

Children and adolescents

Before risperidone is prescribed to a child or adolescent with conduct disorder they should be fully assessed for physical and social causes of the aggressive behaviour such as pain or inappropriate environmental demands.

The sedative effect of risperidone should be closely monitored in this population because of possible consequences on learning ability. A change in the time of administration of risperidone could improve the impact of the sedation on attention faculties of children and adolescents.

Risperidone was associated with mean increases in body weight and body mass index (BMI). Changes in height in the long-term open-label extension studies were within expected age-appropriate norms. The effect of long-term risperidone treatment on sexual maturation and height have not been adequately studied.

Because of the potential effects of prolonged hyperprolactinemia on growth and sexual maturation in children and adolescents, regular clinical evaluation of endocrinological status should be considered, including measurements of height, weight, sexual maturation, monitoring of menstrual functioning, and other potential prolactin-related effects.

During treatment with risperidone regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.

For specific posology recommendations in children and adolescents see Section 4.2.

Excipients

The film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this

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| | medicine.<br>The 2 mg and 6 mg film-coated tablets contain sunset yellow (E110). May cause allergic reactions.<br>The orodispersible tablets contain aspartame. Aspartame is a source of phenylalanine which may be harmful for people with phenylketonuria. |
| **4.5 Interaction with other medicinal products and other forms of interaction** | As with other antipsychotics, caution is advised when prescribing risperidone with medicinal products known to prolong the QT interval, e.g. class Ia antiarrhythmics (e.g. quinidine, dysopiramide, procainamide), class III antiarrhythmics (e.g. amiodarone, sotalol), tricyclic antidepressant (i.e. amitriptyline), tetracyclic antidepressants (i.e. maprotiline), some antihistaminics, other antipsychotics, some antimalarials (i.e. chinice and mefloquine), and with medicines causing electrolyte imbalance (hypokalaemia, hypomagnesiaemia), bradycardia, or those which inhibit the hepatic metabolism of risperidone. This list is indicative and not exhaustive.<br>*Potential for RISPERDAL to affect other medicinal products*<br>Risperidone should be used with caution in combination with other centrally-acting substances notably including alcohol, opiates, antihistamines and benzodiazepines due to the increased risk of sedation.<br>RISPERDAL may antagonise the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.<br>Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment.<br>RISPERDAL does not show a clinically relevant effect on the pharmacokinetics of lithium, valproate, digoxin or topiramate.<br>*Potential for other medicinal products to affect RISPERDAL*<br>Carbamazepine has been shown to decrease the plasma concentrations of the active antipsychotic fraction of risperidone. Similar effects may be observed with e.g. rifampicin, phenytoin and phenobarbital which also induce CYP 3A4 hepatic enzyme as well as P-glycoprotein. When carbamazepine or other CYP 3A4 hepatic enzyme/P-glycoprotein (P-gp) inducers are initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL.<br>Fluoxetine and paroxetine, CYP 2D6 inhibitors, increase the plasma concentration of risperidone, but less so of the active antipsychotic fraction. It is expected that other CYP 2D6 inhibitors, such as quinidine, may affect the plasma concentrations of risperidone in a similar way. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL.<br>Verapamil, an inhibitor of CYP 3A4 and P-gp, increases the plasma concentration of risperidone.<br>Galantamine and donepezil do not show a clinically relevant effect on the pharmacokinetics of risperidone and on the active antipsychotic fraction.<br>Phenothiazines, tricyclic antidepressants, and some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction.<br>The combined use of psychostimulants (e.g. methylphenidate) with RISPERDAL in children and adolescents did not alter the pharmacokinetics and efficacy of RISPERDAL.<br>See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.<br>Concomitant use of oral RISPERDAL with paliperidone is not recommended as paliperidone is the active metabolite of risperidone and the combination of the two may lead to additive active antipsychotic fraction exposure. |
| **4.6 Pregnancy and lactation** | As with other antipsychotics, caution is advised when prescribing risperidone with medicinal products known to prolong the QT interval, e.g. class Ia antiarrhythmics (e.g. quinidine, dysopiramide, procainamide), class III antiarrhythmics (e.g. amiodarone, sotalol), tricyclic antidepressant (i.e. amitriptyline), tetracyclic antidepressants (i.e. maprotiline), some antihistaminics, other antipsychotics, some antimalarials (i.e. chinice and mefloquine), and with medicines causing electrolyte imbalance (hypokalaemia, hypomagnesiaemia), bradycardia, or those which inhibit the hepatic metabolism of risperidone. This list is indicative and not exhaustive.<br>*Potential for RISPERDAL to affect other medicinal products*<br>Risperidone should be used with caution in combination with other centrally-acting substances notably including alcohol, opiates, antihistamines and benzodiazepines due to the increased risk of sedation. |

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| **4.7 Effects on ability to drive and use machines** | RISPERDAL can have minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects (see section 4.8). Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known. |
| **4.8 Undesirable effects** | The most frequently reported adverse drug reactions (ADRs) (incidence ≥ 10%) are: Parkinsonism, headache, and insomnia.<br>The following are all the ADRs that were reported in clinical trials and postmarketing. The following terms and frequencies are applied:<br>very common ( ≥ 1/10), common ( ≥ 1/100 to <1/10),<br>uncommon ( ≥ 1/1000 to <1/100), rare ( ≥ 1/10,000 to <1/1000),<br>very rare (<1/10,000), and not known (cannot be estimated from the available clinical trial data).<br>Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.<br>Adverse Drug Reactions by System Organ Class and Frequency<br>**Investigations**<br>*Common* — Blood prolactin increased[a] , Weight increased<br>*Uncommon* — Electrocardiogram QT prolonged, Electrocardiogram abnormal, Blood glucose increased, Transaminases increased, White blood cell count decreased Body temperature increased, Eosinophil count increased, Haemoglobin decreased, Blood creatine phosphokinase increased<br>*Rare* — Body temperature decreased<br>**Cardiac disorders**<br>*Common* — Tachycardia<br>*Uncommon* — Atrioventricular block, Bundle branch block, Atrial fibrillation, |

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| | | Sinus bradycardia, Palpitations |
| | **Blood and lymphatic system disorders** | |
| | *Uncommon* | Anaemia, Thrombocytopenia |
| | *Rare* | Granulocytopenia |
| | *Not known* | Agranulocytosis |
| | **Nervous system disorders** | |
| | *Very common* | Parkinsonism[b] , Headache |
| | *Common* | Akathisia[b] , Dizziness, Tremor[b] , Dystonia[b] , Somnolence, Sedation, Lethargy, Dyskinesia[b] |
| | *Uncommon* | Unresponsive to stimuli, Loss of consciousness, Syncope, Depressed level of consciousness, Cerebrovascular accident, Transient ischaemic attack, Dysarthria, Disturbance in attention, Hypersomnia, Dizziness postural, Balance disorder, Tardive dyskinesia, Speech disorder, Coordination abnormal, Hypoaesthesia |
| | *Rare* | Neuroleptic malignant syndrome, Diabetic coma, Cerebrovascular disorder, Cerebral ischaemia, Movement disorder |
| | **Eye disorders** | |
| | *Common* | Vision blurred |
| | *Uncommon* | Conjunctivitis, Ocular hyperaemia, Eye discharge, Eye swelling, Dry eye, Lacrimation increased, Photophobia |
| | *Rare* | Visual acuity reduced, Eye rolling, Glaucoma |
| | **Ear and labyrinth disorders** | |
| | *Uncommon* | Ear pain, Tinnitus |
| | **Respiratory, thoracic and mediastinal disorders** | |
| | *Common* | Dyspnoea, Epistaxis, Cough, Nasal congestion, Pharyngolaryngeal pain |
| | *Uncommon* | Wheezing, Pneumonia aspiration, Pulmonary congestion, Respiratory disorder, Rales, Respiratory tract congestion, Dysphonia |
| | *Rare* | Sleep apnea syndrome, Hyperventilation |
| | **Gastrointestinal disorders** | |
| | *Common* | Vomiting, Diarrhoea, Constipation, Nausea, Abdominal pain, Dyspepsia, Dry mouth, Stomach discomfort |
| | *Uncommon* | Dysphagia, Gastritis, Faecal incontinence, Faecaloma |
| | *Rare* | Intestinal obstruction, Pancreatitis, Lip swelling, Cheilitis |
| | **Renal and urinary disorders** | |
| | *Common* | Enuresis |
| | *Uncommon* | Dysuria, Urinary incontinence, Pollakiuria |
| | **Skin and subcutaneous tissue disorders** | |
| | *Common* | Rash, Erythema |
| | *Uncommon* | Angioedema, Skin lesion, Skin disorder, Pruritus, Acne, Skin discolouration, Alopecia, Seborrhoeic dermatitis, Dry skin, Hyperkeratosis |
| | *Rare* | Dandruff |
| | **Musculoskeletal and connective tissue disorders** | |
| | *Common* | Arthralgia, Back pain, Pain in extremity |

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| | *Uncommon* | Muscular weakness, Myalgia, Neck pain, Joint swelling, Posture abnormal, Joint stiffness, Musculoskeletal chest pain |
| | *Rare* | Rhabdomyolysis |
| | **Endocrine disorders** | |
| | *Rare* | Inappropriate antidiuretic hormone secretion |
| | **Metabolism and nutrition disorders** | |
| | *Common* | Increased appetite, Decreased appetite |
| | *Uncommon* | Anorexia, Polydipsia |
| | *Very rare* | Diabetic ketoacidosis |
| | *Not known* | Water intoxication |
| | **Infections and infestations** | |
| | *Common* | Pneumonia, Influenza, Bronchitis, Upper respiratory tract infection, Urinary tract infection |
| | *Uncommon* | Sinusitis, Viral infection, Ear infection, Tonsillitis, Cellulitis, Otitis media, Eye infection, Localised infection, Acarodermatitis, Respiratory tract infection, Cystitis, Onychomycosis |
| | *Rare* | Otitis media chronic |
| | **Vascular disorders** | |
| | *Uncommon* | Hypotension, Orthostatic hypotension, Flushing |
| | **General disorders and administration site conditions** | |
| | *Common* | Pyrexia, Fatigue, Peripheral oedema, Asthenia, Chest pain |
| | *Uncommon* | Face oedema, Gait disturbance, Feeling abnormal, Sluggishness, Influenza like illness, Thirst, Chest discomfort, Chills |
| | *Rare* | Generalised oedema, Hypothermia, Drug withdrawal syndrome, Peripheral coldness |
| | **Immune system disorders** | |
| | *Uncommon* | Hypersensitivity |
| | *Rare* | Drug hypersensitivity |
| | *Not known* | Anaphylactic reaction |
| | **Hepatobiliary disorders** | |
| | *Rare* | Jaundice |
| | **Reproductive system and breast disorders** | |
| | *Uncommon* | Amenorrhoea, Sexual dysfunction, Erectile dysfunction, Ejaculation disorder, Galactorrhoea, Gynaecomastia, Menstrual disorder, Vaginal discharge, |
| | *Not known* | Priapism |
| | **Psychiatric disorders** | |
| | *Very common* | Insomnia |
| | *Common* | Anxiety, Agitation, Sleep disorder |
| | *Uncommon* | Confusional state, Mania, Libido decreased, Listless, Nervousness |
| | *Rare* | Anorgasmia, Blunted affect |
| | [a] Hyperprolactinemia can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhoea, galactorrhea.<br>[b] Extrapyramidal disorder may occur: Parkinsonism (salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies, muscle tightness, akinesia, nuchal rigidity, muscle rigidity, parkinsonian gait, and glabellar | |

reflex abnormal),akathisia ( akathisia, restlessness, hyperkinesia, and restless leg syndrome), tremor, dyskinesia (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia.
Dystonia includes dystonia, muscle spasms, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus. Tremor includes tremor and parkinsonian rest tremor. It should be noted that a broader spectrum of symptoms are included, that do not necessarily have an extrapyramidal origin.
The following is a list of additional ADRs associated with risperidone that have been identified as ADRs during clinical trials investigating the long-acting injectable risperidone formulation (RISPERDAL CONSTA) but were not determined to be ADRs in the clinical trials investigating oral RISPERDAL. This table excludes those ADRs specifically associated with the formulation or injection route of administration of RISPERDAL CONSTA.

| Additional Adverse Drug Reactions Reported With RISPERDAL CONSTA but Not With Oral RISPERDAL by System Organ Class |
|---|
| **Investigations** |
| Weight decreased, Gamma-glutamyltransferase increased, Hepatic enzyme increased |
| **Cardiac Disorders** |
| Bradycardia |
| **Blood and Lymphatic Disorders** |
| Neutropenia |
| **Nervous System Disorders** |
| Paresthesia, Convulsion |
| **Eye Disorders** |
| Blepharospasm |
| **Ear and Labyrinth Disorders** |
| Vertigo |
| **Gastrointestinal Disorders** |
| Toothache, Tongue spasm |
| **Skin and Subcutaneous Tissue Disorders** |
| Eczema |
| **Musculoskeletal, Connective Tissue, and Bone Disorders** |
| Buttock pain |
| **Infections and Infestations** |
| Lower respiratory tract infection, Infection, Gastroenteritis, Subcutaneous abscess |
| **Injury and Poisoning** |
| Fall |
| **Vascular Disorders** |
| Hypertension |
| **General Disorders and Administration Site Conditions** |
| Pain |
| **Psychiatric Disorders** |
| Depression |

*Class effects*
As with other antipsychotics, very rare cases of QT prolongation have been reported postmarketing with risperidone. Other class-related cardiac effects reported with

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| | antipsychotics which prolong QT interval include ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia, sudden death, cardiac arrest and Torsades de Pointes.<br>*Weight gain*<br>The proportions of RISPERDAL and placebo-treated adult patients with schizophrenia meeting a weight gain criterion of ≥7% of body weight were compared in a pool of 6- to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL (18%) compared to placebo (9%). In a pool of placebo-controlled 3-week studies in adult patients with acute mania, the incidence of weight increase of ≥7% at endpoint was comparable in the RISPERDAL (2.5%) and placebo (2.4%) groups, and was slightly higher in the active-control group (3.5%).<br>In a population of children and adolescents with conduct and other disruptive behaviour disorders, in long-term studies, weight increased by a mean of 7.3 kg after 12 months of treatment. The expected weight gain for normal children between 5-12 years of age is 3 to 5 kg per year. From 12-16 years of age, this magnitude of gaining 3 to 5 kg per year is maintained for girls, while boys gain approximately 5 kg per year.<br>Additional information on special populations<br>Adverse drug reactions that were reported with higher incidence in elderly patients with dementia or paediatric patients than in adult populations are described below:<br>*Elderly patients with dementia*<br>Transient ischaemic attack and cerebrovascular accident were ADRs reported in clinical trials with a frequency of 1.4% and 1.5%, respectively, in elderly patients with dementia. In addition, the following ADRs were reported with a frequency ≥5% in elderly patients with dementia and with at least twice the frequency seen in other adult populations: urinary tract infection, peripheral oedema, lethargy, and cough.<br>Paediatric patients<br>The following ADRs were reported with a frequency ≥5% in paediatric patients (5 to 17 years) and with at least twice the frequency seen in clinical trials in adults: somnolence/sedation, fatigue, headache, increased appetite, vomiting, upper respiratory tract infection, nasal congestion, abdominal pain, dizziness, cough, pyrexia, tremor, diarrhoea, and enuresis. |
| **4.9 Overdose** | *Symptoms* In general, reported signs and symptoms have been those resulting from an exaggeration of the known pharmacological effects of risperidone. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, QT-prolongation and convulsions have been reported. Torsade de Pointes has been reported in association with combined overdose of RISPERDAL and paroxetine. In case of acute overdose, the possibility of multiple drug involvement should be considered.<br>*Treatment* Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal together with a laxative should be considered only when drug intake was less than one hour before. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. There is no specific antidote to RISPERDAL. Therefore, appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, an anticholinergic medicinal product should be administered. Close medical supervision and monitoring should continue until the patient recovers. |
| **5.** PHARMACOLOGICAL PROPERTIES | |
| **5.1 Pharmacodynamic properties** | *Pharmacotherapeutic group:* Other antipsychotics, ATC code: N05AX08<br>*Mechanism of action*<br>Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-$HT_2$ and dopaminergic $D_2$ receptors. Risperidone binds also to alpha$_1$-adrenergic receptors, and, with lower affinity, to $H_1$-histaminergic and alpha$_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent $D_2$ antagonist, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical antipsychotics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.<br>*Pharmacodynamic effects*<br>*Schizophrenia*<br>The efficacy of risperidone in the short-term treatment of schizophrenia was established in four studies, 4- to 8-weeks in duration, which enrolled over 2500 patients who met DSM-IV criteria for schizophrenia. In a 6-week, placebo-controlled trial involving titration of risperidone in doses up to 10 mg/day administered twice daily, risperidone was superior to placebo on the Brief Psychiatric Rating Scale (BPRS) total score. In an 8-week, placebo-controlled trial involving four fixed doses |

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| | of risperidone (2, 6, 10, and 16 mg/day, administered twice daily), all four risperidone groups were superior to placebo on the Positive and Negative Syndrome Scale (PANSS) total score. In an 8-week, dose comparison trial involving five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day administered twice-daily), the 4, 8, and 16 mg/day risperidone dose groups were superior to the 1 mg risperidone dose group on PANSS total score. In a 4-week, placebo-controlled dose comparison trial involving two fixed doses of risperidone (4 and 8 mg/day administered once daily), both risperidone dose groups were superior to placebo on several PANSS measures, including total PANSS and a response measure (>20% reduction in PANSS total score). In a longer-term trial, adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medicinal product were randomised to risperidone 2 to 8 mg/day or to haloperidol for 1 to 2 years of observation for relapse. Patients receiving risperidone experienced a significantly longer time to relapse over this time period compared to those receiving haloperidol.<br>Manic episodes in bipolar disorder<br>The efficacy of risperidone monotherapy in the acute treatment of manic episodes associated with bipolar I disorder was demonstrated in three double-blind, placebo-controlled monotherapy studies in approximately 820 patients who had bipolar I disorder, based on DSM-IV criteria. In the three studies, risperidone 1 to 6 mg/day (starting dose 3 mg in two studies and 2 mg in one study) was shown to be significantly superior to placebo on the pre-specified primary endpoint, i.e. the change from baseline in total Young Mania Rating Scale (YMRS) score at Week 3. Secondary efficacy outcomes were generally consistent with the primary outcome. The percentage of patients with a decrease of ≥50% in total YMRS score from baseline to the 3-week endpoint was significantly higher for risperidone than for placebo. One of the three studies included a haloperidol arm and a 9-week double-blind maintenance phase. Efficacy was maintained throughout the 9-week maintenance treatment period. Change from baseline in total YMRS showed continued improvement and was comparable between risperidone and haloperidol at Week 12.<br>The efficacy of risperidone in addition to mood stabilisers in the treatment of acute mania was demonstrated in one of two 3-week double-blind studies in approximately 300 patients who met the DSM-IV criteria for bipolar I disorder. In one 3-week study, risperidone 1 to 6 mg/day starting at 2 mg/day in addition to lithium or valproate was superior to lithium or valproate alone on the pre-specified primary endpoint, i.e. the change from baseline in YMRS total score at Week 3. In a second 3-week study, risperidone 1 to 6 mg/day starting at 2 mg/day, combined with lithium, valproate, or carbamazepine was not superior to lithium, valproate, or carbamazepine alone in the reduction of YMRS total score. A possible explanation for the failure of this study was induction of risperidone and 9-hydroxy-risperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxy-risperidone. When the carbamazepine group was excluded in a post-hoc analysis, risperidone combined with lithium or valproate was superior to lithium or valproate alone in the reduction of YMRS total score.<br>*Persistent aggression in dementia*<br>The efficacy of risperidone in the treatment of Behavioural and Psychological Symptoms of Dementia (BPSD), which includes behavioural disturbances, such as aggressiveness, agitation, psychosis, activity, and affective disturbances was demonstrated in three double-blind, placebo-controlled studies in 1150 elderly patients with moderate to severe dementia. One study included fixed risperidone doses of 0.5, 1, and 2 mg/day. Two flexible-dose studies included risperidone dose groups in the range of 0.5 to 4 mg/day and 0.5 to 2 mg/day, respectively. Risperidone showed statistically significant and clinically important effectiveness in treating aggression and less consistently in treating agitation and psychosis in elderly dementia patients (as measured by the Behavioural Pathology in Alzheimer's Disease Rating Scale [BEHAVE-AD] and the Cohen-Mansfield Agitation Inventory [CMAI]). The treatment effect of risperidone was independent of Mini-Mental State Examination (MMSE) score (and consequently of the severity of dementia); of sedative properties of risperidone; of the presence or absence of psychosis; and of the type of dementia, Alzheimer's, vascular, or mixed. (See also section 4.4)<br>*Conduct disorder*<br>The efficacy of risperidone in the short-term treatment of disruptive behaviours was demonstrated in two double-blind placebo-controlled studies in approximately 240 patients 5 to 12 years of age with a DSM-IV diagnosis of disruptive behaviour disorders (DBD) and borderline intellectual functioning or mild or moderate mental retardation/learning disorder. In the two studies, risperidone 0.02 to 0.06 mg/kg/day was significantly superior to placebo on the pre-specified primary endpoint, i.e. the change from baseline in the Conduct Problem subscale of the Nisonger-Child Behaviour Rating Form (N-CBRF) at Week 6. |
| **5.2 Pharmacokinetic properties** | RISPERDAL orodispersible tablets and oral solutionare bio-equivalent to RISPERDAL film-coated tablets.<br>Risperidone is metabolised to 9-hydroxy-risperidone, which has a similar pharmacological activity to risperidone (see *Biotransformation and Elimination*). |

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| | *Absorption*<br>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.<br>*Distribution*<br>Risperidone is rapidly distributed. The volume of distribution is 1-2 l/kg. In plasma, risperidone is bound to albumin and alpha$_1$-acid glycoprotein. The plasma protein binding of risperidone is 90%, that of 9-hydroxy-risperidone is 77%.<br>*Biotransformation and elimination*<br>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.<br>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.<br>*Linearity* Risperidone plasma concentrations are dose-proportional within the therapeutic dose-range.<br>Elderly, hepatic and renal impairment - A single-dose study showed on average a 43% higher active antipsychotic fraction plasma concentration, a 38% longer half-life and a reduced clearance of the active antipsychotic fraction by 30% in the elderly. Higher active antipsychotic fraction plasma concentrations and a reduced clearance of the active antipsychotic fraction by on average 60% were observed in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency, but the mean free fraction of risperidone in plasma was increased by about 35%.<br>*Paediatric patients*- The pharmacokinetics of risperidone, 9-hydroxy-risperidone and the active antipsychotic fraction in children are similar to those in adults.<br>*Gender, race and smoking habits* - A population pharmacokinetic analysis revealed no apparent effect of gender, race or smoking habits on the pharmacokinetics of risperidone or the active antipsychotic fraction. |
| **5.3 Preclinical safety data** | In (sub)chronic toxicity studies, in which dosing was started in sexually immature rats and dogs, dose-dependant 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 $D_2$-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 $D_2$ 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. |
| **6.** PHARMACEUTICAL PARTICULARS | |
| **6.1 List of excipients** | RISPERDAL 0.5,1,2, 3, 4 & 6 mg film-coated tablets:<br>*Tablet core:* Lactose monohydrate, Maize starch, Cellulose microcrystalline (E460), Hypromellose (E464), Magnesium stearate, Silica colloidal anhydrous, Sodium laurilsulfate. |

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| | *Film-coating:* Hypromellose (E464), Propylene glycol (E490), Titanium dioxide (E171): 0.5, 2, 3, 4 & 6 mg; Talc (E553B):0.5, 2, 3, 4 & 6 mg; Red Ferric Oxide (E172): 0.5 mg; Orange yellow S aluminium lake (E110) : 2 & 6 mg; Quinoline yellow (E104): 3, 4 & 6 mg; Indigotindisulfonate aluminium lake (E132): 4 mg<br>RISPERDAL oral solution: Tartaric acid (E334), Benzoic acid (E210), Sodium hydroxide, Purified water<br>RISPERDAL 0.5,1, 2,3 & 4 mg orodispersible tablets: Polacrilex resin, Gelatin (E485), Mannitol (E421), Glycine (E640), Simeticone Carbomer, Sodium hydroxide, Aspartame (E951) Red Ferric Oxide (E172), Peppermint oil, Xanthan Gum (2, 3 & 4 mg orodispersible tablets) |
| **6.2 Incompatibilities** | RISPERDAL oral solution: incompatible with tea. |
| **6.3 Shelf life** | 2 years (0.5 & 6 mg film-coated tablet, 0.5,1, 2,3 & 4 mg orodispersible tablet)<br>3 years (1,2,3 &4 mg film-coated tablet).<br>RISPERDAL oral solution: 3 years. Chemical and physical in-use stability has been demonstrated for 3 months at 25°C. |
| **6.4 Special precautions for storage** | Do not store above 30°C.<br>RISPERDAL orodispersible tablets: Do not store above 30°C. Store in the original package.<br>RISPERDAL oral solution: Do not store above 30°C. Do not freeze. Store in the original package. |
| **6.5 Nature and contents of container** | *Film-coated Tablets*<br>Blister strips consisting of 200 µm polyvinylchloride (PVC)/25 µm low density polyethylene (LDPE)/90 g/$m^2$ polyvinylidene chloride (PVDC) and 20 µm aluminium foil. The strips are packed in cardboard cartons to contain either 6[a], 20, 28[b] or 60 tablets per pack.<br>[a]1mg film-coated tablet only<br>[b]6 mg film-coated tablet only<br>*Oral Solution*<br>Amber glass bottle with a plastic child-resistant and tamper-evident cap. Risperdal Liquid may be presented in bottle sizes of 30 and 100 ml.<br>The pipette supplied with the 30 ml bottle is calibrated in milligrams and milliliters with a minimum volume of 0.25 ml and a maximum volume of 3 ml. Calibration marks every 0.25 ml up to 3 ml are printed on this pipette.<br>The pipette supplied with the 100 ml bottle is calibrated in milligrams and milliliters with a minimum volume of 0.25 ml and a maximum volume of 3 ml. Calibration marks every 0.25 ml up to 3 ml are printed on this pipette.<br>*Note:* not all bottle sizes are marketed.<br>*Orodispersible Tablets*<br>Blister strips consisting of polychlorotrifluoroethylene/polyvinylchloride/polyethylene film and aluminium foil (film/foil) or aluminium foil and aluminium foil (foil/foil). The strips are packed in cardboard cartons to contain 8, 28 or 56 tablets per pack. |
| **6.6 Special precautions for disposal and other handling** | Film-coated Tablets: No special requirement. Oro-dispersible Tablets (see section 4.2)<br>Oral Solution |

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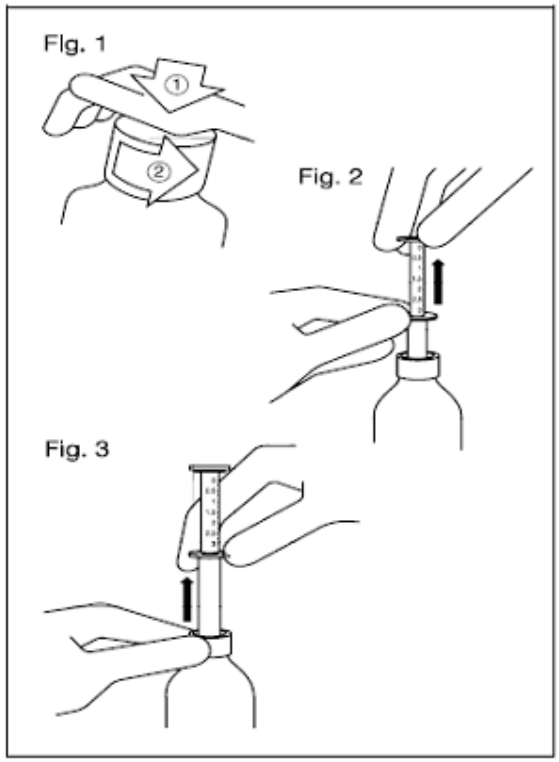
| | Fig. 1: The bottle comes with a child-resistant cap, and should be opened as follows: – Push the plastic screw cap down while turning it counter clockwise. Remove the unscrewed cap.<br>Fig. 2: Insert the pipette into the bottle. While holding the bottom ring, pull the top ring up to the mark that corresponds to the number of millilitres or milligrams you need to give.<br>Fig.3: Holding the bottom ring, remove the entire pipette from the bottle. Empty the pipette into any non-alcoholic drink, except for tea, by sliding the upper ring down. Close the bottle. Rinse the pipette with some water.<br>  |
| **7.** MARKETING AUTHORISATION HOLDER | Janssen-Cilag Ltd, 50-100 Holmers Farm Way, High Wycombe, Buckinghamshire. HP12 4EG UK |
| **8.** MARKETING AUTHORISATION NUMBER(S) | PL 00242/0347; PL 00242/0186; PL 00242/0187; PL 00242/0188;<br>PL 00242/0189; PL 00242/0317; PL 00242/0199; PL 00242/0378;<br>PL 00242/0379; PL 00242/0380; PL 00242/0407; PL 00242/0408 |
| **9.** DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION | 30 June 2000/28 February 2004 (0.5 mg film-coated tablet)<br>8 December 1992/ 28 February 2004 (1,2,3 & 4 mg film-coated tablet)<br>15 July 1997/28 February 2004 (6 mg film-coated tablet)<br>7 January 2003/28 February 2004 (0.5 &1 mg orodispersible tablet)<br>7 December 2006 (3 & 4 mg orodispersible tablet)<br>21 November 1995/ 28 February 2004 (oral solution) |
| **10.** DATE OF REVISION OF THE TEXT | 8 DECEMBER 2008 |

# 3. Efficacy Data

## Literature Review of current Evidence Base

Many studies to date show that Risperidone can reduce behavioural disturbances associated with autism and other pervasive developmental disorders. It can alleviate irritability, aggression and hyperactivity but does not usually improve social and communication skills in this patient group[8]. A Cochrane meta-analysis[1] of three randomised controlled trials[4,5,9] suggested significant improvement in some core features of Autistic spectrum disorders (ASD) such as irritability, hyperactivity, stereotypical behaviours and social withdrawal as well as non-core symptom severity[1]. However, these results should be interpreted cautiously as the studies used heterogeneous outcome measures and were also limited by relatively small sample sizes, variable age groups studied, variable diagnostic inclusion criteria, different dosing regimens and a lack of long-term efficacy data. Of note, 20-25% of those studied dropped out of the RUPPAN 2002[4] and McDougle 1998[9] studies. The evidence base from double-blind, placebo-controlled trials in children and adults to date and their extension phases is reviewed below and summarised in Table 1.

The largest randomised controlled trial in children and adolescents studied 101 children in the US who met the DSM–IV criteria for autistic disorder accompanied by aggression, severe tantrums or self-injurious behaviour (Research Units on Paediatric Psychopharmacology network)[4]. Of the 101 children (82 boys, 19 girls; mean age 8.8 years; range, 5-17 years), 49 children entered the Risperidone arm and 52 received placebo in this 8 week double-blind trial[4]. Other inclusion criteria were a mental age ≥ 18 months, weight ≥ 15kg and no serious medical or other psychiatric disorder requiring pharmacological treatment. If a child was receiving effective medication for behavioural disturbance they were excluded from the study. Primary outcome measures were scores on the Irritability subscale of the Aberrant Behaviour Checklist and the Clinical Global Impressions – Improvement (CGI-I) scale at 8 weeks. Children who had ≥ 25% reduction on the irritability score and a rating of much or very much improved on the CGI-I were considered to have a positive response. Risperidone dose range over the 8-week study was 0.5- 3.5mg daily. Mean daily dose in final week was 1.8mg (+/- 0.7mg). The results following intention to treat analysis were that treatment with Risperidone for 8 weeks (dose range, 0.5 – 3.5mg daily) resulted in a 56.9% reduction on the Irritability score compared with a 14.1% decrease in placebo group ($p< 0.001$). The rate of positive response (as defined above) was 69% in the Risperidone group compared with 12% in placebo group ($p< 0.001$). Weight gain was significantly greater in the Risperidone group than placebo group (average 2.7 +/- 2.9kg versus 0.8 +/- 2.2kg $p< 0.001$). There were no serious adverse events in the Risperidone group although fatigue, increased appetite, dizziness and drooling were more common than with placebo. The authors conclude that Risperidone was well tolerated and effective for the treatment of aggression, tantrums and self-injurious behaviour in children with autistic disorder[4]. The study is limited by its short treatment length with Risperidone and limited generalisability (results cannot be generalised to all children with autism as the group studied were those with severe behavioural disturbance which was resistant to other treatments).

The RUPPAN study was followed by a 4 month open label trial and 8 week randomized, double-blind, placebo-substitution study of Risperidone withdrawal. At the end of the 8 week RCT study[4] positive responders in the Risperidone arm were offered open-label treatment with Risperidone for a further 4 months. Placebo non-responders were offered 8 weeks open-label Risperidone treatment followed by the 4-month extension phase if they showed a positive response. Of the 34 children classified as having a positive response after the first 8 week RCT, 23 (68%) had continued benefit at 6 months[4]. The 4 month open label extension followed by discontinuation study[6] enrolled 63 (49 boys) of the original 101 children. They were monitored every 4 weeks for medication efficacy, safety and dose adjustment[6]. After 4 months open-label treatment with Risperidone, those who continued to show a positive response entered the discontinuation phase. Subjects were randomly assigned to continue with Risperidone or be gradually tapered off with placebo (the Risperidone was reduced by 25% a week). The subjects were observed weekly during the discontinuation phase. Primary outcome measures were as in the 8-week double blind study[4] (ABC & CGI-I). In the discontinuation phase, relapse was defined as a CGI-I rating of much worse or very much worse and a 25% increase on the irritability subscale score. 51 (81%) completed the 4-month open label trial, all of which continued to show a positive response to Risperidone. Five dropped out due to lack of efficacy and one due to constipation. 38 of these children entered the discontinuation phase. Relapse in the placebo group (N=10, 62.5%), was significantly higher than in the Risperidone group (N=2, 12.5%). The trial was therefore stopped after 32 children completed the

discontinuation phase. Median time to relapse was 34 days for placebo group compared with 57 days in Risperidone group[6]. Mean daily Risperidone dose was 1.96 at entry rising to 2.08 at 4 months.
The study demonstrates that use of Risperidone for up to 6 months duration can continue to reduce behaviours associated with autism such as tantrums, self-injury, and aggression[6]. It also demonstrates a return of these behaviours on drug withdrawal implying that Risperidone is an effective treatment in this group for up to 6 months[6]. However, it must be noted that only 38 out of 101 children (37.6%) entered the final discontinuation phase of the study (others dropped out due to lack of efficacy, side-effects or other reasons). Slower dose reduction may reduce relapse on drug withdrawal. Of note, 37% (n=6) of children in the placebo withdrawal group did not relapse during the discontinuation phase, indicating variability in outcome.

Another 8-week randomised controlled trial by Shea et al investigated the efficacy and safety of risperidone for the treatment of disruptive behavioural symptoms in 79 children with both autism (n=55) and other pervasive developmental disorders (PDD)[5]. Eligibility criteria were diagnosis using DSM-IV and a total score ≥ 30 on the Childhood Autism Rating Scale (CARS) with or without mental retardation. Subjects were excluded if they had previously received Risperidone without response. The primary outcome measure was the irritability subscale of the ABC. At study endpoint the mean daily dose of Risperidone was 1.48mg, mean dosage 0.05mg/kg/day. 41 children were randomised to receive Risperidone and 39 to receive placebo and were aged 5 to 12 years old. By the study endpoint, risperidone treated children had a significantly greater decrease in the irritability subscale of the ABC than the placebo group, (64% baseline score improvement versus 31%). They also had significantly greater decreases in scores on the other 4 ABC subscales, the Nisonger Child Behaviour Rating Form conduct problems, hyperactive, insecure/anxious and overly sensitive subscales and the Visual Analogue scale of the most troublesome symptom[5]. Using the CGI-I, 51% (N=21) of Risperidone group were rated as much or very much improved compared with 18% (N=7) in the placebo group ($p \leq 0.05$). The study shows that Risperidone is efficacious in treating behavioural symptoms in children with autism and other PDD"s in the short term. There was a marked improvement in the placebo group in this study but a significantly greater improvement in the Risperidone group. The efficacy demonstrated in the Shea study is less than in the RUPPAN study, perhaps due to the less severe symptomatology in the former study group.

A Cochrane review[1] noted that these two studies used different outcome measures making direct comparison difficult. Secondary analysis of Shea study data[7] evaluated the same behaviour and clinical assessment measures used in the RUPPAN autism study[4]. Post-hoc analysis was carried out and treatment response was determined as in the RUPPAN study[4] – 'positive response' ≥ 25% reduction on the irritability subscale score of the ABC and a rating of much or very much improved on the CGI-I. Analysis revealed a 'positive response' in 58% and 21% of risperidone and placebo subjects respectively[7,] (compared with 69% and 12% in RUPPAN[4] study). Hyperactivity and aggression also appeared to be improved.

The efficacy of Risperidone in a RCT carried out in adults with pervasive developmental disorders[9] showed improvement in repetitive behaviour, sensory motor behaviours, affectual relations, self-injurious behaviours and overall behavioural symptoms[9].

Secondary outcome measures using the RUPPAN database[4] examined the efficacy of Risperidone on the core symptoms of autism[10] – a qualitative impairment in social interaction and communication and restricted repetitive and stereotyped patterns of behaviour, interests and activities. The Risperidone group had a significantly greater reduction in the overall score of the Ritvo-Freeman real Life Rating Scale[11] and subscale scores for sensory motor behaviours, affectual reactions and sensory responses; but no significant difference was observed on the social relatedness or language subscale scores. A significant reduction was also seen in the compulsion scale of the Children's Yale Brown Obsessive Compulsive Scale[12] to measure repetitive behaviour and the maladaptive behaviour domain of the Vineland Adaptive Behaviour Scales[13] in the Risperidone group[10].
The study found that the improvements in restricted repetitive and stereotyped patterns of behaviour, interests and activities were sustained over the six-month period but that Risperidone was ineffective in improving social interaction and communication[10].

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Table 1
Randomised controlled trials and their extensions of Risperidone in Children with ASD/PDD and Adults.

| Study | Design | Age (Yrs) | No. Patients | Mean dose mg / day | Results |
|---|---|---|---|---|---|
| McDougle et al 1998 [9] | RCT, DB, PC 12 weeks | 18- 43 | 31 | 2.9 | Sig. Improvement in repetitive behaviour using Y-BOCS, aggression using SIB-Q, & anxiety, depression, irritability & overall behaviour using R-FRLRS & CGI-I |
| RUPPAN 2002 [4] | RCT, DB, PC 8 weeks | 5-17 | 101 | 1.8 | Sig. Improvement in ABC irritability, hyperactivity & stereotypy subscales & improved CGI-I ratings |
| Shea et al 2004 [5] | RCT, DB, PC 8 week | 5-12 | 79 | 1.48 | Sig. Improvement in ABC irritability, hyperactivity, stereotypic behaviour & lethargy subscales & N-CBRF conduct, hyperactivity, insecure/anxious, oversensitive subscales |
| McDougle et al 2005[10] | database from RUPPAN | 5-17 | 101 | 1.8 | Sig. Improvement affectual reactions, sensory responses & motor behaviours and stereotypy on C-YBOCS. No improvement social & communication skills R-FRLRS. |
| RUPPAN 2005 [6] | OL 4 month study, then 8 week DB, PC discontinuation phase | 5-17 | 63<br><br>51 | 1.96 wk 0<br>2.08 wk 16 | Sustained improvement in CGI-I & irritability subscale ABC during 4-month extension. Discontinuation – placebo group relapsed more quickly & more often |
| Pandina et al 2007[7] | Secondary analysis Shea study | 5-12 | 79 | 1.48 | Sig. Improvement CGI-I and irritability subscale ABC |
| Luby 2006 [24] | RCT, DB, PC, 6 months | 2.5- 6 | 24 | 0.5- 1.5 | Slight improvement in core symptoms (CARS) |
| Nagaraj 2006 [25] | DB, PC, 6 months | 2- 9 | 40 | 1mg fixed dose | CARS, C-GAS |
| Miral 2008 [28] | RCT, DB, Risperidone vs Haloperidol 12 wks | 8- 18 | 30 | 2.6 | Sig greater improvement RF-RLRS sensory motor & language subscales, sig greater reduction ABC & Turgay PDD scores. |

RCT = Randomised Controlled Trial, DB = double-blind; PC = placebo-controlled; ASD/PDD = autism spectrum disorder/pervasive developmental disorders; ABC = Aberrant Behavior Checklist; N-CBRF = Nisonger–Child Behavior Rating Form; CGI-I = Clinical Global Impressions -Improvement; Y-BOCS = Yale-Brown Obsessive Compulsive Scale; SIB-Q = Self-Injurious Behaviour Questionnaire; RUPPAN = Research Units on Pediatric Psychopharmacology Autism Network; CY-BOCS = Children's Yale–Brown Obsessive Compulsive Scale; R-FRLRS = Ritvo–Freeman Real Life Rating Scale; OL = open-label; CARS-Childhood Autism Rating Scale.

There have been two randomized controlled trials of Risperidone in preschool children with ASD. The first, a six month trial by Luby et al[24], aimed to assess both safety and effectiveness of risperidone in improving behavioural disturbance and core social deficits of autistic spectrum disorders in preschool children. 24 children aged 2.5 to 6 years were recruited who met DSM-IV criteria for autism, PDD or PDD-NOS. Main outcome measures included CARS and Gillian autism rating scale. Socialisation and general adaptive development were assessed with the Vineland Adaptive Behaviour Scales[13]. Most children were also undergoing intensive behavioural treatment. Low doses were used with final mean daily dose 0.05mg/kg. Risperidone was well tolerated but caused increased weight gain, leptin and prolactin. One third experienced weight gain; mean weight gain 2.96kg versus 0.61 in risperidone and placebo groups respectively. No subjects dropped out due to side-effects. Significant improvement in CARS was found when baseline and end-point scores were compared and baseline characteristics controlled for (effect size 0.95) but no difference was found if assessments were included at 2 and 4 months. Socialisation or other scores did not improve. Overall, only minimal greater improvement was seen in treatment group. The study conclusions are limited by small size, differences in baseline characteristics and concurrent behavioural therapy. It appears however that Risperidone was relatively well tolerated in this young age group over 6 months.

A further RCT in preschool children by Nagaraj[25] studied whether risperidone in comparison with placebo improved functioning in children with autism with regard to behaviour (aggressiveness, hyperactivity, irritability), social and emotional responsiveness, and communication skills[25]. 40 children with autism, ages 2 to 9 years, were given either

risperidone or placebo orally at a dose of 1 mg/day for 6 months. Significant improvements in outcome measures (Childhood Autism Rating Scale (CARS) and the Children's Global Assessment Scale (CGAS)) were seen in risperidone group versus placebo. Social responsiveness improved and it was well tolerated. Risperidone was associated with increased appetite and a mild weight gain, mild sedation in 20%, and transient dyskinesias in three children[25].

A recent randomized controlled trial compared safety, efficacy, and tolerability of risperidone with haloperidol in the treatment of autistic disorder[28] in 30 children aged 8-18 years over 12 weeks. Risperidone led to a significant reduction in Ritvo-Freeman Real Life Rating Scale[11] (RF-RLRS) sensory motor and language subscales from baseline. It also led to a significantly greater reduction in ABC and Turgay PDD scale scores than haloperidol.

Several open-label trials[14,15] found significant improvement in behavioural symptoms associated with autism following treatment with Risperidone but little improvement in the core symptoms of autism. Numbers studied in these trials were small.

# 4. Safety

## Adverse Effects:

Adverse effects are extremely common with relatively low doses of Risperidone in children and adolescents with autism and pervasive developmental disorders and appear to be more common than in adults[1]. The SPC for risperidone states that the following adverse drug reactions were reported with a frequency ≥5% in paediatric patients (5 to 17 years) and with at least twice the frequency seen in clinical trials in adults: somnolence/sedation, fatigue, headache, increased appetite, vomiting, upper respiratory tract infection, nasal congestion, abdominal pain, dizziness, cough, pyrexia, tremor, diarrhoea, and enuresis. The commonest side effects are weight gain[4], somnolence or sedation[5,16] and extrapyramidal side effects[5] (EPS). Constipation is also a common and important side effect[4], others include dry mouth, sialorrhea and enuresis[1]. Other metabolic adverse events such as glucose dysregulation, hypercholesterolemia and hyperprolactinemia are associated with Risperidone treatment and can occur as a result of weight gain or independently. It is essential to monitor vigilantly for adverse effects in children and adolescents and to carefully balance the risk-benefit ratio of prescribing Risperidone in this patient group. If side effects are marked or troublesome, withdrawal of the medication and alternative treatment should be considered.

Weight gain with second generation antipsychotics is greater in children and adolescents[26] than in adults. It seems to be above that expected in normal development[17] but appears to follow a curvilinear trajectory and decelerate over time[17]. It appears to be greater than that seen with conventional antipsychotics such as Haloperidol. Data from a RCT treating children and adolescents with Risperidone for disruptive behaviour disorders showed that weight gain increased over the first 12 weeks then plateaued over the following few months of the study[18]. Meta-analysis of weight gain from the 8-week RUPPAN and Shea studies gave a mean weight increase of 1.78kg in the Risperidone group compared with 1.0kg in placebo group[1]. Over a 6-month open label treatment and discontinuation phase, the RUPPAN cohort showed an absolute weight gain of 16.7% (mean = 5.6kg) and 10.6% (mean=2.0 kg/m$^2$) increase in BMI over the 6-month treatment. The rate of weight gain appears to lessen over time and weight gain at 1 month appeared to powerfully predict later weight gain in this study[17].
*It is recommended that if weight increases 15% from baseline then treatment should be stopped.*

Hyperprolactinemia is an important adverse-event with Risperidone[15] but is not always symptomatic. It can be associated with hypogonadism in both genders and can lead to decreased bone mineral density and osteoporosis. Elevated prolactin is also associated with galactorrhea, menstrual disturbances and gynecomastia[21]. It is often transient in nature as shown in a pooled analysis of 5 studies using Risperidone in children with disruptive behavioural disorders[19]. Three studies had open-label phases of 48 weeks treatment. In both genders mean peak prolactin levels occurred at weeks 4 to 7 and steadily decreased thereafter to normal levels by after week 24 for males and week 12 for females. End-point mean prolactin levels at 48 weeks mostly remained within normal limits[19]. although were higher than pre-treatment levels. Only 2.2% of children and adolescents developed side effects hypothetically attributable to prolactin (some 'side effects' may be masked by or attributable to puberty) - 2/3rds of which had resolved by study end-point. No correlation was found between these side effects and prolactin levels[19].

Unfortunately, there was no long-term control group for these studies showing incidences of galactorrhea, menstrual disturbances and gynecomastia normally occurring in this population.

Meta-analysis of these 5 large studies of long-term treatment with Risperidone[20] found no evidence of clinically or statistically significant growth failure or delay in pubertal onset or progression in children aged 5-17 years (number 222 )[20].

Extra-pyramidal side effects (EPSE) are more common in young people than adults and a review of several studies reported rates of EPS of 8.6% to 26%[27]. RUPPAN studies did not identify any cases of EPSE using the Simpson-Angus Scale and the Abnormal Involuntary Movement Scale [4,6], although parents reported abnormal movements that were not seen on examination[6]. The Shea study[5] reported 27.5% EPSE in the Risperidone group compared with 12.8% in placebo group. A study in young people with disruptive behaviour disorders[18] reported EPSE in 1.5% in the first 12 weeks and 1.7% Risperidone group over the next 6 months of treatment. Medication was used to treat two patients with EPSE and there were no cases of tardive dyskinesia[18].

Somnolence is common[5] but appears to be transient or can usually be managed by dose adjustment.

Atypical antipsychotics have been used in increasing frequency in recent years, with many feeling there is inadequate information in relation to drug safety, and there have been several case reports of sudden death in children[29]. These deaths may have been attributable to ventricular arrhythmias caused by prolongation of the QT interval, as seen on ECG. Atypical antipsychotics can cause QT prolongation, a risk factor for sudden death. A recent study showed that these atypical drugs may be no safer than the older drugs in regards to this adverse effect[30]. Other factors such as genetic susceptibility, pre-existing heart disease, drug clearance abnormalities and concurrent use of other medication that affect the QT interval increase the risk of conduction abnormalities[29]. It is therefore essential that a detailed history and appropriate investigations are carried out prior to commencing Risperidone as discussed below.

## 5.0 Recommendations for Prescribing

Janssen-Cilag (license holder for Risperidone) applied to the Medicines and Healthcare Regulatory Agency (MHRA) for its license to include irritability in autism[22]. The MHRA produced an assessment report[23] recommending that Risperidone be prescribed to this patient group by experts in the treatment of autism after careful diagnosis, with appropriate screening and monitoring[22]. The MHRA consulted with experts and reviewed the RUPPAN and Shea studies[4,5] put forward by Janssen-Cilag and offered a conditional approval limiting the use of Risperidone to the symptomatic treatment of severe aggression and violence in children with autism. They required safety monitoring and a register of children on Risperidone to be set up. Janssen-Cilag withdrew its application for the license and an opportunity for formalising careful administration and monitoring of this medication in autistic children was lost[22]. The recommendations set out in the MHRA document and SPC for use of Risperidone in conduct disorder with sub-average intelligence for dosages and safety monitoring have been adopted in this protocol below.

## 5.1 Indication

Oral risperidone is indicated in this case for the short-term treatment of severe aggression and violence whether directed towards self or others in autistic children and adolescents where available non-pharmacological methods have first been tried and failed[23]. It should be noted that the MHRA license conditions included a restriction of the use of Risperidone in children aged 5-12 years (as there was little evidence in the evidence presented to them[4,5] in children older than 12 years.) It was noted by the MHRA that Risperidone appeared less effective in the older children studied[23].

However, several open label studies have used Risperidone in older children and there is evidence of its safety in other studies[18,19,20]. Therefore, this guidance relates to children and adolescents aged 5 to 18 years.

It must be stressed that pharmacological treatment should be considered SECOND LINE to non-pharmacological methods when dealing with irritability and behavioural disturbance in autistic children and adolescents.

## 5.2 Pre-treatment assessment[23]

Before risperidone is prescribed the young person must be fully assessed for physical, psychological and social causes of the aggressive behaviour such as pain, attention-deficit hyperactivity disorder (ADHD) or inappropriate environmental demands. Non-pharmacological methods should be tried before medication is considered.

**Pre-treatment assessment should include:**

i. **Thorough history** –
**Child** – ask about history of congenital heart disease or cardiac problems, syncope or unexplained seizures, disorders involving or medications causing electrolyte imbalance & use of medications that can cause QT prolongation (e.g. erythromycin, salmeterol, chloroquine, domperidone, fosphenytoin).

**Family history** of cardiac problems or sudden death, unexplained syncope or seizures or long QT syndrome.

**ii. Routine blood tests – FBC, UEC's, LFTs, Prolactin, Glucose, Lipid profile & cholesterol**

NOTE: Blood samples should be fasting levels. If prolactin raised check TFT's.

Clinicians, parents and children may find invasive monitoring unacceptable in this patient population, therefore routine blood monitoring is not a condition of prescribing[22]. However, careful consideration must be given to blood monitoring if a child is more than 10 centile points above the expected weight[22]. Clinicians must ensure that these children are not deprived of safe prescribing measures

**iii. Cardiovascular assessment including pulse and blood pressure monitoring.**
ECG is recommended at baseline including QTc interval calculation (QT corrected for heart rate) if indicated by history (as per (i) above) or clinical examination.
Note: upper limit of normal QTc is defined as 450ms in males & 460ms in females.

**ECG essential if suspicious history, pre-existing risk factors present or patient on other medication that may interact with Risperidone & increase cardiac risk**. Consider paediatric cardiology opinion.

iv. Measurement of **height, weight** and **developmental status** including sexual maturation. BMI or weight for height calculation.

v. **Bowel habit** should be monitored to avoid constipation

vi. **Somnolence** and other behavioural changes*

vii. **Neurological examination** for movement disorders, including tardive dyskinesia or motor complications**

*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.
**Movement disorders, abnormal posturing and disorders of muscle tone can be present as an integral part of autistic disorder. Hence, a thorough 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 should be alerted to both movement disorders associated with underlying autism and extra pyramidal symptoms that may emerge in the course of treatment with risperidone.

## 5.3 Dosage

The dosage of risperidone should be individualised according to patient weight, response, and the occurrence of side effects. It may be appropriate to start at lower doses in very small or young children, those with learning disabilities or other co-morbidities and those prescribed other medicines.

Dosage can either be done according to weight on a total mg/day basis, or on a mg/kg/day basis at the prescribers discretion.

| Weight | Days 1-3 | Days 4-14+ | Dose increments | Dose range |
|---|---|---|---|---|
| 15-20kg | 0.25mg/day | 0.5mg/day | 0.25mg at ≥2 weekly intervals | 0.5mg-1.5mg |
| ≥20kg | 0.5mg/day | 1.0mg/day | 0.5mg at ≥2 weekly intervals | 1.0mg-2.5mg* |
| ALL | 0.01mg/kg/day | 0.02mg/kg/day | 0.01mg/kg/day at ≥2 weekly intervals | 0.02mg/kg/day – 0.06mg/kg/day |

*Subjects >45kg may require higher doses: maximum dose studied was 3.5mg/day [4,5]

Dosing should be initiated at 0.25mg per day for patients 15-20kg and 0.5mg per day for patients ≥20kg. On day 4, the dose may be increased by 0.25mg for patients 15-20kg and 0.5mg for patients ≥20kg.
Only in patients not achieving sufficient clinical response should additional dose increases be considered.
Dose increases may proceed at two-week intervals in increments of 0.25mg for patients 15-20kg and 0.5mg for patients ≥20kg.

In clinical controlled studies reviewed by the MHRA[4,5], the maximum dose did not exceed a total daily dose of 1.5mg in patients 15-20kg, 2.5mg in patients ≥20kg, or 3.5mg in patients >45kg. Low doses were used in studies of preschool children[24,25].

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 establish the safety of risperidone therapy for long-term treatment.

**Controlled trial evidence is for a duration of 8 weeks [4,5] only with open-label trial continuation of up to 8-months in total[6]. Therapy should be continued with caution after this time period.**

*An attempt to gradually withdraw risperidone should be made after a maximum of 8 weeks treatment. Therapy should not be continued unless gradual, supported withdrawal has resulted in severe relapse of aggression, which is not manageable by other means.*

There is longer term data available (up to 48 weeks [19,20)] in children with disruptive behaviour disorders. It should be noted that after 6-month open label treatment and randomised withdrawal[6], 37% children in the placebo withdrawal group did not relapse during the 2-month discontinuation phase, showing variability in outcome. It is possible that more gradual tapering of medication may lead to a reduced resurgence of behavioural symptoms[6].

*Continued treatment with Risperidone should not be at the expense of significant side effects*. It is recommended that if a child's weight increases 7% from baseline (corrected for age) then treatment should be stopped. Blood monitoring is recommended in all young people but stronger consideration should be given to this if longer term treatment is considered.

## 5.4 Frequency

Risperidone can be administered once or twice daily, and the decision should be based on ease of compliance and tolerability (side effects). For example, patients suffering daytime drowsiness may benefit from a once daily night-time dose, or divided of doses to twice a day, or a dose reduction.

## 5.5 Restrictions on prescribing

Risperidone therapy should only be initiated and supervised by a Consultant Child and Adolescent Psychiatrist. Prescribing and physical monitoring should remain the responsibility of the prescribing Consultant throughout the duration of treatment. In autistic children and adolescents who have epilepsy, prescribers should NOT initiate risperidone within 6 months of the last seizure. Particular care should be taken if the child is taking Fluoxetine. Treatment with Risperidone should not be considered in children under the age of 5 years.

## 5.6 Information for patients, parents or carers

Individual patients should be given information that meets their needs about unlicensed medicines. (Appendix 1 of the East London Unlicensed Medicines Policy).
A leaflet on risperidone is also available on the East London intranet, which is useful to highlight any potential side effects for patients, parents and carers. (Please note this leaflet is more focused on the use of risperidone in psychosis).

## 6.0 Recommendations for Monitoring

As per the Summary of Product Characteristics (SPC) for adults and children aged 5-18 years with conduct disorder and intellectual disability. Particular attention should be paid to the apparent increased risk of EPS and akathisia in children with autism compared to adults; and weight gain, effect on glucose tolerance and other metabolic complications.

**Thorough history at baseline** – (see section 5.2 above also)

**Child** – ask about history of congenital heart disease or cardiac problems, syncope or unexplained seizures, disorders involving or medications causing electrolyte imbalance & use of medications that can cause QT prolongation (eg erythromycin, salmeterol, chloroquine, domperidone, fosphenytoin).

**Family history** of cardiac problems or sudden death, unexplained syncope or seizures or long QT syndrome

**FBC, UEC's, LFTs, Prolactin, Glucose, Lipid profile & cholesterol** –

All at baseline (pre-treatment), 3 months, 6 months then 6 monthly thereafter. If prolactin raised check TFT's.

NOTE: Blood samples should be fasting levels

Clinicians, parents and children may find invasive monitoring unacceptable in this patient population, therefore routine blood monitoring is not a condition of prescribing[22]. However, careful consideration must be given to blood monitoring if a child is more than 10 centile points above the expected weight[22]. Clinicians must ensure that these children are not deprived of safe prescribing measures.

**ECG:** recommended at baseline (pre-treatment) if history or clinical examination indicates.
**Essential if suspicious history, pre-existing risk factors present or patient on other medication that may interact with Risperidone & increase cardiac risk**. Consider paediatric cardiology opinion.

ECG should be repeated at 3 months & every 6 months thereafter only if clinically indicated following baseline investigations.
**If longer treatment is used (4-6 months) – then ECG recommended due to the risk of prolonged QT interval & risk of sudden death (even in those where ECG not indicated at baseline)**.
NOTE: QT interval should be calculated corrected for heart rate (QTc).
Normal upper limit of QTc interval is 450ms in males and 460ms in females[29].

**Weight**: at baseline then monthly initially, every 3-6 months thereafter. It is preferable to calculate BMI and weight for height. (Recommended STOP Risperidone if weight increases more than 7% from baseline, corrected for age.

**Height and growth**: Height and developmental status including sexual maturation should be monitored as per weight.

**Cardiovascular assessment**: including pulse and blood pressure at every review.

**Bowel Habit**: monitor for constipation.

**Somnolence** and other behavioural changes

**Neurological examination** for movement disorders: Screening for symptoms of acute movement disorders, as well as tardive dyskinesia, should be part of clinical assessments at each follow-up visit. Caregivers should be alerted to both movement disorders associated with underlying autism and extra pyramidal symptoms that may emerge in the course of treatment with risperidone.

## 7. Summary

**Summary**:
Risperidone is an effective and relatively safe choice of drug in the management of serious behavioural problems (e.g. tantrums, aggression, self-injury) in children and adolescents with autistic spectrum disorders. However, the potential advantages should be weighed against the risk of unwanted side effects (such as raised prolactin and weight gain), and their potentially significant consequences. Risperidone should only be used in the management of autism where other appropriate non-pharmacological methods have failed.

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