

**RISPERIDONE 1MG/ML ORAL SOLUTION
PL 10622/0285**

UKPAR

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**RISPERIDONE 1MG/ML ORAL SOLUTION
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LAY SUMMARY

On 19th December 2008, the MHRA today granted Pliva Pharma Limited a Marketing Authorisation (licence) for Risperidone 1mg/ml Oral Solution (PL 10622/0285), in the treatment of the following indications:

- Schizophrenia, where you may see, hear or feel things that are not there, believe things that are not true or feel unusually suspicious, or confused
- Mania, where you may feel very excited, elated, agitated, enthusiastic or hyperactive. Mania occurs in an illness called ‘bipolar disorder’
- Short-term treatment (up to 6 weeks) of long-term aggression in people with Alzheimer’s dementia, who harm themselves or others. Alternative (non-drug) treatments should have been used previously
- Short-term treatment (up to 6 weeks) of long-term aggression in intellectually disabled children (at least 5 years of age) and adolescents with conduct disorder

Risperidone belongs to a group of drugs known as “anti-psychotics”.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Risperidone 1mg/ml Oral Solution outweigh the risks, hence a Marketing Authorisation has been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Risperidone 1mg/ml Oral Solution (PL 10622/0285) to Pliva Pharma Limited on 19th December 2008. The product is a prescription-only medicine for the following indications:

- the treatment of schizophrenia
- the treatment of moderate to severe manic episodes associated with bipolar disorders
- 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
- the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours require pharmacologic treatment.

This application for Risperidone 1mg/ml Oral Solution is submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product to Risperdal 1mg/ml Liquid, first authorised to Janssen-Cilag Limited in November 1995.

The product contains the active substance risperidone, an antipsychotic agent used to treat schizophrenia. The antipsychotic effect is thought to be related to its ability to block dopamine (DA) D₂ receptors and serotonin (5-HT₂) receptors. Risperidone is also a potent alpha1-adrenergic and histamine H₁ antagonist. The pharmacodynamic effects of the major metabolite 9-hydroxyrisperidone are very similar to those of risperidone itself.

PHARMACEUTICAL ASSESSMENT

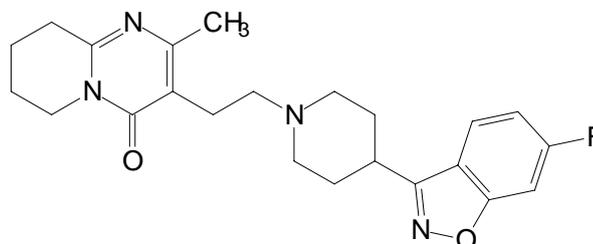
DRUG SUBSTANCE

Risperidone

INN: Risperidone

Chemical name: 4-[2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-1-piperidyl]ethyl]-3-methyl-2,6-diazabicyclo[4.4.0]deca-1,3-dien-5-one

Structure:



CAS registry number: 106266-06-2

Physical form: White to off-white powder, practically insoluble in water, freely soluble in methylene chloride, and sparingly soluble in alcohol. It dissolves in dilute acid solutions.

Molecular formula: $C_{23}H_{27}FN_4O_2$

Molecular weight: 410.5

A European pharmacopoeial monograph has been written for active risperidone.

All aspects of the manufacture of the active substance risperidone from its starting materials are controlled by a Certificate of Suitability.

An appropriate active substance specification has been provided that is in compliance with the pharmacopoeial monograph and in-line with the Certificate of Suitability.

Batch analysis data are provided and comply with the proposed specification.

A retest period of 2 years when drug substance is stored in polyethylene bags (which are kept in fibre drums) has been stated on the certificate of suitability.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely tartaric acid (E 334), benzoic acid (E 210), hydrochloric acid and purified water. All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain materials of animal or human origin.

Product development

The objective of the development programme was to produce a product that could be considered a generic medicinal product of Risperdal 1mg/ml Liquid (Janssen-Cilag Limited, 1995). The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid.

Comparative impurity data have been provided for the finished product versus the reference product Risperdal 1mg/ml Liquid (Janssen-Cilag Limited).

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of finished product and the results appear satisfactory.

Finished product specification

The finished product specification is satisfactory. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis for all working standards used have been provided and are satisfactory.

Container-Closure System

The primary packaging is a Type III amber glass bottle, with a polypropylene/low-density polyethylene child-resistant and tamper-evident cap. Bottle sizes are 30ml, 60ml, 100ml and 120ml. A dosing pipette, consisting of a polystyrene plunger and a low-density polyethylene barrel and piston, is also supplied.

Specifications and Certificates of Analysis for all packaging have been provided. These are satisfactory. The primary packaging has been shown to comply with relevant regulations regarding the contact of materials with foodstuff.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set when unopened (which reduces to 4 months once opened), with no specific storage instructions.

ADMINISTRATIVE

Expert Report

A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SPC)

This is pharmaceutically satisfactory.

Labelling

These are pharmaceutically satisfactory.

Patient Information Leaflet (PIL)

This is pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form

This is pharmaceutically satisfactory.

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

PRECLINICAL ASSESSMENT

This application for Risperidone 1mg/ml Oral Solution is submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product of Risperdal 1mg/ml Liquid, first authorised to Janssen-Cilag Limited in November 1995.

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

To support the applications, the marketing authorisation holder has submitted one single-dose bioequivalence study.

An open-label, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose comparative oral bioavailability study of the test product Risperidone 1mg/ml solution versus the reference product Risperdal 1mg/ml Solution (Janssen-Cilag, France) in healthy, adult, male, human subjects under fasted conditions.

All subjects fasted for at least 11 hours before dosing. Blood samples were taken pre and up to 120 hours post dose, with a washout period of at least 12.5 days between doses. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

Treatment	AUC _{0-t} (ng/ml/h)	AUC _{0-∞} (ng/ml/h)	C _{max} (ng/ml)
Risperidone:			
Test	23.290	27.654	9.111
Reference	25.192	29.853	9.572
Ratio (90% CI)	92.45 (81.19; 105.26)	92.63 (82.10; 104.52)	95.19 (82.20; 110.23)

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for active risperidone lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in this study.

EFFICACY

No new data has been provided.

SAFETY

No new data has been provided.

EXPERT REPORTS

The clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

This is consistent with that for the reference product and is satisfactory.

LABELLING

These are satisfactory

APPLICATION FORMS (MAA)

These are satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

This is consistent with that for the reference product and is satisfactory.

DISCUSSION

The applicant has satisfactorily demonstrated bioequivalence between the test and reference products.

MEDICAL CONCLUSION

The bioequivalence study submitted has shown that these products can be considered as generic medicinal products to the originator products Risperdal 1mg/ml Liquid (Janssen-Cilag Limited, UK).

The grant of a marketing authorisation is recommended for this application.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Risperidone 1mg/ml Oral Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Risperidone 1mg/ml Oral Solution and the reference product Risperdal 1mg/ml Liquid (Janssen-Cilag Limited, UK).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference product Risperdal 1mg/ml Liquid.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the reference products are interchangeable. Extensive clinical experience with risperidone is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications on 4 th April 2006
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 18 th May 2006
3	Following assessment of the applications, the MHRA requested further information relating to the quality dossiers on 27 th September 2006 and 8 th July 2008. No requests for further information were made for the clinical dossiers.
4	The applicant responded to the MHRA's requests, providing further information on 18 th July 2007 and 16 th September 2008 for the quality sections.
5	The applications were determined on 19 th December 2008

**RISPERIDONE 1MG/ML ORAL SOLUTION
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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

1 NAME OF THE MEDICINAL PRODUCT

Risperidone 1mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains 1 mg of risperidone
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution
The solution is clear and colourless

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

Risperidone is indicated for the treatment of schizophrenia.

Risperidone is indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders.

Risperidone 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.

Risperidone is indicated for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive 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*

Risperidone may be given once daily or twice daily.

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*

Risperidone 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 Risperidone 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.

Risperidone 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 Risperidone must be evaluated and justified on an ongoing basis.

Risperidone 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.

Risperidone should be used with caution in these groups of patients.

Method of administration

Risperidone is for oral use. Food does not affect the absorption of Risperidone.

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 Risperidone therapy is initiated is recommended. Also, if medically appropriate, when switching patients from depot antipsychotics, initiate Risperidone therapy in place of the next scheduled injection. The need for continuing existing anti-Parkinson medicines should be re-evaluated periodically.

For instructions on handling Risperidone Oral Solution see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients

4.4 Special warnings and precautions for useElderly patients with dementia*Overall mortality*

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 risperidone. In placebo-controlled trials with risperidone in this population, the incidence of mortality was 4.0% for risperidone-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).

Concomitant use with furosemide

In the risperidone 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.

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.

Cerebrovascular Adverse Events (CVAE)

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 risperidone 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.

Risperidone should be used with caution in patients with risk factors for stroke.

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.

Physicians are advised to assess the risks and benefits of the use of Risperidone in elderly patients with dementia, taking into account risk predictors for stroke in the individual patient. 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.

Risperidone 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.

Patients should be reassessed regularly, and the need for continuing treatment reassessed.

Orthostatic hypotension

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. Risperidone 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.

Tardive dyskinesia/extrapyramidal symptoms (TD/EPS)

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 Risperidone, should be discontinued.

Parkinson's disease and dementia with Lewy bodies

Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including Risperidone, 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 Risperidone. 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.

Risperidone 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

Risperidone 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 Risperidone 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 Risperidone 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.

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, hypomagnesaemia), bradycardia, or those which inhibit the hepatic metabolism of risperidone. This list is indicative and not exhaustive.

Potential for Risperidone to affect other medicinal products

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.

Risperidone 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.

Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment.

Risperidone does not show a clinically relevant effect on the pharmacokinetics of lithium, valproate, digoxin or topiramate.

Potential for other medicinal products to affect Risperidone

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 Risperidone.

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 Risperidone.

Verapamil, an inhibitor of CYP 3A4 and P-gp, increases the plasma concentration of risperidone.

Galantamine and donepezil do not show a clinically relevant effect on the pharmacokinetics of risperidone and on the active antipsychotic fraction.

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.

The combined use of psychostimulants (e.g., methylphenidate) with Risperidone in children and adolescents did not alter the pharmacokinetics and efficacy of Risperidone.

See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

Concomitant use of oral Risperidone 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

Pregnancy

There are no adequate data from the use of risperidone in pregnant women. According to postmarketing data reversible extrapyramidal symptoms in the neonate were observed following the use of risperidone during the last trimester of pregnancy. Consequently newborns should be monitored carefully. Risperidone was not teratogenic in animal studies but other types of reproductive toxicity were seen (see section 5.3). The potential risk for humans is unknown. Therefore, Risperidone should not be used during pregnancy unless

clearly necessary. If discontinuation during pregnancy is necessary, it should not be done abruptly.

Lactation

In animal studies, risperidone and 9-hydroxy-risperidone are excreted in the milk. It has been demonstrated that risperidone and 9-hydroxy-risperidone are also excreted in human breast milk in small quantities. There are no data available on adverse reactions in breast-feeding infants. Therefore, the advantage of breastfeeding should be weighed against the potential risks for the child.

4.7 Effects on ability to drive and use machines

Risperidone 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 $\geq 10\%$) are: Parkinsonism, headache and insomnia.

The following are all the ADRs that were reported in clinical trials and postmarketing. The following terms and frequencies are applied: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available clinical trial data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse Drug Reactions by System Organ Class and Frequency

Investigations

<i>Common</i>	Blood prolactin increased, Weight increased
<i>Uncommon</i>	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
<i>Rare</i>	Body temperature decreased

Cardiac disorders

<i>Common</i>	Tachycardia
<i>Uncommon</i>	Atrioventricular block, Bundle branch block, Atrial fibrillation, Sinus bradycardia, Palpitations

Blood and lymphatic system disorders

<i>Uncommon</i>	Anaemia, Thrombocytopenia
<i>Rare</i>	Granulocytopenia
<i>Not known</i>	Agranulocytosis

Nervous system disorders

<i>Very common</i>	Parkinsonism, Headache
<i>Common</i>	Akathisia, Dizziness, Tremor, Dystonia, Somnolence, Sedation, Lethargy, Dyskinesia
<i>Uncommon</i>	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
<i>Rare</i>	Neuroleptic malignant syndrome, Diabetic coma, Cerebrovascular disorder, Cerebral ischaemia, Movement disorder

Eye disorders

<i>Common</i>	Vision blurred
<i>Uncommon</i>	Conjunctivitis, Ocular hyperaemia, Eye discharge, Eye swelling, Dry eye, Lacrimation increased, Photophobia
<i>Rare</i>	Visual acuity reduced, Eye rolling, Glaucoma

Ear and labyrinth disorders

<i>Uncommon</i>	Ear pain, Tinnitus
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Respiratory, thoracic and mediastinal disorders

<i>Common</i>	Dyspnoea, Epistaxis, Cough, Nasal congestion, Pharyngolaryngeal Pain
<i>Uncommon</i>	Wheezing, Pneumonia aspiration, Pulmonary congestion, Respiratory disorder, Rales, Respiratory tract congestion, Dysphonia
<i>Rare</i>	Sleep apnea syndrome, Hyperventilation

Gastrointestinal disorders

<i>Common</i>	Vomiting, Diarrhoea, Constipation, Nausea, Abdominal pain, Dyspepsia, Dry mouth, Stomach discomfort
<i>Uncommon</i>	Dysphagia, Gastritis, Faecal incontinence, Faecaloma
<i>Rare</i>	Intestinal obstruction, Pancreatitis, Lip swelling, Cheilitis

Renal and urinary disorders

<i>Common</i>	Enuresis
<i>Uncommon</i>	Dysuria, Urinary incontinence, Pollakiuria

Skin and subcutaneous tissue disorders

<i>Common</i>	Rash, Erythema
<i>Uncommon</i>	Angioedema, Skin lesion, Skin disorder, Pruritus, Acne, Skin discolouration, Alopecia, Seborrhoeic dermatitis, Dry skin, Hyperkeratosis
<i>Rare</i>	Dandruff

Musculoskeletal and connective tissue disorders

<i>Common</i>	Arthralgia, Back pain, Pain in extremity
<i>Uncommon</i>	Muscular weakness, Myalgia, Neck pain, Joint swelling, Posture abnormal, Joint stiffness, Musculoskeletal chest pain
<i>Rare</i>	Rhabdomyolysis

Endocrine disorders

<i>Rare</i>	Inappropriate antidiuretic hormone secretion
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Metabolism and nutrition disorders

<i>Common</i>	Increased appetite, Decreased appetite
<i>Uncommon</i>	Anorexia, Polydipsia
<i>Very rare</i>	Diabetic ketoacidosis
<i>Not known</i>	Water intoxication

Infections and infestations

<i>Common</i>	Pneumonia, Influenza, Bronchitis, Upper respiratory tract infection, Urinary tract infection
<i>Uncommon</i>	Sinusitis, Viral infection, Ear infection, Tonsillitis, Cellulitis, Otitis media, Eye infection, Localised infection, Acarodermatitis, Respiratory tract infection, Cystitis, Onychomycosis
<i>Rare</i>	Otitis media chronic

Vascular disorders

<i>Uncommon</i>	Hypotension, Orthostatic hypotension, Flushing
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General disorders and administration site conditions

<i>Common</i>	Pyrexia, Fatigue, Peripheral oedema, Asthenia, Chest pain
<i>Uncommon</i>	Face oedema, Gait disturbance, Feeling abnormal, Sluggishness, Influenza like illness, Thirst, Chest discomfort, Chills
<i>Rare</i>	Generalised oedema, Hypothermia, Drug withdrawal syndrome, Peripheral coldness

Immune system disorders

<i>Uncommon</i>	Hypersensitivity
<i>Rare</i>	Drug hypersensitivity
<i>Not known</i>	Anaphylactic reaction

Hepatobiliary disorders

<i>Rare</i>	Jaundice
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Reproductive system and breast disorders

<i>Uncommon</i>	Amenorrhoea, Sexual dysfunction, Erectile dysfunction, Ejaculation disorder, Galactorrhoea, Gynaecomastia, Menstrual disorder, Vaginal discharge,
<i>Not known</i>	Priapism

Psychiatric disorders

<i>Very common</i>	Insomnia
<i>Common</i>	Anxiety, Agitation, Sleep disorder
<i>Uncommon</i>	Confusional state, Mania, Libido decreased, Listless, Nervousness
<i>Rare</i>	Anorgasmia, Blunted affect

- a Hyperprolactinemia can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhoea, galactorrhea.
- 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, but were not determined to be ADRs in the clinical trials investigating oral risperidone. This table excludes those ADRs specifically associated with the formulation or injection route of administration of the long acting injectable risperidone.

Additional Adverse Drug Reactions Reported with the long acting injectable risperidone but not with the oral risperidone 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 antipsychotics which prolong QT interval include ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia, sudden death, cardiac arrest and Torsades de Pointes.

Weight gain

The proportions of risperidone and placebo-treated adult patients with schizophrenia meeting a weight gain criterion of $\geq 7\%$ 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 risperidone (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 $\geq 7\%$ at endpoint was comparable in the risperidone (2.5%) and placebo (2.4%) groups, and was slightly higher in the active-control group (3.5%).

In a population of children and adolescents with conduct and other disruptive behaviour disorders, in longterm 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.

Additional information on special populations

Adverse drug reactions that were reported with higher incidence in elderly patients with dementia or paediatric patients than in adult populations are described below:

Elderly patients with dementia

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 $\geq 5\%$ 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.

Paediatric patients

The following ADRs were reported with a frequency $\geq 5\%$ 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 Risperidone and paroxetine.

In case of acute overdose, the possibility of multiple drug involvement should be considered.

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 Risperidone. 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.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties***Pharmacotherapeutic group:*

Other antipsychotics, ATC code: N05AX08

Mechanism of action

Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotonergic 5-HT₂ and dopaminergic D₂ receptors. Risperidone binds also to alpha₁-adrenergic receptors, and, with lower affinity, to H₁-histaminergic and alpha₂-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D₂ 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.

Pharmacodynamic effects*Schizophrenia*

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 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, placebocontrolled 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.

Manic episodes in bipolar disorder

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 $\geq 50\%$ 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.

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.

Persistent aggression in dementia

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)

Conduct disorder

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

Risperidone is metabolised to 9-hydroxy-risperidone, which has a similar pharmacological activity to risperidone (see Biotransformation and Elimination).

Absorption

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

Distribution

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

Biotransformation and elimination

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

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

Linearity

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

Elderly, hepatic and renal impairment

A single-dose study showed on average a 43% higher active antipsychotic fraction plasma concentrations, 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%.

Paediatric patients

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

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

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Tartaric acid (E 334)
Benzoic acid (E 210)
Hydrochloric acid
Purified water

6.2 Incompatibilities

Tartaric acid (E 334)
Benzoic acid (E 210)
Hydrochloric acid
Purified water

6.3 Shelf life

30ml, 60ml, 100 ml and 120ml presentations:
Unopened: 3 years
Opened: 4 months

6.4 Special precautions for storage

No special storage precautions

6.5 Nature and contents of container

Type III Amber glass bottle with a PP/LDPE child-resistant and tamper-evident cap.
Bottle sizes of 30 ml, 60 ml, 100 ml and 120 ml with a dosing pipette.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The bottle comes with a child resistant cap and should be opened as follows:

1. Push the plastic screw cap down while turning it counter clockwise.
2. Remove the unscrewed cap.
3. Insert the pipette into the bottle.
4. 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.
5. Holding the bottom ring, remove the entire pipette from the bottle.
6. Empty the pipette into any non-alcoholic drink, except for a tea, by sliding the upper ring down.
7. Close the bottle.
8. Rinse the pipette with some water.

7 MARKETING AUTHORISATION HOLDER

PLIVA Pharma Ltd
Vision House
Bedford Road
Petersfield
Hampshire
GU32 3QB
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 10622/0285

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/12/2008

10 DATE OF REVISION OF THE TEXT

19/12/2008

PACKAGE LEAFLET:
INFORMATION FOR THE USER**Risperidone 1mg/ml
Oral Solution**

Risperidone

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again
- If you have further questions, ask your doctor or pharmacist
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

In this leaflet:

1. What Risperidone Oral Solution is and what it is used for
2. Before you take Risperidone Oral Solution
3. How to take Risperidone Oral Solution
4. Possible side effects
5. How to store Risperidone Oral Solution
6. Further Information

1 What Risperidone Oral Solution is and what it is used for

Risperidone Oral Solution belongs to a group of medicines called 'anti-psychotics'.

Risperidone Oral Solution is used to treat the following:

- Schizophrenia, where you may see, hear or feel things that are not there, believe things that are not true or feel unusually suspicious, or confused
- Mania, where you may feel very excited, elated, agitated, enthusiastic or hyperactive. Mania occurs in an illness called 'bipolar disorder'
- Short-term treatment (up to 6 weeks) of long-term aggression in people with Alzheimer's dementia, who harm themselves or others. Alternative (non-drug) treatments should have been used previously
- Short-term treatment (up to 6 weeks) of long-term aggression in intellectually disabled children (at least 5 years of age) and adolescents with conduct disorder

2 Before you take Risperidone Oral Solution**Do not take Risperidone Oral Solution if:**

- You are allergic (hypersensitive) to risperidone or any of the other ingredients of Risperidone Oral Solution (listed in Section 6 below)

If you are not sure if the above applies to you, talk to your doctor or pharmacist before using Risperidone Oral Solution.

Take special care with Risperidone Oral Solution

Check with your doctor or pharmacist before taking Risperidone Oral Solution if:

- You have a heart problem. Examples include an irregular heart rhythm or if you are prone to low blood pressure or if you are using medicines for your blood pressure. Risperidone may cause low blood pressure. Your dose may need to be adjusted
- You know of any factors which would favour you having a stroke, such as high blood pressure, cardiovascular disorder or blood vessel problems in the brain
- You have Parkinson's disease or dementia
- You are diabetic
- You have epilepsy
- You are a man and you have ever had a prolonged or painful erection. If you experience this while taking Risperidone Oral Solution, contact your doctor straight away
- You have problems controlling your body temperature or overheating
- You have kidney problems
- You have liver problems
- You have an abnormally high level of the hormone prolactin in your blood or if you have a tumour, which is possibly dependent on prolactin

Tell your doctor immediately if you experience:

- Involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of risperidone may be needed
- Fever, severe muscle stiffness, sweating or a lowered level of consciousness (a disorder called 'neuroleptic malignant syndrome'). Immediate medical treatment may be needed

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Risperidone Oral Solution.

Risperidone Oral Solution may cause you to gain weight.

Elderly people with dementia

In elderly patients with dementia, there is an increased risk of stroke. You should not take risperidone if you have dementia caused by stroke.

During treatment with risperidone you should frequently see your doctor.

Medical treatment should be sought straight away if you or your care-giver notice a sudden change in your mental state or sudden weakness or numbness of your face, arms or legs, especially on one side, or slurred speech,

even for a short period of time. These may be signs of a stroke.

Children and adolescents

Before treatment is started in conduct disorder, other causes of aggressive behaviour should have been ruled out.

If during treatment with risperidone tiredness occurs, a change in the time of administration might improve attention difficulties.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal medicines. It is especially important to talk to your doctor or pharmacist if you are taking any of the following:

- Medicines that work on your brain such as to help you calm down (benzodiazepines) or some medicines for pain (opioids), medicines for allergy (some antihistamines), as risperidone may increase the sedative effect of all of these
- Medicines that may change the electrical activity of your heart, such as medicines for malaria, heart rhythm problems (such as quinidine), allergies (anti-histamines), some antidepressants or other medicines for mental problems
- Medicines that cause a slow heart beat
- Medicines that cause low blood potassium (e.g. certain diuretics)
- Medicines to treat elevated blood pressure. Risperidone can lower blood pressure
- Medicines for Parkinson's disease (such as levodopa)
- Water tablets (diuretics) used for heart problems or swelling of parts of your body due to a build up of too much fluid (such as furosemide or chlorothiazide). Risperidone Oral Solution taken by itself or with furosemide, may have an increased risk of stroke or death in elderly people with dementia

The following medicines may reduce the effect of risperidone

- Rifampicin (a medicine for treating some infections)
- Carbamazepine, phenytoin (medicines for epilepsy)
- Phenobarbital

If you start or stop taking such medicines you may need a different dose of risperidone.

The following medicines may increase the effect of risperidone

- Quinidine (used for certain types of heart disease)
- Antidepressants such as paroxetine, fluoxetine, tricyclic antidepressants

- Medicines known as beta blockers (used to treat high blood pressure)
- Phenothiazines (e.g. used to treat psychosis or to calm down)
- Cimetidine, ranitidine (blockers of the acidity of stomach)

If you start or stop taking such medicines you may need a different dose of risperidone.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Risperidone Oral Solution

Taking Risperidone Oral Solution with food and drink

You can take this medicine with or without food. You should avoid drinking alcohol when taking Risperidone Oral Solution.

Pregnancy and breast-feeding

- Talk to your doctor before using Risperidone Oral Solution if you are pregnant, trying to become pregnant or breast-feeding. Your doctor will decide if you can take it
- Shaking, muscle stiffness and problems feeding, all of which are reversible, have been seen in newborn babies when Risperidone Oral Solution was used during the last trimester of pregnancy.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Dizziness, tiredness, and vision problems may occur during treatment with Risperidone Oral Solution. Do not drive or use any tools or machines without talking to your doctor first.

3 How to take Risperidone Oral Solution**How much to take****For the treatment of schizophrenia****Adults**

- The usual starting dose is 2mg per day, this may be increased to 4mg per day on the second day
- Your dose may then be adjusted by your doctor depending on how you respond to the treatment
- Most people feel better with daily doses of 4 to 6mg
- This total daily dose can be divided into either one or two doses a day. Your doctor will tell you which is the best for you

Elderly people

- Your starting dose will normally be 0.5mg twice a day
- Your dose may then be gradually increased by your doctor to 1mg to 2mg twice a day
- Your doctor will tell you which is the best for you

Children and adolescents

- Children and adolescents under 18 years old should not be treated with Risperidone Oral Solution for schizophrenia

For the treatment of mania**Adults**

- Your starting dose will usually be 2mg once a day
- Your dose may then be gradually adjusted by your doctor depending on how you respond to the treatment
- Most people feel better with doses of 1 to 6mg once a day

Elderly people

- Your starting dose will usually be 0.5mg twice a day
- Your dose may then be gradually adjusted by your doctor to 1mg to 2mg twice a day depending on how much you respond to the treatment

Children and adolescents

- Children and adolescents under 18 years old should not be treated with Risperidone Oral Solution for bipolar mania

For the treatment of long-standing aggression in people with Alzheimer's dementia**Adults (including elderly people)**

- Your starting dose will normally be 0.25mg twice a day
- Your dose may then be gradually adjusted by your doctor depending on how you respond to the treatment
- Most people feel better with 0.5mg twice a day. Some patients may need 1mg twice a day
- Treatment duration in patients with Alzheimer's dementia should be not more than 6 weeks

For the treatment of conduct disorder in children and adolescents

The dose will depend on your child's weight:

For children who weigh less than 50kg

- The starting dose will normally be 0.25mg once a day
- The dose may be increased every other day in steps of 0.25mg per day
- The usual maintenance dose is 0.25mg to 0.75mg once a day

For children who weigh 50kg or more

- The starting dose will normally be 0.5mg once a day
- The dose may be increased every other day in steps of 0.5mg per day
- The usual maintenance dose is 0.5mg to 1.5mg once a day.

Treatment duration in patients with conduct disorder should be not more than 6 weeks.

Children under 5 years old should not be treated with Risperidone Oral Solution for conduct disorder.

People with kidney or liver problems

Regardless of the disease to be treated, all starting doses and following doses of risperidone should be halved. Dose increases should be slower in these patients.

Risperidone should be used with caution in this patient group.

How to take Risperidone Oral Solution

Always take Risperidone Oral Solution exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Your doctor will tell you how much medicine to take and for how long. This will depend on your condition and varies from person to person. The amount of medicine you should take is explained under the 'How much to take' sub-heading below.

Risperidone Oral Solution

The solution comes with a syringe (pipette). This should be used to help you measure the exact amount of medicine you need.

Follow these steps:

1. Remove the child-proof cap. Push the plastic screw cap down while turning it counter clockwise
2. Insert the syringe into the bottle
3. While holding the bottom ring, pull the top ring up to the mark that corresponds to the number of millilitres or mg you need to take
4. Holding the bottom ring, remove the entire syringe from the bottle
5. Empty the syringe into any non-alcoholic drink, except for tea. Slide the upper ring down
6. Close the bottle
7. Rinse the syringe with some water

If you take more Risperidone Oral Solution than you should

- See a doctor right away. Take the medicine pack with you
- In case of overdose you may feel sleepy or tired, or have abnormal body movements, problems standing and walking, feel dizzy due to low blood pressure, or have abnormal heart beats or fits.

If you forget to take Risperidone Oral Solution

- If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose and continue as usual. If you miss two or more doses, contact your doctor
- Do not take a double dose (two doses at the same time) to make up for a forgotten dose

If you stop taking Risperidone Oral Solution

You should not stop taking this medicine unless told to do so by your doctor. Your symptoms

may return. If your doctor decides to stop this medicine, your dose may be decreased gradually over a few days.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 Possible side effects

Like all medicines, Risperidone Oral Solution can cause side effects, although not everybody gets them.

Very common: affects more than 1 user in 10
Common: affects 1 to 10 users in 100

Uncommon: affects 1 to 10 users in 1,000

Rare: affects 1 to 10 users in 10,000

Very rare: affects less than 1 user in 10,000

Not known: frequency cannot be estimated from the available data.

The following side effects may happen:

Very Common (affect more than 1 user in 10):

- Parkinsonism. This is a medical term that includes many symptoms. Each individual symptom may occur less frequently than in 1 in 10 people. Parkinsonism includes: increase in saliva secretion or watery mouth, musculoskeletal stiffness, drooling, jerks when bending the limbs, slow, reduced or impaired body movements, no expression on the face, muscle tightness, stiff neck, muscle stiffness, small, shuffling, hurried steps and lack of normal arm movements when walking, persistent blinking in response to tapping of the forehead (an abnormal reflex)
- Headache, difficulty falling or staying asleep

Common (affect 1 to 10 users in 100):

- Drowsiness, fatigue, restlessness, inability to sit still, irritability, anxiety, sleepiness, dizziness, poor attention, feeling exhausted, sleep disorder
- Vomiting, diarrhoea, constipation, nausea, increased appetite, abdominal pain or discomfort, sore throat, dry mouth
- Weight increased, increase in body temperature, decreased appetite
- Difficulty breathing, lung infection (pneumonia), flu, infection of the breathing passages, blurred vision, nose congestion, nose bleeding, cough
- Urinary tract infection, bed wetting
- Muscle spasm, involuntary movements of face or arms and legs, joint pain, back pain, swelling of arms and legs, pain in arms and legs
- Rash, skin redness
- Fast beating heart, chest pain
- Blood prolactin hormone level increased

Uncommon (affect 1 to 10 users in 1000):

- Excessive drinking of water, stool incontinence, thirsty, very hard faeces, hoarseness or voice disorder

- Lung infection caused by inhaling of food into the breathing passages, bladder infection, 'pink eye', sinus infection, viral infection, ear infection, tonsil infection, infection under the skin, eye infection, stomach infection, eye discharge, yeast infection of nails

- Abnormal electrical conduction of the heart, drop in blood pressure after standing, low blood pressure, feeling dizzy after changing body position, abnormal electric activity tracing of the heart (ECG), abnormal heart rhythm, awareness of heart beating, heart rate increased or decreased

- Urinary incontinence, pain when passing urine, frequent passing of urine
- Confused, disturbance in attention, low level of consciousness, excessive sleep, nervousness, elated mood (mania), lack of energy and interest

- Blood sugar increased, liver enzymes increased, white blood cell count decreased, low haemoglobin or red blood cell count (anaemia), increase in eosinophils (special white blood cells), blood creatinine phosphokinase increased, decrease in platelets (blood cells that help you stop bleeding)

- Muscle weakness, muscle pain, ear pain, neck pain, joint swelling, abnormal posture, joint stiffness, musculoskeletal chest pain, chest discomfort

- Skin lesion, skin disorder, dry skin, intense itching of skin, acne, hair loss, skin inflammation caused by mites, skin discoloration, thickening of skin, flushing, reduced skin sensitivity to pain or touch, inflammation of oily skin

- No menstruation, sexual dysfunction, erectile dysfunction, ejaculation disorder, breast discharge, enlargement of breast in men, decreased sexual drive, irregular menstruation, vaginal discharge

- Fainting, gait disturbance, sluggishness, decreased appetite resulting in malnutrition and low body weight, feeling 'out of sorts', balance disorder, allergy, edema, speech disorder, chills, abnormal coordination

- Painful oversensitivity to light, increased blood flow to the eye, eye swelling, dry eye, increase in tears

- Breathing passage disorder, lung congestion, crackly lung noise, congestion of breathing passages, trouble speaking, difficulty swallowing, cough with sputum, coarse/whistling sound during breathing, flu-like illness, sinus congestion

- Unresponsive to stimuli, loss of consciousness, sudden swelling of lips and eyes along with difficulty breathing, sudden weakness or numbness of the face, arms, or legs, especially on one side, or instances of

slurred speech that last for less than 24 hours (these are called mini-strokes or strokes), involuntary movements of face, arms, or legs, ringing in ears, face edema

Rare (affect 1 to 10 users in 10,000):

- Inability to reach orgasm, menstrual disorder
- Dandruff
- Drug allergy, coldness in arms and legs, lip swelling, lip inflammation
- Glaucoma, reduced visual clarity, eyelid margin crusting, eye rolling
- Lack of emotion
- Change in consciousness with increased body temperature and twitching of muscles, edema all over the body, drug withdrawal syndrome, body temperature decreased
- Fast shallow breathing, trouble breathing during sleep, chronic otitis media
- Obstruction of intestine
- Reduced blood flow to the brain
- Decrease in white blood cells, inappropriate secretion of a hormone that controls urine volume
- Breakdown of muscle fibers and pain in muscles (rhabdomyolysis), movement disorder
- Coma due to uncontrolled diabetes
- Yellowing of the skin and the eyes (jaundice)
- Inflammation of the pancreas

Very rare (affect less than 1 user in 10,000):

- Life threatening complications of uncontrolled diabetes

Unknown frequency of occurrence

(frequency cannot be estimated from the available data):

- Severe allergic reaction resulting in difficulty in breathing and shock
- No granulocytes (a type of white blood cell to help you against infection)
- Prolonged and painful erection
- Dangerously excessive intake of water

The Long Acting Injectable Risperidone

The following side effects have been reported with the use of a long acting injection of risperidone. Even if you are not being treated with long acting injections of risperidone but you experience any of the following, talk to your doctor.

- Infection of the intestine
- Abscess under the skin, tingling pricking or numbness of skin, inflammation of the skin
- Decrease in white blood cell counts that helps to protect you against bacterial infection
- Depression
- Convulsion
- Eye blinking
- Sensation of spinning or swaying
- Slow beating heart, high blood pressure

- Toothache, tongue spasm
- Buttock pain
- Weight decreased

If any of the side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.

5 How to store Risperidone Oral Solution

Keep out of the reach and sight of children. Store in the original package.

Do not use the solution after the expiry date printed on the carton and bottle label. The expiry date refers to the last day of that month. Once opened do not use the solution for longer than 4 months.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 Further Information**What Risperidone Oral Solution contains**

The active substance is risperidone.

The other ingredients are: tartaric acid (E 334), benzoic acid (E 210), hydrochloric acid and purified water.

What Risperidone Oral Solution looks like and contents of the pack

Risperidone Oral Solution is a clear, colourless solution. It is available in bottles containing 30ml, 60ml, 100ml and 120ml; not all pack sizes may be marketed.

Marketing Authorisation Holder

PLIVA Pharma Ltd
Vision House, Bedford Road
Petersfield,
Hampshire, GU32 3QB
United Kingdom.

Manufacturer

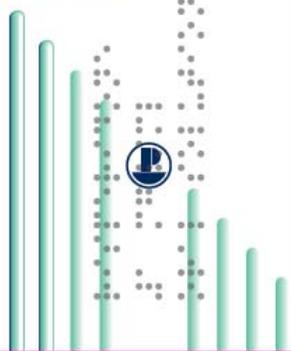
Chanelle Medical
Loughrea, Co. Galway, Ireland
or
Pliva Lachema a.s.
Karasek 1/1767
62133 Brno, Czech Republic
This leaflet was last revised in
December 2008.

PL 10622/0285



Risperidone
1mg/ml
Oral Solution

Contains 1mg risperidone
per 1ml of solution
30ml bottle



Batch:
Expiry:

Risperidone
1mg/ml
Oral Solution

Contains 1mg risperidone
per 1ml of solution
30ml bottle

PLIVA

Risperidone
1mg/ml
Oral Solution

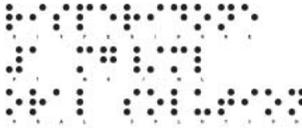
Contains 1mg risperidone per 1ml of solution.
For oral use.
Shake well before use.

Dosage:
As directed by your doctor.
Use within 4 months after opening.
Read the package leaflet before use.

**KEEP OUT OF THE REACH AND SIGHT
OF CHILDREN**

30ml bottle

PLIVA



Risperidone
1mg/ml
Oral Solution

30ml bottle

MA Holder:
PLIVA Pharma Ltd
Vision House
Bedford Road
Petersfield
Hampshire
GU32 3QB
United Kingdom

[POM]
PL 10622/0285
77782-C1



PLIVA

MA Holder:
PLIVA Pharma Ltd
Vision House
Bedford Road
Petersfield
Hampshire, GU32 3QB
United Kingdom

[POM]
PL 10622/0285
77782-L1

Batch:
Expiry:

Risperidone
1mg/ml
Oral Solution

Contains 1mg risperidone
per 1ml of solution.
30ml bottle

For oral use.
Shake well before use.
To be taken as directed by
your doctor.
Use within 4 months after opening.
Read the package leaflet
before use.

**KEEP OUT OF THE REACH
AND SIGHT OF CHILDREN**

MA Holder:
PLIVA Pharma Ltd
Vision House
Bedford Road
Petersfield
Hampshire, GU32 3QB
United Kingdom

[POM]
PL 10622/0285
77782-L1

Batch:
Expiry:

Risperidone
1mg/ml
Oral Solution
 60ml bottle

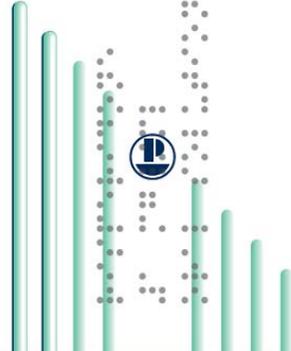
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<p style="font-size: x-small;">MA Holder: PLIVA Pharma Ltd Vision House Bedford Road Petersfield Hampshire GU32 3QB United Kingdom</p> <p style="font-size: x-small; border: 1px solid black; display: inline-block; padding: 2px;">POM</p> <p style="font-size: x-small;">PL 10622/0285 77883-C1</p>		<p style="font-size: x-small; text-align: center;">5 020220 778836</p> <p style="text-align: center; font-weight: bold; margin-top: 10px;">PLIVA</p>

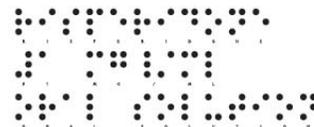
UKPAR

Risperidone
1mg/ml
Oral Solution
 60ml bottle

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Risperidone 1mg/ml Oral Solution
 100ml bottle

<h2 style="margin: 0;">Risperidone 1mg/ml Oral Solution</h2> <p>Contains 1mg risperidone per 1ml of solution 100ml bottle</p>  <p>Batch: Expiry:</p>	<h3 style="margin: 0;">Risperidone 1mg/ml Oral Solution</h3> <p>Contains 1mg risperidone per 1ml of solution 100ml bottle</p> <p>Contains 1mg risperidone per 1ml of solution. For oral use. Shake well before use.</p> <p>Dosage: As directed by your doctor. Use within 4 months after opening. Read the package leaflet before use.</p> <p>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN</p> <p style="text-align: center;">100ml bottle</p> <p style="text-align: center;"> PLIVA</p>	<p>MA Holder: PLIVA Pharma Ltd Vision House Bedford Road Petersfield Hampshire GU32 3QB United Kingdom</p> <p>POM PL 10622/0285 77522-C1</p>  <p>5 020220 775224</p> <p style="text-align: center;"> PLIVA</p>
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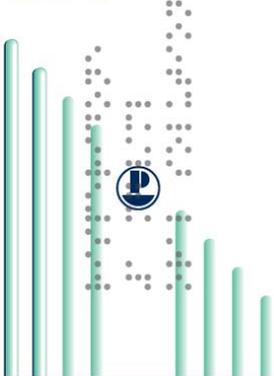


Risperidone 1mg/ml Oral Solution
 100ml bottle

<p>Contains 1mg risperidone per 1ml of solution.</p> <p>POM PL 10622/0285 77522-C1</p>	<p>For oral use. Shake well before use. To be taken as directed by your doctor. Use within 4 months after opening. Read the package leaflet before use. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN</p> <p>MA Holder: PLIVA Pharma Ltd Vision House, Bedford Road Petersfield Hampshire, GU32 3QB United Kingdom</p>
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POM
 PL 10622/0285
 77522-C1
 Batch:
 Expiry:

<p>Risperidone 1mg/ml Oral Solution</p> <p>Contains 1mg risperidone per 1ml of solution 120ml bottle</p> 	<p>Risperidone 1mg/ml Oral Solution</p> <p>Contains 1mg risperidone per 1ml of solution 120ml bottle</p> <p>PLIVA</p>	<p>Contains 1mg risperidone per 1ml of solution. For oral use. Shake well before use.</p> <p>Dosage: As directed by your doctor. Use within 4 months after opening. Read the package leaflet before use.</p> <p>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN</p> <p>120ml bottle</p> <p>PLIVA</p>	<p>Risperidone 1mg/ml Oral Solution</p> <p>120ml bottle</p> <p>MA Holder: PLIVA Pharma Ltd Vision House Bedford Road Peterfield Hampshire GU32 3GB United Kingdom</p> <p>POM PL 10622/0285 77681-C1</p>  <p>5 020220 776818</p> <p>PLIVA</p>
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<p>Risperidone 1mg/ml Oral Solution</p> <p>120ml bottle</p>			<p>Risperidone 1mg/ml Oral Solution</p> <p>120ml bottle</p> <p>Contains 1mg risperidone per 1ml of solution.</p> <p>For oral use. Shake well before use. To be taken as directed by your doctor. Use within 4 months after opening. Read the package leaflet before use. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN</p> <p>MA Holder: PLIVA Pharma Ltd Vision House, Bedford Road Peterfield Hampshire, GU32 3GB United Kingdom</p> <p>POM PL 10622/0285 77681-U</p> <p>Batch: Expiry:</p>