

RISPERIDONE 1 MG/ML ORAL SOLUTION

PL 00289/0816-7

UKPAR

TABLE OF CONTENTS

Lay summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 14
Steps taken after authorisation	Page 11
Summary of product characteristics	Page 12
Patient information leaflet	Page 31
Labelling	Page 36

RISPERIDONE 1 MG/ML ORAL SOLUTION

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) for the medicinal product Risperidone 1 mg/ml Oral Solution (Product Licence numbers: 00289/0816 and 00289/0817).

Risperidone 1 mg/ml Oral Solution contains the active ingredient risperidone, which is used to treat mental disorders. The solution is used to treat conditions that affect the way you think, feel or act. It is also used to treat a type of mental illness called bipolar disorder, which causes dramatic mood swings.

Risperidone 1 mg/ml Oral Solution raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence Marketing Authorisations have been granted.

RISPERIDONE 1 MG/ML ORAL SOLUTION

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SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 7
Clinical assessment (including statistical assessment)	Page 8
Overall conclusions and risk benefit assessment	Page 10

INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal product Risperidone 1 mg/ml Oral Solution to Teva UK Limited on 7 December 2007. This medicine is only available on prescription.

These applications (one complex and one standard) were made under Directive 2001/83/EC Article 10.1, first paragraph, claiming that this medicinal product is a generic version of the reference product Risperdal liquid (PL 00242/0199), marketed by Jansen Cilag in the UK since 1995. The 10-year rule is, therefore, adhered to and this is considered satisfactory.

Risperidone Oral Solution contains the active ingredient risperidone, an antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives. Risperidone is a selective monoaminergic antagonist with a high affinity for both 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, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extra pyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

Risperidone Oral Solution is used for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. The solution can also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia. Risperidone is also effective in maintaining clinical improvement during continuation therapy in patients who have shown an initial treatment response. Risperidone Oral Solution is indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Chemical name: 3-{2-[4[(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one
CAS registry number: 106266-06-2
Generic name: Risperidone (Form I)

The structural formula is provided in support of the proposed name. The molecular formula $C_{23}H_{27}FN_4O_2$ is also provided and both are in agreement with the Ph. Eur. monograph for this active substance.

Risperidone with a molecular weight of 410.5 is a 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. The melting point is recorded as between 169 and 173 °C. Risperidone is known to show polymorphism. The active substance is the subject of a Ph. Eur. monograph.

An appropriate specification in line with the Ph Eur monograph has been provided.

Results of batch analyses are satisfactory with respect to the drug substance specification as set by the company.

Full specifications are provided for the packaging used to store the risperidone, these are satisfactory.

Appropriate stability data have been generated supporting a retest period of 2 years, with no specific storage instructions.

DRUG PRODUCT

Description and Composition of the Drug Product

The qualitative composition of the drug product is as follows:

Ingredient	Function	Reference to Standards
Risperidone	Drug substance	Ph. Eur.
Benzoic acid	Preservative	Ph. Eur.
Sorbitol 70% solution	Sweetening agent	Ph. Eur.
Purified water	Solvent	Ph. Eur.

All excipients are the subject of Ph. Eur. monographs and suitable specifications have been provided that are supported by certificates of analysis from both the supplier and the finished product manufacturer.

The applicant has provided satisfactory certificates stating that neither the excipients nor the active substance contain substances of human or animal origin.

Manufacture

A description and flow-chart of the manufacturing method has been provided. The in-process controls and acceptance criteria are acceptable.

Process validation has been carried out. All in-process results comply with the proposed acceptance criteria, demonstrating that the manufacturing process is consistent. The manufacturing process may be considered validated.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Certificates of analysis have been provided for batches of the product and confirm that they meet the proposed specifications. Certificates of analysis have been provided for any working standards used.

Container Closure System

The finished product is packed in amber glass bottles with white plastic child-resistant polypropylene closures. White plastic LDPE oral dosing syringes are provided.

Satisfactory specifications supported by certificates of analysis from the container supplier have been provided.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years before opening and of 3 months once the product is first opened are appropriate. No special storage precautions are necessary.

Bioequivalence / Bioavailability

No bioequivalence study is required as the product is an aqueous oral solution at the time of administration and contains the active substance in the same concentration as an oral solution currently approved as a medicinal product.

Product literature

All product literature (SPCs, PILs and labelling) are satisfactory. The 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. 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.

Conclusions

Licences may be granted for these applications.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

INTRODUCTION

These are national abridged applications claiming to be generic to Risperdal liquid (PL 00242/0199), which has been licensed to Jansen Cilag in the UK for more than 10 years.

BACKGROUND

Risperidone is well characterised in the literature and is indicated for treatment of acute and chronic schizophrenic psychoses. It belongs to a new class of antipsychotic agents, the benzisoxazole-derivatives.

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT₂ and dopaminergic D₂ receptors. It binds also to alpha₁-adrenergic receptors and, with lower affinity, to H₁-histaminergic and alpha₂-adrenergic receptors. It has no affinity for cholinergic receptors. Although Risperidone is a potent D₂ antagonist, which is considered to be the principal mechanism by which it improves the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extrapyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

INDICATIONS

The applicant has submitted the following:

“Risperidone is indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperidone also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Risperidone is also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response. Risperidone is indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviour.

Risperidone is not licensed for the treatment of behavioural symptoms of dementia (see section 4.4).”

The description above is essentially identical to the SPC text for the licensed indications of the reference product and is satisfactory.

DOSE AND DOSE SCHEDULE

Section 4.2 of the SPC is essentially identical to that of the current originator SPC and no changes are required.

TOXICOLOGY

No new data.

CLINICAL PHARMACOLOGY

There is no requirement for a bioequivalence study, as the two formulations are aqueous solutions.

EFFICACY

No new data.

SAFETY

No new data.

EXPERT REPORTS

A satisfactory expert report is provided by an appropriately qualified physician.

PATIENT INFORMATION LEAFLET (PIL)

A satisfactory PIL has been provided.

LABELLING

All product labelling is satisfactory

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is considered to be consistent with the current originator SPC.

DISCUSSION

All product literature is satisfactory. Bioequivalence to the reference product is established, as the two formulations are aqueous solutions.

MEDICAL CONCLUSION

Marketing authorisations may be granted for these preparations.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Risperidone 1 mg/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 applications of this type.

EFFICACY

The efficacy of risperidone is well established.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with Risperidone 1 mg/ml Oral Solution. The risk benefit is therefore considered to be positive.

RISPERIDONE 1 MG/ML ORAL SOLUTION

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 31 December 2004
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 17 August 2005
4	Following assessment of the application the MHRA requested further information relating to the quality dossier on 17 March 2006 and the clinical dossier on 24 July 2006
5	The applicant responded to the MHRA's requests, providing further information on the quality and clinical dossiers on 8 August 2006
6	Following assessment of the response the MHRA requested further information relating to the quality dossier on 11 October 2006
7	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 6 April 2007
8	Following assessment of the response the MHRA requested further information relating to the quality dossier on 15 October 2007
9	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 31 October 2007
10	The application was determined on 7 December 2007

SUMMARY OF PRODUCT CHARACTERISTICS

PL 00289/0816:

1 NAME OF THE MEDICINAL PRODUCT

Risperidone 1 mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 1 mg of risperidone.

Excipients

1 ml solution contains 150.0 mg of sorbitol.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution

Clear, colourless to yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Risperidone is indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperidone also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Risperidone is also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response. Risperidone is indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviour.

Risperidone is not licensed for the treatment of behavioural symptoms of dementia (see section 4.4).

4.2 Posology and method of administration

1 ml of Risperidone Solution contains 1 mg risperidone. If necessary risperidone may be diluted with mineral water, orange juice or black coffee. When diluted in this way, the product should be used immediately. The liquid should not be mixed with tea (see Section 6. Pharmaceutical Particulars).

4.2.a Schizophrenia:

Switching from other antipsychotics: where medically appropriate, gradual discontinuation of the previous treatment while risperidone therapy is initiated

is recommended. Where medically appropriate when switching patients from depot antipsychotics, consider initiating risperidone therapy in place of the next scheduled injection. The need for continuing existing antiparkinson medication should be re-evaluated periodically.

Adults

Risperidone may be given once or twice daily. All patients, whether acute or chronic, should start with 2 mg/day risperidone. The dosage may be increased to 4 mg/day on the second day. Some patients, such as first episode patients, may benefit from a slower rate of titration. From then on the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6 mg/day although in some, an optimal response may be obtained at lower doses.

Doses above 10 mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extrapyramidal symptoms.

Doses above 10 mg/day should only be used in individual patients if the benefit is considered to outweigh the risk. Doses above 16 mg/day have not been extensively evaluated for safety and therefore should not be used.

Elderly

A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Children

Use of risperidone for schizophrenia in children aged less than 15 years has not been formally evaluated.

Renal and liver disease

A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Risperidone should be used with caution in this group of patients until further experience is gained.

4.2.b Bipolar Mania:

Adults

Risperidone should be administered on a once daily schedule, starting with 2 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. A dosing range between 1 and 6 mg per day is recommended.

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 bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Renal and liver disease

A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Risperidone should be used with caution in this group of patients until further

experience is gained.

Combined use with mood stabilisers

There is limited information on the combined use of risperidone with carbamazepine in bipolar mania. Carbamazepine has been shown to induce the metabolism of risperidone producing lower plasma levels of the antipsychotic fraction of risperidone (see Section 4.5). It is therefore not recommended to coadminister risperidone with carbamazepine in bipolar mania patients until further experience is gained. The combined use with lithium or valproate does not require any adjustment of the dose of risperidone.

Method of administration

Oral use.

4.3 Contraindications

Risperidone Oral Solution is contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

4.4 Special warnings and precautions for use

Elderly patients with dementia

Elderly patients with dementia treated with atypical antipsychotic drugs had an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including Risperdal. In placebocontrolled 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 mean age (range) of patients who died was 86 years (67-100).

In these trials treatment with furosemide plus risperidone was associated with a higher incidence of mortality compared to treatment with risperidone or furosemide alone, however, the mechanism for an interaction is unclear. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use. 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)

Risperidone is not recommended for the treatment of behavioural symptoms of dementia because of an increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks).

Treatment of acute psychoses in patients with a history of dementia should be limited to short term only and should be under specialist advice.

Data from randomised clinical trials conducted in elderly (>65 years) patients with dementia indicate that there is an approximately 3-fold increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks) with risperidone, compared with placebo.

Cerebrovascular adverse events occurred in 3.3% (33/989) of patients treated

with risperidone and 1.2% (8/693) of patients with placebo. The Odds Ratio (95% exact confidence interval) was 2.96 (1.33, 7.45).

Physicians should consider carefully the risk of cerebrovascular adverse events with Risperidone (given the observations in elderly patients with dementia detailed above) before treating any patient with a previous history of CVA/TIA. Consideration should also be given to other risk factors for cerebrovascular disease including hypertension, diabetes, current smoking, atrial fibrillation, etc.

Alpha-blocking activity

Due to the alpha-blocking activity of risperidone, orthostatic hypotension can occur, especially during the initial dose-titration period. A dose reduction should be considered if hypotension occurs.

Risperidone should be used with caution in patients with known cardiovascular disease including those associated with prolongation of the QT interval and the dose should be gradually titrated. In clinical trials, risperidone was not associated with an increase in QTc intervals. As with other antipsychotics, caution is advised when prescribing with medications known to prolong the QT interval.

If further sedation is required, an additional drug (such as a benzodiazepine) should be administered rather than increasing the dose of risperidone.

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)

Drugs 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. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

Neuroleptic Malignant Syndrome (NMS)

Neuroleptic malignant syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels, has been reported to occur with neuroleptics. In this event all antipsychotic drugs including risperidone should be discontinued.

It is recommended to halve both the starting dose and the subsequent dose increments in geriatric patients and in patients with renal or liver insufficiency. Caution should also be exercised when prescribing risperidone to patients with Parkinson's disease since, theoretically, it may cause a deterioration of the disease.

Hyperglycemia

Hyperglycaemia 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 (see also section 4.8 Undesirable effects).

Other

Classical neuroleptics are known to lower the seizure threshold. Caution is

recommended when treating patients with epilepsy.

As with other antipsychotics, patients should be advised of the potential for weight gain.

Acute withdrawal symptoms, including nausea, vomiting, sweating and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

Use of risperidone for schizophrenia in children aged less than 15 years has not been formally evaluated.

This product contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Possible interactions of risperidone with other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone it should be used with caution in combination with other centrally acting drugs including alcohol.

Risperidone may antagonise the effect of levodopa and other dopamineagonists.

Carbamazepine has been shown to decrease the plasma levels of the antipsychotic fraction of Risperidone. A similar effect might be anticipated with other drugs which stimulate metabolising enzymes in the liver. On initiation of carbamazepine or other hepatic enzyme-inducing drugs, the dosage of risperidone should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of risperidone should be re-evaluated and decreased if necessary.

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Fluoxetine and paroxetine, CYP2D6 inhibitors, may increase the plasma concentration of risperidone but less so of the active antipsychotic fraction. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of Risperdal. Based on *in vitro* studies, the same interaction may occur with haloperidol. 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 cholinesterase inhibitor galantamine does not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

When risperidone is taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma

proteins.

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

Risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate or topiramate. The potential for reduced toleration of the combination treatment should be taken into consideration when coadministering risperidone and topiramate.

In patients on long-term lithium and older/typical neuroleptic therapy, no significant change occurred in the pharmacokinetics of lithium after substitution of the concomitant neuroleptic with risperidone.

Food does not affect the absorption of risperidone from the stomach.

4.6 Pregnancy and lactation

Although, in experimental animals, risperidone did not show direct reproductive toxicity, some indirect, prolactin- and CNS-mediated effects were observed, typically delayed oestrus and changes in mating and nursing behaviour in rats. No teratogenic effect of risperidone was noted in any study. The safety of risperidone for use during human pregnancy has not been established. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of risperidone during the last trimester of pregnancy. Therefore, risperidone should only be used during pregnancy if the benefits outweigh the risks.

In animal studies, risperidone and 9-hydroxyrisperidone are excreted in the milk. It has been demonstrated that risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breastfeed.

4.7 Effects on ability to drive and use machines

Risperidone may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 Undesirable effects

Risperidone is generally well tolerated and in many instances it has been difficult to differentiate adverse events from symptoms of the underlying disease. Adverse events observed in association with the use of risperidone include:

Common: insomnia, agitation, anxiety, headache.

Less common: somnolence, fatigue, dizziness, impaired concentration, constipation, dyspepsia, nausea/vomiting, abdominal pain, blurred vision, priapism, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, urinary incontinence, rhinitis, rash and other allergic reactions.

Cerebrovascular accidents have been observed during treatment with risperidone (see section 4.4).

Hyperglycemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment.

The incidence and severity of extrapyramidal symptoms are significantly less than with haloperidol. However, in some cases the following extrapyramidal symptoms may occur: tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia including oculogyric crisis. If acute in nature, these symptoms are usually mild and are reversible upon dose reduction and/or administration of antiparkinson medication, if necessary. In clinical trials in patients with acute mania risperidone treatment resulted in an incidence of EPS > 10%. This is lower than the incidence observed in patients treated with classical neuroleptics.

Occasionally, orthostatic dizziness, hypotension including orthostatic, tachycardia including reflex tachycardia and hypertension have been observed following administration of risperidone.

Risperidone can induce a dose-dependent increase in plasma prolactin concentration. Possible associated manifestations are: galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and amenorrhoea. Weight gain, oedema and increased hepatic enzyme levels have been observed during treatment with risperidone.

A decrease in neutrophil and/or thrombocyte count has been reported.

As with classical neuroleptics, rare cases of the following have been reported in schizophrenic patients: water intoxication with hyponatraemia, either due to polydipsia or to the syndrome of inappropriate secretion of antidiuretic hormone; tardive dyskinesia, body temperature dysregulation and seizures.

Benign pituitary adenomas have been reported very rarely in risperidone users during postmarketing surveillance. No causal association has been established.

Very rare cases of angioedema have been reported in postmarketing experience.

Sedation has been reported more frequently in children and adolescents than in adults. In general, sedation is mild and transient.

Withdrawal reactions have been reported in association with antipsychotic drugs (see section 4.4).

4.9 Overdose

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, rare cases of QT-prolongation have been reported. In case of acute overdosage, the possibility of multiple drug involvement should

be considered.

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. 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, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous system – Psycholeptics – Antipsychotics – Other antipsychotics

ATC code: N05A X08

Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

Risperidone is a selective monoaminergic antagonist with a high affinity for both 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, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extrapyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

5.2 Pharmacokinetic properties

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. Food does not affect the absorption of risperidone from the stomach. The effect of food particles in the mouth on absorption has not been studied.

The most important route of metabolism of is hydroxylation by cytochrome CYP 2D6 to 9-hydroxy-risperidone which has a similar pharmacological activity to risperidone. This hydroxylation is subject to debrisoquine-type genetic polymorphism but this does not affect the active antipsychotic fraction since this consists of risperidone and its active metabolite 9-hydroxyrisperidone. After oral administration, the elimination half-life of the active antipsychotic fraction is 24 hours.

A single-dose study showed higher active plasma concentrations and a slower elimination of risperidone in the elderly and in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency.

Topiramate modestly reduces the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance. The bioavailability of topiramate is slightly decreased when administered in combination with risperidone. This interaction is not likely to be clinically significant.

Risperidone oro-dispersible tablets and oral solution are bioequivalent to Risperidone oral tablets.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber other than those already provided in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzoic acid
Sorbitol 70% solution
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Before opening: 3 years
After first opening: 3 months

6.4 Special precautions for storage

Before opening: This medicinal product does not require any special storage conditions.

After first opening: This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Amber glass bottles with white plastic child-resistant polypropylene closures. 30 & 100 ml of Risperidone. 1 mg/ml Oral Solution.

3 ml or 5 ml white plastic LDPE oral dosing syringes graduated at every 0.05 ml.

5 ml white plastic LDPE oral dosing syringes graduated at every 0.1 ml.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
England

- 8 MARKETING AUTHORISATION NUMBER(S)**
PL 00289/0816
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**
07/12/2007
- 10 DATE OF REVISION OF THE TEXT**
07/12/2007

PL 00289/0817:

- 1 NAME OF THE MEDICINAL PRODUCT**
Risperidone 1 mg/ml Oral Solution
- 2 QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each ml of solution contains 1 mg of risperidone.
Excipients
1 ml solution contains 150.0 mg of sorbitol.
For a full list of excipients, see section 6.1.
- 3 PHARMACEUTICAL FORM**
Oral solution
Clear, colourless to yellow solution.
- 4 CLINICAL PARTICULARS**

4.1 Therapeutic indications

Risperidone is indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperidone also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Risperidone is also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response. Risperidone is indicated for the treatment of mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviour.

Risperidone is not licensed for the treatment of behavioural symptoms of

dementia (see section 4.4).

4.2 Posology and method of administration

1 ml of Risperidone Solution contains 1 mg risperidone. If necessary risperidone may be diluted with mineral water, orange juice or black coffee. When diluted in this way, the product should be used immediately. The liquid should not be mixed with tea (see Section 6. Pharmaceutical Particulars).

4.2.a Schizophrenia:

Switching from other antipsychotics: where medically appropriate, gradual discontinuation of the previous treatment while risperidone therapy is initiated is recommended. Where medically appropriate when switching patients from depot antipsychotics, consider initiating risperidone therapy in place of the next scheduled injection. The need for continuing existing antiparkinson medication should be re-evaluated periodically.

Adults

Risperidone may be given once or twice daily. All patients, whether acute or chronic, should start with 2 mg/day risperidone. The dosage may be increased to 4 mg/day on the second day. Some patients, such as first episode patients, may benefit from a slower rate of titration. From then on the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6 mg/day although in some, an optimal response may be obtained at lower doses.

Doses above 10 mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extrapyramidal symptoms.

Doses above 10 mg/day should only be used in individual patients if the benefit

is considered to outweigh the risk. Doses above 16 mg/day have not been extensively evaluated for safety and therefore should not be used.

Elderly

A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Children

Use of risperidone for schizophrenia in children aged less than 15 years has not been formally evaluated.

Renal and liver disease

A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Risperidone should be used with caution in this group of patients until further experience is gained.

4.2.b Bipolar Mania:

Adults

Risperidone should be administered on a once daily schedule, starting with 2

mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. A dosing range between 1 and 6 mg per day is recommended.

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 bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Renal and liver disease

A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

Risperidone should be used with caution in this group of patients until further experience is gained.

Combined use with mood stabilisers

There is limited information on the combined use of risperidone with carbamazepine in bipolar mania. Carbamazepine has been shown to induce the metabolism of risperidone producing lower plasma levels of the antipsychotic fraction of risperidone (see Section 4.5). It is therefore not recommended to coadminister risperidone with carbamazepine in bipolar mania patients until further experience is gained. The combined use with lithium or valproate does not require any adjustment of the dose of risperidone.

Method of administration

Oral use.

4.3 Contraindications

Risperidone Oral Solution is contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

4.4 Special warnings and precautions for use

Elderly patients with dementia

Elderly patients with dementia treated with atypical antipsychotic drugs had an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including Risperdal. In placebocontrolled 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 mean age (range) of patients who died was 86 years (67-100).

In these trials treatment with furosemide plus risperidone was associated with a higher incidence of mortality compared to treatment with risperidone or furosemide alone, however, the mechanism for an interaction is unclear.

Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use. 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)

Risperidone is not recommended for the treatment of behavioural symptoms of dementia because of an increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks).

Treatment of acute psychoses in patients with a history of dementia should be limited to short term only and should be under specialist advice.

Data from randomised clinical trials conducted in elderly (>65 years) patients with dementia indicate that there is an approximately 3-fold increased risk of cerebrovascular adverse events (including cerebrovascular accidents and transient ischaemic attacks) with risperidone, compared with placebo.

Cerebrovascular adverse events occurred in 3.3% (33/989) of patients treated with risperidone and 1.2% (8/693) of patients with placebo. The Odds Ratio (95% exact confidence interval) was 2.96 (1.33, 7.45).

Physicians should consider carefully the risk of cerebrovascular adverse events with Risperidone (given the observations in elderly patients with dementia detailed above) before treating any patient with a previous history of CVA/TIA. Consideration should also be given to other risk factors for cerebrovascular disease including hypertension, diabetes, current smoking, atrial fibrillation, etc.

Alpha-blocking activity

Due to the alpha-blocking activity of risperidone, orthostatic hypotension can occur, especially during the initial dose-titration period. A dose reduction should be considered if hypotension occurs.

Risperidone should be used with caution in patients with known cardiovascular disease including those associated with prolongation of the QT interval and the dose should be gradually titrated. In clinical trials, risperidone was not associated with an increase in QTc intervals. As with other antipsychotics, caution is advised when prescribing with medications known to prolong the QT interval.

If further sedation is required, an additional drug (such as a benzodiazepine) should be administered rather than increasing the dose of risperidone.

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)

Drugs 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. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

Neuroleptic Malignant Syndrome (NMS)

Neuroleptic malignant syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels, has been reported to occur with neuroleptics. In this event all antipsychotic drugs including risperidone should be discontinued.

It is recommended to halve both the starting dose and the subsequent dose

increments in geriatric patients and in patients with renal or liver insufficiency. Caution should also be exercised when prescribing risperidone to patients with Parkinson's disease since, theoretically, it may cause a deterioration of the disease.

Hyperglycemia

Hyperglycaemia 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 (see also section 4.8 Undesirable effects).

Other

Classical neuroleptics are known to lower the seizure threshold. Caution is recommended when treating patients with epilepsy.

As with other antipsychotics, patients should be advised of the potential for weight gain.

Acute withdrawal symptoms, including nausea, vomiting, sweating and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

Use of risperidone for schizophrenia in children aged less than 15 years has not been formally evaluated.

This product contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Possible interactions of risperidone with other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone it should be used with caution in combination with other centrally acting drugs including alcohol.

Risperidone may antagonise the effect of levodopa and other dopamine agonists.

Carbamazepine has been shown to decrease the plasma levels of the antipsychotic fraction of Risperidone. A similar effect might be anticipated with other drugs which stimulate metabolising enzymes in the liver. On initiation of carbamazepine or other hepatic enzyme-inducing drugs, the dosage of risperidone should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of risperidone should be re-evaluated and decreased if necessary.

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Fluoxetine and paroxetine, CYP2D6 inhibitors, may increase the plasma concentration of risperidone but less so of the active antipsychotic fraction. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of Risperdal.

Based on *in vitro* studies, the same interaction may occur with haloperidol. 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 cholinesterase inhibitor galantamine does not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

When risperidone is taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.

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

Risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate or topiramate. The potential for reduced toleration of the combination treatment should be taken into consideration when coadministering risperidone and topiramate.

In patients on long-term lithium and older/typical neuroleptic therapy, no significant change occurred in the pharmacokinetics of lithium after substitution of the concomitant neuroleptic with risperidone.

Food does not affect the absorption of risperidone from the stomach.

4.6 Pregnancy and lactation

Although, in experimental animals, risperidone did not show direct reproductive toxicity, some indirect, prolactin- and CNS-mediated effects were observed, typically delayed oestrus and changes in mating and nursing behaviour in rats. No teratogenic effect of risperidone was noted in any study. The safety of risperidone for use during human pregnancy has not been established. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of risperidone during the last trimester of pregnancy. Therefore, risperidone should only be used during pregnancy if the benefits outweigh the risks.

In animal studies, risperidone and 9-hydroxyrisperidone are excreted in the milk. It has been demonstrated that risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breastfeed.

4.7 Effects on ability to drive and use machines

Risperidone may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 Undesirable effects

Risperidone is generally well tolerated and in many instances it has been difficult to differentiate adverse events from symptoms of the underlying disease. Adverse events observed in association with the use of risperidone include:

Common: insomnia, agitation, anxiety, headache.

Less common: somnolence, fatigue, dizziness, impaired concentration, constipation, dyspepsia, nausea/vomiting, abdominal pain, blurred vision, priapism, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, urinary incontinence, rhinitis, rash and other allergic reactions.

Cerebrovascular accidents have been observed during treatment with risperidone (see section 4.4).

Hyperglycemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment.

The incidence and severity of extrapyramidal symptoms are significantly less than with haloperidol. However, in some cases the following extrapyramidal symptoms may occur: tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia including oculogyric crisis. If acute in nature, these symptoms are usually mild and are reversible upon dose reduction and/or administration of antiparkinson medication, if necessary. In clinical trials in patients with acute mania risperidone treatment resulted in an incidence of EPS > 10%. This is lower than the incidence observed in patients treated with classical neuroleptics.

Occasionally, orthostatic dizziness, hypotension including orthostatic, tachycardia including reflex tachycardia and hypertension have been observed following administration of risperidone.

Risperidone can induce a dose-dependent increase in plasma prolactin concentration. Possible associated manifestations are: galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and amenorrhoea. Weight gain, oedema and increased hepatic enzyme levels have been observed during treatment with risperidone.

A decrease in neutrophil and/or thrombocyte count has been reported.

As with classical neuroleptics, rare cases of the following have been reported in schizophrenic patients: water intoxication with hyponatraemia, either due to polydipsia or to the syndrome of inappropriate secretion of antidiuretic hormone; tardive dyskinesia, body temperature dysregulation and seizures.

Benign pituitary adenomas have been reported very rarely in risperidone users during postmarketing surveillance. No causal association has been established.

Very rare cases of angioedema have been reported in postmarketing experience.

Sedation has been reported more frequently in children and adolescents than in adults. In general, sedation is mild and transient.

Withdrawal reactions have been reported in association with antipsychotic drugs (see section 4.4).

4.9 Overdose

In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, rare cases of QT-prolongation have been reported. In case of acute overdosage, the possibility of multiple drug involvement should be considered.

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. 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, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous system – Psycholeptics – Antipsychotics – Other antipsychotics

ATC code: N05A X08

Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

Risperidone is a selective monoaminergic antagonist with a high affinity for both 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, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may

reduce the tendency to cause extrapyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

5.2 Pharmacokinetic properties

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. Food does not affect the absorption of risperidone from the stomach. The effect of food particles in the mouth on absorption has not been studied.

The most important route of metabolism of is hydroxylation by cytochrome CYP 2D6 to 9-hydroxy-risperidone which has a similar pharmacological activity to risperidone. This hydroxylation is subject to debrisoquine-type genetic polymorphism but this does not affect the active antipsychotic fraction since this consists of risperidone and its active metabolite 9-hydroxyrisperidone. After oral administration, the elimination half-life of the active antipsychotic fraction is 24 hours.

A single-dose study showed higher active plasma concentrations and a slower elimination of risperidone in the elderly and in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency.

Topiramate modestly reduces the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance. The bioavailability of topiramate is slightly decreased when administered in combination with risperidone. This interaction is not likely to be clinically significant.

Risperidone oro-dispersible tablets and oral solution are bioequivalent to Risperidone oral tablets.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber other than those already provided in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzoic acid
Sorbitol 70% solution
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Before opening: 3 years
After first opening: 3 months

6.4 Special precautions for storage

Before opening: This medicinal product does not require any special storage conditions.

After first opening: This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Amber glass bottles with white plastic child-resistant polypropylene closures. 30 & 100 ml of Risperidone. 1 mg/ml Oral Solution.

3 ml or 5 ml white plastic LDPE oral dosing syringes graduated at every 0.05 ml.

5 ml white plastic LDPE oral dosing syringes graduated at every 0.1 ml.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
England

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0817

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/12/2007

10 DATE OF REVISION OF THE TEXT

07/12/2007

PATIENT INFORMATION LEAFLETS

RISPERIDONE 1 mg/ml ORAL SOLUTION

PACKAGE LEAFLET : INFORMATION FOR THE USER

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 any 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 is and what it is used for
2. Before you take Risperidone
3. How to take Risperidone
4. Possible side effects
5. How to store Risperidone
6. Further information

1 WHAT RISPERIDONE IS AND WHAT IT IS USED FOR

- Risperidone belongs to a group of drugs called antipsychotics. It is used to treat conditions which affect the way you feel, think and act.
- Risperidone is used to treat and prevent symptoms of acute and chronic psychotic disorders, such as:
 - Hallucinations, delusions and thought disturbances
 - Emotional and social withdrawal
 - Depression, guilt, anxiety, confusion, paranoia
 - Unfriendly and aggressive feelings or behaviour.

In addition Risperidone may be used to control symptoms of mania or to treat people with bipolar disorder (manic depressive illness).

2 BEFORE YOU TAKE RISPERIDONE

Do NOT take Risperidone:

- If you are allergic (hypersensitive) to risperidone or any of the other ingredients of this medicine
- If you have an intolerance to fructose.

Talk to your doctor or pharmacist:

- If you have any heart problems
- If you have liver or kidney problems
- If you have Parkinson's disease
- If you have dementia (severe short term memory loss) as there is an increased risk of stroke or an ischaemic attack (temporary reduction in blood to the brain)
- If you have epilepsy
- If you have risk factors for blood vessel disease (high blood pressure, diabetes, current smoker or a heart disorder called atrial fibrillation)
- If you are taking a medicine called furosemide. Furosemide is a medicine which is sometimes used to treat high blood pressure, or to treat swelling of parts of the body by the build-up of too much fluid. Studies have shown that it might be harmful if elderly patients take Risperidone in combination with furosemide.

Taking other medicines

Talk to your doctor or pharmacist if you are taking any of the following:

- Drugs used to treat Parkinson's disease e.g. levodopa and amantadine

- Carbamazepine (used to treat epilepsy)
- Antidepressants, e.g. clomipramine, fluoxetine and paroxetine
- Drugs known as beta-blockers (used to treat heart problems), e.g. atenolol and propranolol
- Haloperidol
- Phenothiazines (anti-sickness or antipsychotic medicines) e.g. chlorpromazine and thioridazine.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Risperidone with food and drink

Risperidone can be taken with or without food. The liquid should be swallowed with a drink of water. If necessary Risperidone may be diluted with mineral water, orange juice or black coffee and used immediately. **Risperidone Oral Solution should not be mixed with tea.** While taking Risperidone you should be careful on how much alcohol you drink.

Pregnancy and breast-feeding

Unless your doctor says otherwise, do not take Risperidone if you are pregnant or planning on becoming pregnant. Do not take Risperidone if you are breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Do not drive or use any tools or machines until your doctor has assessed how your medicine affects you.

Important information about some of the ingredients of Risperidone

Risperidone contains sorbitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3 HOW TO TAKE RISPERIDONE

Always take Risperidone exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Instructions for using the oral dosing syringe with Risperidone Oral Solution:

1. Remove the child-resistant cap from the bottle by pushing down on the cap while turning it anti-clockwise
2. Place the bottle on a flat surface
3. Insert the syringe into the liquid in the bottle
4. While holding the lower ring of the syringe, pull the top ring upwards until the mark that matches the number of mg or ml to be taken is just visible
5. Holding the lower ring, remove the whole syringe from the bottle
6. To empty the syringe, push down on the top ring while holding the lower ring
7. The contents of the syringe may be emptied directly into the mouth or into a drink of mineral water, orange juice or black coffee
8. Rinse the syringe with some water
9. Replace the child-resistant cap on the bottle by screwing it down clockwise until it locks fully.

If you do not understand these instructions, or you are in any doubt, ask your doctor or pharmacist. Your doctor will tell you how much Risperidone to take and how long you should continue to take it. This will vary from person to person and your doctor will adjust the amount of liquid to suit you. Remember - each millilitre (ml) of liquid is equivalent to 1 mg of Risperidone.

The usual dose is:

Schizophrenia:

Adults

The starting dose is 2 mg (2 ml) on the first day. Your doctor may then increase this to 4 mg (4 ml) on the second day. This may be taken as a single dose or as a half a dose in the morning and half in the evening. After this the usual daily dose is 4-6 mg (4-6 ml) although some patients may require less than 4 mg (4 ml).

The elderly or those with a liver or kidney disorder

The usual starting dose is 0.5 mg (0.5 ml) twice a day. Your doctor may then increase your dose to 1-2 mg (1-2 ml) twice a day.

Children

The use of Risperidone is not recommended in children under 15 years old.

Bipolar Mania:

Adults

The starting dose is 2 mg (2 ml) on the first day. Your doctor may gradually increase your daily dose to 6 mg (6 ml).

The elderly or those with a liver or kidney disorder

The starting dose is 0.5 mg (0.5 ml) twice a day. Your doctor may increase this to 1-2 mg (1-2 ml) twice daily.

If you take more Risperidone than you should

If you (or someone else) swallow a lot of the liquid all together, or if you think a child has swallowed any of the liquid, contact your nearest hospital casualty department or your doctor immediately. An overdose is likely to cause drowsiness, low blood pressure (feeling dizzy or faint), fast heart rate, tremors and tics. Please take this leaflet, any remaining liquid and the container with you to the hospital or doctor so that they know which medicine was consumed.

If you forget to take Risperidone

If you forget to take a dose, take your next dose as usual and continue your course.

If you stop taking Risperidone

If you suddenly stop taking Risperidone you may experience the following:

- Feeling or being sick, sweating, difficulty in sleeping, muscle stiffness or jerky movements
- Your original medical problem may come back.

These effects are rare but it is advisable to gradually stop taking Risperidone. Always follow your doctor's instructions.

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 can cause side effects, although not everybody gets them. If you experience the following, stop taking Risperidone and tell your doctor immediately or go to the casualty department of the nearest hospital:

- A severe allergic reaction (swelling of the face, neck or lips, shortness of breath).

This is a very serious but very rare side effect. You may need urgent medical attention or hospitalisation. The following side effects have been reported at the approximate frequencies shown:

Common (affecting fewer than one person in 10 but more than one person in 100):

- Agitation and anxiety
- Headache, decreased alertness and difficulty in sleeping.

Uncommon (affecting fewer than one person in 100 but more than one person in 1,000):

- Milk secretion from breasts, absence of periods
- Shaking, restlessness, muscle stiffness, production of excessive saliva, sluggish or slow physical movement
- Feeling dizzy or faint on standing, low blood pressure
- Fast heartbeat, high blood pressure.

Rare (affecting fewer than one person in 1,000 but more than one person in 10,000):

- Male breast swelling
- Dizziness, tiredness, poor concentration
- Itchy and runny nose, blurred vision, rash, allergic reactions
- Constipation, feeling or being sick, indigestion, abdominal pain, incontinence
- Painful erection often occurring without sexual desire, impotence, sexual problems.

Very rare (affecting fewer than one person in 10,000):

- Blood disorders, high blood sugar levels, worsening of existing diabetes
- Low levels of sodium in the blood resulting in lethargy, confusion, fits and possibly coma
- Difficulty in moving, a combination of stiffness, change in consciousness levels, unstable blood pressure, high temperature.

Other side effects that have been reported:

- Stroke, irregular periods, weight gain, water retention and changes in levels of liver enzymes.
- Very rarely people taking this medicine have been reported to have swellings of a gland at the base of the brain, called the pituitary gland. This however, also occurs in people who are not currently taking risperidone or have never taken risperidone.

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.

5 HOW TO STORE RISPERIDONE

Keep out of the reach and sight of children. There are no special storage conditions. Do not use Risperidone after the expiry date that is stated on the outer packaging. Once opened, use within 3 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 ingredient is risperidone, 1 mg/ml
- The other ingredients are benzoic acid (E210), sorbitol (E420) and purified water.

What Risperidone looks like and contents of the pack:

- Risperidone Oral Solution is a clear colourless to yellow solution
- The product is available in 30 and 100 ml bottles with a 3 ml or 5 ml plastic oral dosing syringe graduated at every 0.05 ml or a 5 ml plastic oral dosing syringe graduated at every 0.1 ml. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation holder and company responsible for manufacture: TEVA UK Limited, Eastbourne, BN22 9AG.

This leaflet was last revised: October 2007.

PL 00289/0816

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RISPERIDONE 1 mg/ml ORAL SOLUTION

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- If you have liver or kidney problems
- If you have Parkinson's disease
- If you have dementia (severe short term memory loss) as there is an increased risk of stroke or an ischaemic attack (temporary reduction in blood to the brain)
- If you have epilepsy
- If you have risk factors for blood vessel disease (high blood pressure, diabetes, current smoker or a heart disorder called atrial fibrillation)
- If you are taking a medicine called furosemide. Furosemide is a medicine which is sometimes used to treat high blood pressure, or to treat swelling of parts of the body by the build-up of too much fluid. Studies have shown that it might be harmful if elderly patients take Risperidone in combination with furosemide.

Taking other medicines

Talk to your doctor or pharmacist if you are taking any of the following:

- Drugs used to treat Parkinson's disease e.g. levodopa and amantadine

- Carbamazepine (used to treat epilepsy)
- Antidepressants, e.g. clomipramine, fluoxetine and paroxetine
- Drugs known as beta-blockers (used to treat heart problems), e.g. atenolol and propranolol
- Haloperidol
- Phenothiazines (anti-sickness or antipsychotic medicines) e.g. chlorpromazine and thioridazine.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Risperidone with food and drink

Risperidone can be taken with or without food. The liquid should be swallowed with a drink of water. If necessary Risperidone may be diluted with mineral water, orange juice or black coffee and used immediately. **Risperidone Oral Solution should not be mixed with tea.** While taking Risperidone you should be careful on how much alcohol you drink.

Pregnancy and breast-feeding

Unless your doctor says otherwise, do not take Risperidone if you are pregnant or planning on becoming pregnant. Do not take Risperidone if you are breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Do not drive or use any tools or machines until your doctor has assessed how your medicine affects you.

Important information about some of the ingredients of Risperidone

Risperidone contains sorbitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3 HOW TO TAKE RISPERIDONE

Always take Risperidone exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Instructions for using the oral dosing syringe with Risperidone Oral Solution:

1. Remove the child-resistant cap from the bottle by pushing down on the cap while turning it anti-clockwise
2. Place the bottle on a flat surface
3. Insert the syringe into the liquid in the bottle
4. While holding the lower ring of the syringe, pull the top ring upwards until the mark that matches the number of mg or ml to be taken is just visible
5. Holding the lower ring, remove the whole syringe from the bottle
6. To empty the syringe, push down on the top ring while holding the lower ring
7. The contents of the syringe may be emptied directly into the mouth or into a drink of mineral water, orange juice or black coffee
8. Rinse the syringe with some water
9. Replace the child-resistant cap on the bottle by screwing it down clockwise until it locks fully.

If you do not understand these instructions, or you are in any doubt, ask your doctor or pharmacist. Your doctor will tell you how much Risperidone to take and how long you should continue to take it. This will vary from person to person and your doctor will adjust the amount of liquid to suit you. Remember - each millilitre (ml) of liquid is equivalent to 1 mg of Risperidone.

The usual dose is:

Schizophrenia:

Adults

The starting dose is 2 mg (2 ml) on the first day. Your doctor may then increase this to 4 mg (4 ml) on the second day. This may be taken as a single dose or as a half a dose in the morning and half in the evening. After this the usual daily dose is 4-6 mg (4-6 ml) although some patients may require less than 4 mg (4 ml).

The elderly or those with a liver or kidney disorder

The usual starting dose is 0.5 mg (0.5 ml) twice a day. Your doctor may then increase your dose to 1-2 mg (1-2 ml) twice a day.

Children

The use of Risperidone is not recommended in children under 15 years old.

Bipolar Mania:

Adults

The starting dose is 2 mg (2 ml) on the first day. Your doctor may gradually increase your daily dose to 6 mg (6 ml).

The elderly or those with a liver or kidney disorder

The starting dose is 0.5 mg (0.5 ml) twice a day. Your doctor may increase this to 1-2 mg (1-2 ml) twice daily.

If you take more Risperidone than you should

If you (or someone else) swallow a lot of the liquid all together, or if you think a child has swallowed any of the liquid, contact your nearest hospital casualty department or your doctor immediately. An overdose is likely to cause drowsiness, low blood pressure (feeling dizzy or faint), fast heart rate, tremors and tics. Please take this leaflet, any remaining liquid and the container with you to the hospital or doctor so that they know which medicine was consumed.

If you forget to take Risperidone

If you forget to take a dose, take your next dose as usual and continue your course.

If you stop taking Risperidone

If you suddenly stop taking Risperidone you may experience the following:

- Feeling or being sick, sweating, difficulty in sleeping, muscle stiffness or jerky movements
 - Your original medical problem may come back.
- These effects are rare but it is advisable to gradually stop taking Risperidone. Always follow your doctor's instructions.

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 can cause side effects, although not everybody gets them. If you experience the following, stop taking Risperidone and tell your doctor immediately or go to the casualty department of the nearest hospital:

- A severe allergic reaction (swelling of the face, neck or lips, shortness of breath).

This is a very serious but very rare side effect. You may need urgent medical attention or hospitalisation. The following side effects have been reported at the approximate frequencies shown:

Common (affecting fewer than one person in 10 but more than one person in 100):

- Agitation and anxiety
- Headache, decreased alertness and difficulty in sleeping.

Uncommon (affecting fewer than one person in 100 but more than one person in 1,000):

- Milk secretion from breasts, absence of periods
- Shaking, restlessness, muscle stiffness, production of excessive saliva, sluggish or slow physical movement
- Feeling dizzy or faint on standing, low blood pressure
- Fast heartbeat, high blood pressure.

Rare (affecting fewer than one person in 1,000 but more than one person in 10,000):

- Male breast swelling
- Dizziness, tiredness, poor concentration
- Itchy and runny nose, blurred vision, rash, allergic reactions
- Constipation, feeling or being sick, indigestion, abdominal pain, incontinence
- Painful erection often occurring without sexual desire, impotence, sexual problems.

Very rare (affecting fewer than one person in 10,000):

- Blood disorders, high blood sugar levels, worsening of existing diabetes
- Low levels of sodium in the blood resulting in lethargy, confusion, fits and possibly coma
- Difficulty in moving, a combination of stiffness, change in consciousness levels, unstable blood pressure, high temperature.

Other side effects that have been reported:

- Stroke, irregular periods, weight gain, water retention and changes in levels of liver enzymes.
- Very rarely people taking this medicine have been reported to have swellings of a gland at the base of the brain, called the pituitary gland. This however, also occurs in people who are not currently taking risperidone or have never taken risperidone.

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.

5

HOW TO STORE RISPERIDONE

Keep out of the reach and sight of children. There are no special storage conditions. Do not use Risperidone after the expiry date that is stated on the outer packaging. Once opened, use within 3 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 ingredient is risperidone, 1 mg/ml
- The other ingredients are benzoic acid (E210), sorbitol (E420) and purified water.

What Risperidone looks like and contents of the pack:

- Risperidone Oral Solution is a clear colourless to yellow solution
- The product is available in 30 and 100 ml bottles with a 3 ml or 5 ml plastic oral dosing syringe graduated at every 0.05 ml or a 5 ml plastic oral dosing syringe graduated at every 0.1 ml. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation holder and company responsible for manufacture: TEVA UK Limited, Eastbourne, BN22 9AG.

This leaflet was last revised: October 2007.

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LABELLING

PL 00289/0816

Label:

100 ml Solution

Risperidone
1 mg/ml
Oral Solution
For Oral Administration



Each 1 ml of solution contains 1 mg of risperidone. Also includes benzoic acid (E210) and sorbitol (E420).

Dosage: Use as directed by the physician. Please read the enclosed leaflet.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. There are no special storage conditions. Once opened, use within 3 months.

MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AG.

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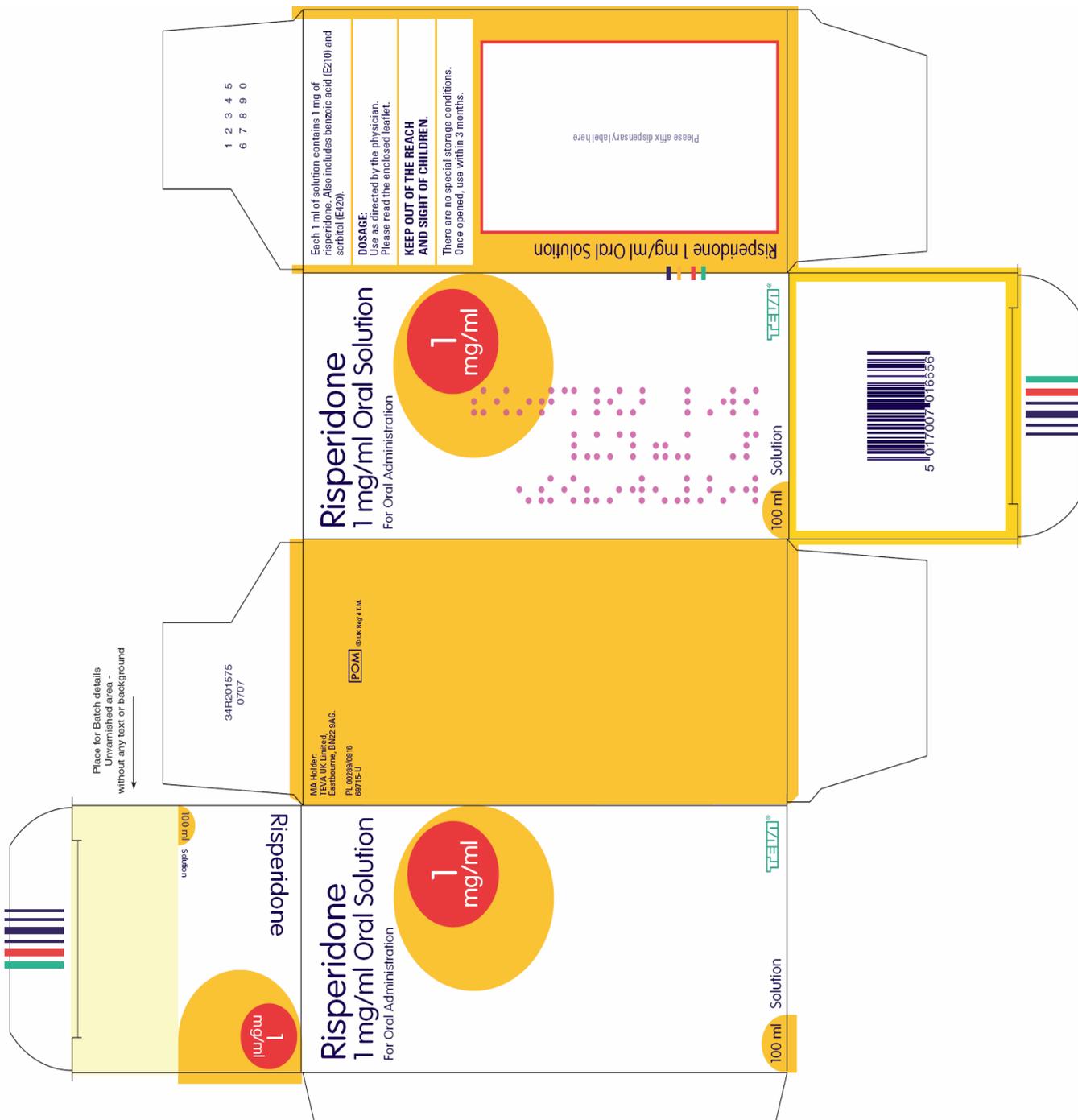
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Carton:



PL 00289/0817

Label:

Risperidone
1 mg/ml
Oral Solution
For Oral Administration

100 ml
Solution



Each 1 ml of solution contains 1 mg of risperidone. Also includes benzoic acid (E210) and sorbitol (E420).

Dosage: Use as directed by the physician. Please read the enclosed leaflet.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. There are no special storage conditions. Once opened, use within 3 months.

MA Holder:
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Carton:

