RISPERIDONE 1 MG/ML ORAL SOLUTION

PL 25954/0001

UKPAR

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The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) for the medicinal product Risperidone 1 mg/ml Oral Solution (Product Licence number: 25954/0001).

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 a Marketing Authorisation has been granted.
RISPERIDONE 1 MG/ML ORAL SOLUTION

PL 25954/0001

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 1 mg/ml Oral Solution to Chanelle Healthcare Limited on 5 February 2008. This medicine is only available on prescription.

This standard abridged application was 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.

This product is an oral solution containing 1 mg/ml of the atypical antipsychotic risperidone. The product 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, social withdrawal, poverty of speech) are prominent. Risperidone also alleviates affective symptoms (such as depression, feelings of guilt, 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 is indicated for the treatment of mania in bipolar disorder. These episodes are characterised by symptoms such as elevated, expansive or irritable mood, excessively ‘high’ or euphoric feelings, inflated self-esteem, decreased need of sleep, pressured speech, racing thoughts, distractibility or poor judgement, including disruptive or aggressive behaviours.

Risperidone is an antipsychotic drug 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 also binds 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.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

General Information

rINNM / BAN: Risperidone

Chemical names:
3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-α]pyrimidin-4-one.

Structure:

\[
\text{C}_{23}\text{H}_{27}\text{FN}_{4}\text{O}_{2} \quad \text{MW: 410.5} \quad \text{CAS No.: 106266-06-2}
\]

Risperidone is a white to almost white powder. It is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol, and dissolves in dilute acid solutions. Risperidone exhibits polymorphism.

All aspects of the manufacture and control of risperidone are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of risperidone for inclusion in this medicinal product. The Certificate of Suitability includes a retest period of 3 years, therefore, no stability data is presented.

MEDICINAL PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely tartaric acid (E 334), benzoic acid (E 210), hydrochloric acid and purified water. Appropriate justification for the inclusion of each excipient has been provided. The proposed product contains the same ingredients as the innovator product, except the innovator uses sodium hydroxide as opposed to hydrochloric acid.

All excipients used comply with their respective European Pharmacopoeial monograph. Satisfactory certificates of analysis have been provided for all excipients.

Declarations have been provided by the excipient suppliers confirming that they contain no material of animal or human origin.

No overages are required.

Impurity profiles

Comparative impurity data of the proposed formulation and the bioequivalent product have been provided. Impurity levels for both products were within specified finished product limits.

Manufacture

A description and flow-chart of the manufacturing method has been provided.
In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on product batches. The results are satisfactory.

**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. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container-Closure System**
The product is packaged in Type III amber glass bottles with PP/LDPE child-resistant and tamper-evident caps. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in bottle sizes of 30 ml, 60 ml, 100 ml and 120 ml. A dosing pipette is provided with the bottles.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set for the 30 ml, 60 ml and 120 ml presentations, and of 3 years for product stored in the 100 ml bottle, which is satisfactory. Once the bottle has been opened, a 4 month shelf life applies.

**Bioequivalence/bioavailability**
As the product is an aqueous oral solution at the time of administration and contains the same concentration of active substance as the reference product, no bioequivalence study is required (as per ‘Note for guidance on the investigation of bioavailability and bioequivalence’). A bioequivalence study was carried out by the applicant but this has not been assessed as it is not required.

**Product literature**
The product literature (Summary of Product Characteristics, Patient Information Leaflet and product labelling) are satisfactory. The Patient Information 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**
A marketing authorisation may be granted.
PRECLINICAL ASSESSMENT

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

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 as for the treatment of mania in bipolar disorder. These episodes are characterised by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgement, including disruptive or aggressive behaviour.

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

This is in line with the reference product and is satisfactory.

DOSE AND DOSE SCHEDULE
The applicant has submitted the following:

“1 ml of Risperidone Oral Solution contains 1 mg risperidone. The solution may be diluted with mineral water, orange juice or black coffee (see section 6.6).

4.2a 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 and children over 15 years:
Risperidone may be given once or twice daily. All patients, whether acute or chronic, should start with 2 mg per day Risperidone. The dosage may be increased to 4 mg per day on the second day. Some patients such as first-episode psychotic 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 per day although in some, an optimal response may be obtained at lower doses.

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

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

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

**4.2b Bipolar Mania**

**Adults:**
A starting dosage of 2 mg once daily is recommended. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. Most patients will benefit from doses between 1 and 6 mg per day.

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.

**Renal and liver disease:**
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.

Risperidone Oral Solution 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 co-administer 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.

This is in line with the reference product and is satisfactory.

**TOXICOLOGY**
No new data are submitted and none are required for this type of application.
CLINICAL PHARMACOLOGY
There is no requirement for a bioequivalence study, as the two formulations are aqueous solutions. Nevertheless, a bioequivalence study is provided with Risperdal 1 mg/ml Solution Buvable from Janssen-Cilag, France as comparator. The study is not reviewed here as it is not required.

EFFICACY
No new data are submitted and none are required for this type of application.

SAFETY
No new data are submitted and none are required for this type of application.

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

PRODUCT LITERATURE
The product literature (Summary of Product Characteristics, Patient Information Leaflet and product labelling) are satisfactory.

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

MEDICAL CONCLUSION
A marketing authorisation may be granted for this preparation.
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 those 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.
# STEPS TAKEN FOR ASSESSMENT

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 16 December 2005</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 11 January 2006</td>
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<tr>
<td>4</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 27 September 2006</td>
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<tr>
<td>5</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality on 11 April 2007</td>
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<tr>
<td>6</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 27 September 2007</td>
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<tr>
<td>7</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 1 November 2007</td>
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<tr>
<td>8</td>
<td>Following assessment of the application the MHRA requested further information relating to the clinical dossier on 9 January 2008</td>
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<tr>
<td>9</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the clinical dossier on 9 January 2008</td>
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<tr>
<td>10</td>
<td>The application was determined on 5 February 2008</td>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Risperidone 1 mg/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 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 as for the treatment of mania in bipolar disorder. These episodes are characterised by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgement, 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 Oral Solution contains 1 mg risperidone. The solution may be diluted with mineral water, orange juice or black coffee (see section 6.6).

4.2a 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 and children over 15 years:
Risperidone may be given once or twice daily. All patients, whether acute or chronic, should start with 2 mg per day Risperidone. The dosage may be increased to 4 mg per day on the second day. Some patients such as first-episode psychotic 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 per day although in some, an optimal response may be obtained at lower doses.

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

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.

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

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

4.2b Bipolar Mania

Adults:
A starting dosage of 2 mg once daily is recommended. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. Most patients will benefit from doses between 1 and 6 mg per day.

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.

Renal and liver disease:
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.

Risperidone Oral Solution 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 co-administer 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 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 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 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, some of which were fatal and transient ischaemic attacks) in patients treated with risperidone, compared with placebo. Cerebrovascular adverse events (CVAEs) occurred in 3.3% (33/989) of patients treated with risperidone and 1.2% (8/693) of patients treated 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 titration period of the dose to be administered. 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 risperidone. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (also see section 4.8).

**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.

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 active antipsychotic fraction of risperidone. A similar effect may 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 Risperidone. 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 increased 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 (Special warnings and special precautions for use) 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. The effect of food particles in the mouth on absorption from risperidone has not been studied.
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 breast feed.

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.

The following adverse events have been reported for risperidone:

**Common:** >1/100, < 1/10

**Uncommon:** >1/1,000, < 1/100

**Nervous system disorders:**

Common: insomnia and headache.

Uncommon: somnolence, fatigue, dizziness and impaired concentration.

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. 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.

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

**Psychiatric disorders:**

Common: agitation and anxiety.

**Gastrointestinal disorders:**

Uncommon: constipation, dyspepsia, nausea/vomiting and abdominal pain

Weight gain has been observed during treatment with Risperidone.

**Eye disorders:**
Uncommon: blurred vision.

Reproductive system and breast disorders:
Uncommon: priapism, erectile dysfunction, ejaculatory dysfunction and orgasmic dysfunction.

Renal and urinary disorders:
Uncommon: urinary incontinence.

Respiratory, thoracic and mediastinal disorders:
Uncommon: rhinitis.

Skin and subcutaneous tissue disorders:
Uncommon: rash and other allergic reactions.

Oedema has been observed during treatment with Risperidone.

Cardiac disorders:
Uncommon: orthostatic dizziness, hypotension including orthostatic, tachycardia including reflex tachycardia and hypertension have been observed following administration of risperidone.

Cerebrovascular adverse events have been observed during treatment with risperidone (see also section 4.4).

Hepatobiliary disorders:
Increased hepatic enzyme levels have been observed during treatment with Risperidone.

Blood and lymphatic system disorders:
A decrease in neutrophil and/or thrombocyte count has been reported.

Endocrine disorders:
Risperidone can induce a dose-dependent increase in plasma prolactin concentration. Possible associated manifestations are: galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and amenorrhoea.

As with classical neuroleptics, the following have occasionally been reported in psychotic patients: water intoxication due to either polydipsia or the syndrome of inappropriate secretion of anti-diuretic hormone; tardive dyskinesia, body temperature dysregulation and seizures.

Withdrawal reactions have been reported in association with antipsychotic drugs (see 4.4 Special warnings and special precautions for use).

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 overdose, 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: Antipsychotics
ATC code: N05AX08

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, an activity which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extrapyramidal side effects, 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 risperidone 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.
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**
- Tartaric acid (E 334)
- Benzoic acid (E 210)
- Hydrochloric acid
- Purified water

6.2 **Incompatibilities**
Risperidone Oral Solution should only be diluted with those beverages listed in section 6.6.

6.3 **Shelf life**
- 30 ml, 60 ml and 120 ml presentations:
  - Unopened: 2 years
  - Opened: 4 months

- 100 ml presentation:
  - Unopened: 3 years
  - Opened: 4 months

Once diluted with mineral water, orange juice or black coffee the product is stable for up to 4 hours, although it is recommended that once diluted in this way Risperidone Oral Solution is used immediately in order to avoid risk of inadvertent consumption.

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 and other handling**
If necessary, Risperidone Oral Solution may be diluted with mineral water, orange juice or black coffee. When diluted in this way, it is recommended that it is used immediately in order to avoid the risk of inadvertent consumption.

A special dosing pipette is supplied with each pack of Risperidone Oral Solution.

Instructions for using the pipette 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 pipette into the solution in the bottle.
4. While holding the lower ring, 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 pipette from the bottle.
6. To empty the pipette, push down on the top ring while still holding the lower ring.
7. The contents of the pipette may be emptied directly into the mouth or into a drink of mineral water, orange juice or black coffee.
8. Rinse the pipette with some water.
9. Replace the child-resistant cap on the bottle by screwing it down clockwise.

7 MARKETING AUTHORISATION HOLDER
Chanelle Healthcare Limited
Loughrea
Co. Galway
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 25954/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
05/02/2008

10 DATE OF REVISION OF THE TEXT
05/02/2008
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, please ask your doctor or your 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 your 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 is one of a group of medicines called antipsychotics. It is used to treat a condition known as schizophrenia which can affect the way you think, feel and/or act. This condition may cause symptoms such as confusion, hallucinations (e.g. hearing, seeing or sensing things which are not there), delusions, unusual or eccentric views (paranoid, emotional or social withdrawal). People with this condition may also feel depressed, guilty, anxious or tense. Risperidone Oral Solution may be taken for both sudden (acute) and long-lasting (chronic) disorders.

In addition Risperidone Oral Solution may be used to control the symptoms of mania (characterised by extremely elevated mood, energy and unusual thoughts) for people with bipolar disorder. Bipolar disorder is a severe depressive disorder which causes episodes of depression, mania and mood swings.

2. Before you take Risperidone Oral Solution:
Do not take Risperidone Oral Solution:
- If you have ever had an allergic reaction to risperidone or any of the ingredients listed in section 6. An allergic reaction may be recognised as a rash, itching, swollen face or lips, or narrowing of breath.

Take special care with Risperidone Oral Solution:
- If you suffer from Parkinson's disease.
- If you suffer from heart or blood vessel disease, liver or kidney disease, epilepsy or dementia (brain disorder associated with memory and behaviour problems).
- If you have had a stroke or transient ischaemic attack (temporary reduction in blood flow to the brain).
- If you have other risk factors for blood vessel diseases, including high blood pressure, diabetes, you are currently smoking or have a heart disorder called atrial fibrillation.
- If you have diabetes or you have a risk of getting diabetes.

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

Taking Risperidone Oral Solution with the following medicines may make you feel more drowsy:
- Medicines taken for anxiety or to help you to sleep (tranquilisers).
- Certain painkillers.
- Some antihistamines (such as chlorphenamine).
- Certain antidepressants.

Only take these medicines while you are on Risperidone Oral Solution if your doctor says that you can.

A drug called cimetidine, commonly used to treat indigestion or peptic ulcers, may increase the effects of Risperidone Oral Solution if taken with alcohol. This can change the effect of Risperidone Oral Solution, so you should tell your doctor if you start or stop taking such medication, as you may need a different dose of Risperidone Oral Solution.

Taking Risperidone Oral Solution with food and drink:
Risperidone Oral Solution can be taken with or without food. The solution can be swallowed directly or mixed with some mineral water, orange juice or black coffee. Do not mix Risperidone Oral Solution with any other beverages. It must be taken immediately.

You should be careful how much alcohol you drink. The combined effect of Risperidone Oral Solution and alcohol might make you feel drowsy.

Pregnancy and breast-feeding:
Before taking your medicine, tell your doctor if you are pregnant, trying to become pregnant, or breast feeding. You should not breast feed if you are taking Risperidone Oral Solution. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:
Risperidone Oral Solution might affect your alertness so you should not drive or operate machinery until the doctor sees how it affects you.

3. 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.

Risperidone Oral Solution is taken with or without food. The solution can be swallowed directly or mixed with some mineral water, orange juice or black coffee. Do not mix Risperidone Oral Solution with any other beverages. It must be taken immediately.

Instructions for using the pipette with Risperidone Oral Solution:
1. Remove the child-resistant cap from the bottle by pushing down on the cap while turning it anticlockwise.
2. Place the bottle on a flat surface.
3. Invert the pipette into the solution in the bottle.
4. While holding the lever ring, pull the top ring upwards until the mark that matches the number of mg or ml to be taken is just visible.
5. Hold the lever ring. Remove the whole pipette from the bottle.
6. To empty the pipette, push down on the top ring while still holding the lever ring.
7. The contents of the pipette may be emptied directly into the mouth or into a drink of mineral water, orange juice or black coffee.
8. Rinse the pipette with water.
9. Replace the child-resistant cap on the bottle by screwing it down clockwise until it locks fully.

Your doctor will tell you how much Risperidone Oral Solution to take and for how long you should continue to take it. This will vary from person to person and your doctor will adjust the amount of solution to suit you.

Remember - each millilitre (ml) of solution is equivalent to 1 mg.
For adults and adolescents over 15 years of age with schizophrenia which can affect the way they think, feel or act:

The dose will be started gradually over the first days of treatment as below. Your doctor will probably have recommended the following dosage to start with:

Day 1: 2 mg (2 ml) as a single dose or 1 mg (1 ml) in the morning and 1 mg (1 ml) in the evening.
Day 2: 4 mg (4 ml) as a single dose or 2 mg (2 ml) in the morning and 2 mg (2 ml) in the evening.

However, if you have not used Risperidone Solution before, your doctor may recommend a more gradual increase.

The dosage will then be set to suit your needs but is usually between 4 mg (4 ml) and 6 mg (6 ml) a day, either as a single dose or split into two doses, once to be taken in the morning and one to be taken in the evening. Some patients may need less than 4 mg (4 ml) for a good effect.

For adults and adolescents over 15 years of age with bipolar disorder:

If you need to take Risperidone Solution to help control the symptoms of mania, a starting dose of 2 mg (2 ml) once a day is recommended, and your doctor will adjust this if necessary. Most people feel better with doses between 1 mg and 5 mg (1 ml to 5 ml) per day. Your doctor will tell you what dose suits your particular situation. Your treatment should be regularly reviewed and changed if appropriate.

Important: never take more than a total of 16 mg (16 ml) per day.
- Risperidone Oral Solution is only for those aged 15 years and over.
- If you are elderly or have a liver or kidney disorder, you should take half the above doses. You will be told by your doctor how much solution you need to take.
- Always read the label. If you are in any doubt as to how much solution you should take you should consult your nurse or pharmacist.

If you take more Risperidone Oral Solution than you should:

If you take more Risperidone Oral Solution than you were told to, or if someone else has taken any Risperidone Oral Solution, contact a doctor or hospital straight away. Symptoms of overdose include sleepiness, sedation, rapid heart beat and low blood pressure.

If you forget to take Risperidone Oral Solution:

If you miss a dose in the initial treatment period, take it as soon as possible instead of your next dose and then continue to take the remaining doses in the order described above. Then continue as usual whatever dose your doctor has prescribed.

If you miss a dose after the first few days, take your next dose as usual and continue your course.

If you stop taking Risperidone Oral Solution:

Do not stop your treatment just because you feel better. It is important that you carry on taking Risperidone Oral Solution as long as your doctor has told you to.

If you stop taking Risperidone Oral Solution you should do so gradually, especially if you have been taking a high dose, unless your doctor has told you otherwise. Stopping treatment suddenly may cause effects such as feeling sick, vomiting, sweating, sleeplessness, muscle stiffness or jerky movements, or your original medical problem may come back. Always follow your doctor's instructions carefully.

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

4. Possible side effects:

Use all medicines. Risperidone Oral Solution can cause side effects, although not everybody gets them. Do not be alarmed by the list of possible side effects. You may not have any of them.

Common (occur in more than 1 in 100 users): headache, sleepiness, anxiety or agitation.

Uncommon (occur in less than 1 in 100 users and more than 1 in 1000 users): sleepiness, tiredness, dizziness, difficulty in concentrating, blurred vision, constipation, difficulty breathing or being short of breath, facial swelling, local skin rash or swelling, other allergic reactions such as itching, swollen face or lips, or tightness of breath. Weight gain or swelling of the ankles may also occur. In some cases, the blood pressure may fall slightly in the early stages of the treatment, resulting in dizziness. This will usually pass off automatically. Somewhat later in the treatment, increased blood pressure may also occur, but this is very rare.

Strokes or transient ischaemic attacks may occur in people taking Risperidone Oral Solution. If you experience sudden weakness or numbness of the face, arm or leg, especially on one side, or if you have slurred speech, seek medical attention.

See your doctor if you experience symptoms such as excessive thirst or urination.

Sometimes tremor, nervous reactions, anxiety, depression, insomnia, movement disorders, voice changes or restlessness can occur but they will usually disappear if your dose of Risperidone Oral Solution is reduced by your doctor or if you discontinue use of an additional medicine.

When used for a long time, women may suffer from milk secretion, an absence of their menstrual periods or changes in the regularity of their periods. Men may experience breast swelling. If these persist, tell your doctor.

Occasionally, changes in blood cell count and increased liver enzymes have been reported.

You might also experience marked changes in your body temperature or uncontrollable movements, mainly of the face or tongue. Rare cases of convulsions (fits) have also occurred. If any of these occur, contact your doctor as soon as possible.

Very rarely, Risperidone Oral Solution might cause fever, fast breathing, swelling, muscle stiffness and reduced consciousness. If this occurs, stop taking the solution and contact a doctor at once.

If continuous erection of the penis occurs, contact your doctor immediately.

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.

6. 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. Risperidone Oral Solution contains 1 mg of risperidone per millilitre (ml). The other ingredients are lactic acid (E 382), lactic acid (E 330), hydrochloric acid and 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 30 ml, 50 ml and 100 ml; not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

The marketing authorisation holder is Channelle Healthcare Ltd, Loughrea, Co. Galway, Ireland. The manufacturer is Channelle Medical, Loughrea, Co. Galway, Ireland. The distributor is Channelle Medical UK Ltd.

This leaflet was last approved in 10/2007.

LA4198
Bottle label:

Risperidone 1mg/ml Oral Solution
Risperidone

Solution for oral use.
Each 1 ml contains risperidone 1 mg.

Read the package leaflet before use. Use as directed by your doctor.
Keep out of the reach and sight of children.

PL 25954/0001
Marketing authorisation holder:
Distributed by:
Chanelle Medical U.K. Ltd.

410740744

100 ml