RISPERIDONE 0.5 MG FILM-COATED TABLETS
PL 08553/0259

RISPERIDONE 1 MG FILM-COATED TABLETS
PL 08553/0255

RISPERIDONE 2 MG FILM-COATED TABLETS
PL 08553/0256

RISPERIDONE 3 MG FILM-COATED TABLETS
PL 08553/0257

RISPERIDONE 4 MG FILM-COATED TABLETS
PL 08553/0258

RISPERIDONE 6 MG FILM-COATED TABLETS
PL 08553/0260

UKPAR

**TABLE OF CONTENTS**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>2</td>
</tr>
<tr>
<td>Scientific discussion</td>
<td>3</td>
</tr>
<tr>
<td>Steps taken for assessment</td>
<td>12</td>
</tr>
<tr>
<td>Steps taken after authorisation – summary</td>
<td>13</td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td></td>
</tr>
<tr>
<td>Product Information Leaflet</td>
<td></td>
</tr>
<tr>
<td>Labelling</td>
<td></td>
</tr>
</tbody>
</table>
LAY SUMMARY

The MHRA granted Dr Reddy’s Laboratories (UK) Limited Marketing Authorisations (licences) for the medicinal products Risperidone 0.5mg Film-Coated Tablets (PL 08553/0259), Risperidone 1mg Film-Coated Tablets (PL 08553/0255), Risperidone 2mg Film-Coated Tablets (PL 08553/0256), Risperidone 3mg Film-Coated Tablets (PL 08553/0257), Risperidone 4mg Film-Coated Tablets (PL 08553/0258) and Risperidone 6mg Film-Coated Tablets (PL 08553/0260) on 29th October 2007. These are prescription-only medicines (POM) 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 film-coated tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Risperidone film-coated tablets are also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Risperidone film-coated tablets are 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.

Risperidone film-coated tablets are not licensed for the treatment of behavioural symptoms of dementia.

Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg, and 6mg Film-coated Tablets contain the active ingredient risperidone. Risperidone is an antipsychotic drug.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg, and 6mg Film-coated Tablets outweighs the risks, hence Marketing Authorisations have been granted.
RISPERIDONE 0.5 MG FILM-COATED TABLETS
PL 08553/0259

RISPERIDONE 1 MG FILM-COATED TABLETS
PL 08553/0255

RISPERIDONE 2 MG FILM-COATED TABLETS
PL 08553/0256

RISPERIDONE 3 MG FILM-COATED TABLETS
PL 08553/0257

RISPERIDONE 4 MG FILM-COATED TABLETS
PL 08553/0258

RISPERIDONE 6 MG FILM-COATED TABLETS
PL 08553/0260

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 11
INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-Coated Tablets (PL 08553/0255-60) on 29th October 2007. The products are prescription-only medicines.

These were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products of the original products Risperdal 0.5mg, 1mg, 2mg, 3mg, 4mg and 6mg Tablets (Janssen-Cilag Limited, UK).

The products contain the active ingredient risperidone and are 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 film-coated tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Risperidone film-coated tablets are also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Risperidone film-coated tablets are 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.

Risperidone film-coated tablets are not licensed for the treatment of behavioural symptoms of dementia.

Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg, and 6mg Film-coated Tablets contain the active ingredient risperidone. 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 extra pyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.
DRUG SUBSTANCE
Risperidone

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

Structure:

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{F} \\
\text{CH}_3 & \quad \text{O} \\
\end{align*}
\]

CAS registry number: 106266-06-2
Physical form: White to off-white powder, practically insoluble in water, freely soluble in methylene chloride, and sparingly soluble in alcohol. It dissolves in dilute acid solutions.
Molecular formula: C\textsubscript{23}H\textsubscript{27}FN\textsubscript{4}O\textsubscript{2}
Molecular weight: 410.5

A European pharmacopoeial monograph has been written for active risperidone.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance risperidone. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Active risperidone is packaged in food grade polyethylene bags, which are sealed and placed in aluminium laminated bags, which are then placed in HDPE drums with a HDPE lid and sealed. Full specifications and suitable certificates of analysis are provided for all packaging.

Stability data provided for the active substance has been provided and supports a retest period of 2 years.

DRUG PRODUCT
Other ingredients
All tablets contain lactose monohydrate, pregelatinised starch, microcrystalline cellulose, sodium laurel sulphate, colloidal anhydrous silica, talc and magnesium stearate. The film-coating material consists of Opadry Brown 03B56980 for the 0.5mg strength, Opadry White OY-58900 for the 1mg strength, Opadry Orange 03B53509 for the 2mg strength, Opadry Yellow 03B52209 for the 3mg strength, Opadry Green 03B551293 for the 4mg strength and Opadry Yellow 03B52222 for the 6mg strength.
All excipients used comply with respective Ph. Eur monograph, with the exception of the film-coating materials, which are controlled to suitable in-house specifications. Satisfactory certificates of analysis have been provided for all excipients.

With the exception of lactose, none of the excipients used contain materials of animal or human origin. The manufacturer of lactose monohydrate has confirmed that this is sourced from healthy animals under the same conditions as milk for human consumption.

**Product development**
The applicant has provided a suitable product development rationale and data.

Satisfactory assay, impurity and dissolution data have been provided, showing that the proposed products are comparable to the originator products.

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

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

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

**Container Closure System**
The finished product is packaged in aluminium/polyvinylchloride/polyvinylidene chloride/polyethylene blisters in pack sizes of 20 tablets (0.5, 1, 2, 3 and 4mg strengths), 28 tablets (1, 2, 3, 4 and 6mg strengths), 50 tablets (all strengths) and 60 tablets (1, 2, 3, 4 and 6mg strengths).

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

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months has been set for all strengths with the storage conditions “Do not store above 25°C” and “Keep container in the outer carton”.

**Bioequivalence**
See clinical assessment.
ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SPC)
These are consistent with those for the reference products and are satisfactory.

Labelling
These are satisfactory

Patient Information Leaflet (PIL)
This is consistent with that for the reference products and is satisfactory. The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Forms
These are satisfactory.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

The requirements for a generic medicinal product have been met with respect to qualitative and quantitative content of the active substance. In addition, similar dissolution, impurity and assay profiles have been demonstrated for the proposed and reference products.
PRECLINICAL ASSESSMENT

These applications for generic products claims essential similarity to Risperdal 0.5mg, 1mg, 2mg, 3mg, 4mg and 6mg Tablets (Janssen-Cilag Limited, UK), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The applicant commissioned one single-centre, randomised, single-dose, fasting, two-way crossover study in healthy fasted male volunteers, comparing the pharmacokinetics of the test product Risperidone 1mg Film-Coated Tablets versus the reference product Risperidal 1mg Film-Coated Tablets (Janssen Cilag, UK).

Serum drug levels were followed for 96 hours post dose, with a 21-day washout period between phases. Results from the bioequivalence studies are presented below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dr. Reddy's Laboratories, Ltd. (A) vs. Janssen-Cilag Ltd. (Risperdal&lt;sup&gt;®&lt;/sup&gt;) (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC 0-t</td>
<td>91.5% (83.5 – 100.1%)</td>
</tr>
<tr>
<td>AUC&lt;inf&gt;</td>
<td>92.7% (84.6 – 101.6%)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>94.7% (85.0 – 105.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>9-Hydroxyrisperidone Dr. Reddy's Laboratories, Ltd. (A) vs. Janssen-Cilag Ltd. (Risperdal&lt;sup&gt;®&lt;/sup&gt;) (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC 0-t</td>
<td>98.7% (93.3 – 104.4%)</td>
</tr>
<tr>
<td>AUC&lt;inf&gt;</td>
<td>98.0% (92.5 – 103.8%)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>103.3% (98.7 – 108.1%)</td>
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</table>

Based on the submitted bioequivalence data, it can be considered that Risperidone 1mg Film-Coated Tablets is a generic medicinal product to Risperdal 1mg Film-Coated Tablets.

As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 1mg strength can be extrapolated to the 0.5, 2, 3, 4 and 6mg strength tablets.

EFFICACY
No new data has been provided.

SAFETY
No new data has been provided.

EXPERT REPORTS
A clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference products and is satisfactory.

LABELLING
These are satisfactory

APPLICATION FORMS (MAA)
These are satisfactory.
SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
These are consistent with those for the reference products and are satisfactory.

DISCUSSION
The applicant has satisfactorily demonstrated bioequivalence between the 1mg strengths of test and originator products. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 1mg strength can be extrapolated to the 0.5, 2, 3, 4 and 6mg strength tablets.

MEDICAL CONCLUSION
The bioequivalence study submitted has shown that these products can be considered as generic medicinal products to the originator products Risperdal Tablets (Janssen-Cilag Limited, UK).

Marketing authorisations are recommended for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-Coated Tablets 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
Bioequivalence has been demonstrated between the applicant’s Risperidone 1mg Film-Coated Tablets and the reference product Risperidal 1mg Tablets (Janssen-Cilag Limited, UK). As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 4mg strength can be extrapolated to the 0.5, 2, 3, 4 and 6mg strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Risperdal Tablets.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with risperidone is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
**RISPERSDONE 0.5 MG FILM-COATED TABLETS**  
PL 08553/0259

**RISPERSDONE 1 MG FILM-COATED TABLETS**  
PL 08553/0255

**RISPERSDONE 2 MG FILM-COATED TABLETS**  
PL 08553/0256

**RISPERSDONE 3 MG FILM-COATED TABLETS**  
PL 08553/0257

**RISPERSDONE 4 MG FILM-COATED TABLETS**  
PL 08553/0258

**RISPERSDONE 6 MG FILM-COATED TABLETS**  
PL 08553/0260

**STEPS TAKEN FOR ASSESMENT**

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<td>1</td>
<td>The MHRA received the marketing authorisation applications on 31st March 2006</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 30th June 2006</td>
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<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the dossiers on 3rd April 2007</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 16th August 2007.</td>
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<tr>
<td>5</td>
<td>The applications were determined on 29th October 2007</td>
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RISPERIDONE 0.5 MG FILM-COATED TABLETS
PL 08553/0259

RISPERIDONE 1 MG FILM-COATED TABLETS
PL 08553/0255

RISPERIDONE 2 MG FILM-COATED TABLETS
PL 08553/0256

RISPERIDONE 3 MG FILM-COATED TABLETS
PL 08553/0257

RISPERIDONE 4 MG FILM-COATED TABLETS
PL 08553/0258

RISPERIDONE 6 MG FILM-COATED TABLETS
PL 08553/0260

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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<tr>
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<th>Application type</th>
<th>Scope</th>
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</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Risperidone 0.5mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 0.5mg risperidone
Excipient(s):
Each film-coated tablet also contains 58.2mg of lactose
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

Brown capsule shaped biconvex film coated tablet embossed with ‘0.5’ on one side and ‘RSP’ on the other side with a score line separating the ‘R’ from the ‘SP’.

The score line is to break the tablet for ease of swallowing; not to divide the tablet into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Risperidone film-coated Tablets are 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 film-coated Tablets also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Risperidone film-coated Tablets are also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Risperidone film-coated Tablets are 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.

Risperidone film-coated Tablets are not licensed for the treatment of behavioural symptoms of dementia (see section 4.4).

4.2 Posology and method of administration

Schizophrenia
Switching from other antipsychotics: where medically appropriate, gradual discontinuation of the previous treatment while treatment with Risperidone film-coated Tablets is initiated is recommended. Where medically appropriate when switching patients from depot antipsychotics, consider initiating Risperidone film-coated Tablets 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 of 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.

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 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
Known hypersensitivity to risperidone or any of the excipients.

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 patients treated with risperidone 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 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 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 film-coated Tablets.

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 film-coated Tablets 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 (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.

4.5 Interaction with other medicinal products and other forms of interaction
Possible interactions of Risperidone film-coated Tablets 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 film-coated Tablets. 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 film-coated Tablets should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperidone film-coated Tablets 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 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 film-coated Tablets are 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 co-administering 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 film-coated Tablets 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 film-coated Tablets 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 film-coated Tablets are 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 film-coated Tablets 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 Special warnings and precautions for use).

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 film-coated Tablets.

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 film-coated Tablets.

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 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 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 film-coated Tablets. 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**

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 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
Tablet core:
Lactose monohydrate
Starch, pregelatinised
Cellulose, microcrystalline (E460)
Sodium laurilsulfate
Silica, colloidal anhydrous
Talc (E553b)
Magnesium stearate (E572)

Tablet coating:
Red iron oxide (E172)
Yellow iron oxide (E172)
Hydroxypropyl methyl cellulose 3cP and 6cP (E464)
Macrogol
Polysorbate 80
Titanium dioxide (E171)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 25°C. Keep blister in the outer carton.

6.5 Nature and contents of container
Aluminium foil/PVC-PE/PVdC blisters in cartons of 20 and 50 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Dr Reddy’s Laboratories (UK) Ltd
6 Riverview Road,
Beverley,
East Yorkshire
HU17 0LD,
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 08553/0259

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/10/2007

10 DATE OF REVISION OF THE TEXT
29/10/2007
1 NAME OF THE MEDICINAL PRODUCT
Risperidone 1mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 1mg risperidone
Excipient(s):
Each film-coated tablet also contains 57.8mg of lactose
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

White capsule shaped biconvex film coated tablet embossed with ‘1’ on one side and ‘RSP’ on the other side with a score line separating the ‘R’ from the ‘SP’.

The score line is to break the tablet for ease of swallowing; not to divide the tablet into equal doses.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Risperidone film-coated Tablets are 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 film-coated Tablets also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Risperidone film-coated Tablets are also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Risperidone film-coated Tablets are 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.

Risperidone film-coated Tablets are not licensed for the treatment of behavioural symptoms of dementia (see section 4.4).

4.2 Posology and method of administration

Schizophrenia
Switching from other antipsychotics: where medically appropriate, gradual discontinuation of the previous treatment while treatment with Risperidone film-coated Tablets is initiated is recommended. Where medically appropriate when switching patients from depot antipsychotics, consider initiating Risperidone film-coated Tablets 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 of 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.

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 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
Known hypersensitivity to risperidone or any of the excipients.

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 patients treated with risperidone 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 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 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 film-coated Tablets.

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 film-coated Tablets 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.
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.

### 4.5 Interaction with other medicinal products and other forms of interaction

Possible interactions of Risperidone film-coated Tablets 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 film-coated Tablets. 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 film-coated Tablets should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperidone film-coated Tablets 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 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 film-coated Tablets are 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 co-administering 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 film-coated Tablets 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 film-coated Tablets 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 film-coated Tablets are 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 film-coated Tablets 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 Special warnings and precautions for use).

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 film-coated Tablets.

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 film-coated Tablets.

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 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 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 film-coated Tablets. 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

Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives (ATC code N05A X08).

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 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
Tablet core:
- Lactose monohydrate
- Starch, pregelatinised
- Cellulose, microcrystalline (E460)
- Sodium laurilsulfate
- Silica, colloidal anhydrous
- Talc (E553b)
- Magnesium stearate (E572)

Tablet coating:
- Hypromellose
- Titanium dioxide (E171)
- Polyethylene glycol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 25°C. Keep blister in the outer carton.

6.5 Nature and contents of container
Aluminium foil/PVC-PE/PVdC blisters in cartons of 20, 28, 50 or 60 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Dr Reddy’s Laboratories (UK) Ltd
6 Riverview Road,
Beverley,
East Yorkshire
HU17 0LD,
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 08553/0255

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHOURISATION
29/10/2007

10 DATE OF REVISION OF THE TEXT
29/10/2007
NAME OF THE MEDICINAL PRODUCT
Risperidone 2mg film-coated Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 2mg risperidone
Excipient(s):
Each film-coated tablet also contains Sunset Yellow ECF (E110) and 115.3mg of lactose.
For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM
Film-coated tablet
Orange capsule shaped biconvex film coated tablet embossed with ‘2’ on one side and ‘RSP’ on the other side with a score line separating the ‘R’ from the ‘SP’.

The score line is to break the tablet for ease of swallowing; not to divide the tablet into equal doses.

CLINICAL PARTICULARS
4.1 Therapeutic indications
Risperidone film-coated Tablets are 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 film-coated Tablets also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Risperidone film-coated Tablets are also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Risperidone film-coated Tablets are 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.

Risperidone film-coated Tablets are not licensed for the treatment of behavioural symptoms of dementia (see section 4.4).

4.2 Posology and method of administration
Schizophrenia
Switching from other antipsychotics: where medically appropriate, gradual discontinuation of the previous treatment while treatment with Risperidone film-coated Tablets is initiated is recommended. Where medically appropriate when switching patients from depot antipsychotics, consider initiating Risperidone film-coated Tablets 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 of 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.

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 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  
Known hypersensitivity to risperidone or any of the excipients.

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 patients treated with risperidone 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 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 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 film-coated Tablets.

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 film-coated Tablets 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 (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.

4.5 Interaction with other medicinal products and other forms of interaction
Possible interactions of Risperidone film-coated Tablets 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 film-coated Tablets. 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 film-coated Tablets should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperidone film-coated Tablets 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 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 film-coated Tablets are 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 co-administering 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 film-coated Tablets 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 film-coated Tablets 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 film-coated Tablets are 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 film-coated Tablets 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 Special warnings and precautions for use).

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 film-coated Tablets.

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 film-coated Tablets.

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 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 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 film-coated Tablets. 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
Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives (ATC code N05A X08).

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 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
Tablet core:
- Lactose monohydrate
- Starch, pregelatinised
- Cellulose, microcrystalline (E460)
- Sodium laurilsulfate
- Silica, colloidal anhydrous
- Talc (E553b)
- Magnesium stearate (E572)

Tablet coating:
- Hypromellose
- Titanium dioxide (E171)
- Polyethylene glycol
- Sunset yellow (E110)
- Quinoline yellow (E104)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 25°C. Keep blister in the outer carton.

6.5 Nature and contents of container
Aluminium foil/PVC-PE/PVdC blisters in cartons of 20, 28, 50 or 60 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Dr Reddy’s Laboratories (UK) Ltd
6 Riverview Road,
Beverley,
East Yorkshire
HU17 0LD,
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 08553/0256

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/10/2007

10 DATE OF REVISION OF THE TEXT
29/10/2007
1 NAME OF THE MEDICINAL PRODUCT
Risperidone 3mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 3mg risperidone
Excipient(s):
Each film-coated tablet also contains 173mg of lactose
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

Yellow capsule shaped biconvex film coated tablet embossed with ‘3’ on one side and ‘RSP’ on the other side with a score line separating the ‘R’ from the ‘SP’.

The score line is to break the tablet for ease of swallowing; not to divide the tablet into equal doses.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Risperidone film-coated Tablets are 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 film-coated Tablets also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Risperidone film-coated Tablets are also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Risperidone film-coated Tablets are 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.

Risperidone film-coated Tablets are not licensed for the treatment of behavioural symptoms of dementia (see section 4.4).

4.2 Posology and method of administration

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

Adolescents
Risperidone may be given once or twice daily. All patients, whether acute or chronic, should start with 2 mg/day of 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.

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 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
Known hypersensitivity to risperidone or any of the excipients.

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 patients treated with risperidone 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 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 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 film-coated Tablets.

**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 film-coated Tablets 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 (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.

4.5 Interaction with other medicinal products and other forms of interaction
Possible interactions of Risperidone film-coated Tablets 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 film-coated Tablets. 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 film-coated Tablets should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperidone film-coated Tablets 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 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 film-coated Tablets are taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.

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 film-coated Tablets 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 film-coated Tablets 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 film-coated Tablets are 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 film-coated Tablets 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, orgastic dysfunction, urinary incontinence, rhinitis, rash and other allergic reactions.

Cerebrovascular accidents have been observed during treatment with risperidone (see Section 4.4 Special warnings and precautions for use).

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 film-coated Tablets.

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 film-coated Tablets.

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 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 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 film-coated Tablets. 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

Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives (ATC code N05A X08).

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 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
Tablet core:
Lactose monohydrate
Starch, pregelatinised
Cellulose, microcrystalline (E460)
Sodium laurilsulfate
Silica, colloidal anhydrous
Talc (E553b)
Magnesium stearate (E572)

Tablet coating:
Hypromellose
Titanium dioxide (E171)
Polyethylene glycol
Quinoline yellow (E104)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 25°C. Keep blister in the outer carton.

6.5 Nature and contents of container
Aluminium foil/PVC-PE/PVdC blisters in cartons of 20, 28, 50 or 60 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Dr Reddy’s Laboratories (UK) Ltd
6 Riverview Road,
Beverley,
East Yorkshire
HU17 0LD,
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 08553/0257

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/10/2007

10 DATE OF REVISION OF THE TEXT
29/10/2007
NAME OF THE MEDICINAL PRODUCT
Risperidone 4mg film-coated Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 4mg risperidone
Excipient(s):
Each film-coated tablet also contains 231mg of lactose
For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM
Film-coated tablet

Green capsule shaped biconvex film coated tablet embossed with ‘4’ on one side and ‘RSP’ on the other side with a score line separating the ‘R’ from the ‘SP’.

The score line is to break the tablet for ease of swallowing; not to divide the tablet into equal doses.

CLINICAL PARTICULARS
4.1 Therapeutic indications
Risperidone film-coated Tablets are 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 film-coated Tablets also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

Risperidone film-coated Tablets are also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Risperidone film-coated Tablets are 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.

Risperidone film-coated Tablets are not licensed for the treatment of behavioural symptoms of dementia (see section 4.4).

4.2 Posology and method of administration
Schizophrenia
Switching from other antipsychotics: where medically appropriate, gradual discontinuation of the previous treatment while treatment with Risperidone film-coated Tablets is initiated is recommended. Where medically appropriate when switching patients from depot antipsychotics, consider initiating Risperidone film-coated Tablets 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 of 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.

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 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
Known hypersensitivity to risperidone or any of the excipients.

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 patients treated with risperidone 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 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 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 film-coated Tablets.

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 film-coated Tablets 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 (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.

4.5 Interaction with other medicinal products and other forms of interaction
Possible interactions of Risperidone film-coated Tablets 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 film-coated Tablets. 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 film-coated Tablets should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperidone film-coated Tablets 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 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 film-coated Tablets are 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 co-administering 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 film-coated Tablets 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 film-coated Tablets 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 film-coated Tablets are 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 film-coated Tablets 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 Special warnings and precautions for use).

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 film-coated Tablets.

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 film-coated Tablets.

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 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 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 film-coated Tablets. 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
Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives (ATC code N05A X08).

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 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
Tablet core:
- Lactose monohydrate
- Starch, pregelatinised
- Cellulose, microcrystalline (E460)
- Sodium laurilsulfate
- Silica, colloidal anhydrous
- Talc (E553b)
- Magnesium stearate (E572)

Tablet coating:
- Hypromellose
- Titanium dioxide (E171)
- Polyethylene glycol
- Quinoline yellow (E104)
- Indigo carmine (E132)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 25°C. Keep blister in the outer carton.

6.5 Nature and contents of container
Aluminium foil/PVC-PE/PVdC blisters in cartons of 20, 28, 50 or 60 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Dr Reddy’s Laboratories (UK) Ltd
6 Riverview Road,
Beverley,
East Yorkshire
HU17 0LD,
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 08553/0258

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/10/2007

10 DATE OF REVISION OF THE TEXT
29/10/2007
1 NAME OF THE MEDICINAL PRODUCT
Risperidone 6mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 6mg risperidone.
Excipient(s):
Each film-coated tablet also contains FD & C Yellow No.5 Al Lake (Tartrazine Lake) (E102)
and 346mg of lactose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Yellow round biconvex film coated tablet embossed with ‘6’ on one side and ‘RSP’ on the
other side with a score line separating the ‘R’ from the ‘SP’.
The score line is to break the tablet for ease of swallowing; not to divide the tablet into equal
doses.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Risperidone film-coated Tablets are 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 film-coated Tablets also alleviates affective symptoms (such as
depression, guilt feelings, anxiety) associated with schizophrenia.
Risperidone film-coated Tablets are also effective in maintaining the clinical improvement
during continuation therapy in patients who have shown an initial treatment response.
Risperidone film-coated Tablets are 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.
Risperidone film-coated Tablets are not licensed for the treatment of behavioural symptoms of
dementia (see section 4.4).

4.2 Posology and method of administration
Schizophrenia
Switching from other antipsychotics: where medically appropriate, gradual discontinuation of
the previous treatment while treatment with Risperidone film-coated Tablets is initiated is
recommended. Where medically appropriate when switching patients from depot
antipsychotics, consider initiating Risperidone film-coated Tablets 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 of 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.

**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 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
Known hypersensitivity to risperidone or any of the excipients.

### 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 patients treated with risperidone 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 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 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 film-coated Tablets.

**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 film-coated Tablets 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 (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.

4.5 Interaction with other medicinal products and other forms of interaction
Possible interactions of Risperidone film-coated Tablets 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 film-coated Tablets. 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 film-coated Tablets should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperidone film-coated Tablets 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 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 film-coated Tablets are 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 co-administering 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 film-coated Tablets 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 film-coated Tablets 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 film-coated Tablets are 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 film-coated Tablets 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 Special warnings and precautions for use).

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 film-coated Tablets.

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 film-coated Tablets.

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 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 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 film-coated Tablets. 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

Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives (ATC code N05A X08).

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 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
Tablet core:
Lactose monohydrate
Starch, pregelatinised
Cellulose, microcrystalline (E460)
Sodium lauriisulfate
Silica, colloidal anhydrous
Talc (E553b)
Magnesium stearate (E572)

Tablet coating:
Titanium dioxide (E171)
FD&C Yellow No.5 Al. Lake (Tartrazine Lake) (E102)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 25°C. Keep blister in the outer carton.

6.5 Nature and contents of container
Aluminium foil/PVC-PE/PVdC blisters in cartons of 28, 50 or 60 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Dr Reddy’s Laboratories (UK) Ltd
6 Riverview Road,
Beverley,
East Yorkshire
HU17 0LD,
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 08553/0260

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/10/2007

10 DATE OF REVISION OF THE TEXT
29/10/2007
UKPAR Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-Coated Tablets
PL 08553/0255-60

PACKAGE LEAFLET: INFORMATION FOR THE USER
Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg and 6mg film-coated Tablets

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 gets 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 film-coated Tablets are and what they are used for
2. Before you take Risperidone film-coated Tablets
3. How to take Risperidone film-coated Tablets
4. Possible side effects
5. How to store your Risperidone film-coated Tablets
6. Further information

1. What Risperidone film-coated Tablets are and what they are used for

Risperidone is a type of medicine called an antipsychotic, which helps to improve the way you think, feel and/or act.

- Sudden and long-lasting schizophrenic conditions and other psychotic conditions; symptoms include hallucinations, delusions, thought disturbances, hostility, suspiciousness, blunted affect, emotional and social withdrawal and poverty of speech.
- Symptoms such as depression, feelings of guilt and anxiety, associated with schizophrenia.
- Mania symptoms in patients with bipolar disorder.

Risperidone may also be used long-term to prevent these symptoms returning.

2. Before you take Risperidone film-coated Tablets

Do not take Risperidone film-coated Tablets if you:
- Are allergic to any of the ingredients of these tablets, listed in Section 6 or Section 2 (important information about some of the ingredients of Risperidone film-coated tablets).

Take special care if you:
- Are sugar intolerant.
- Have heart or blood vessel disease, high blood pressure, Parkinson’s disease, epilepsy, diabetes, kidney or liver problems, or you are a current smoker.
- Are an elderly patient (over 65 years) with dementia or taking diuretics, such as furosemide, as you may become dehydrated.

Risperidone is not recommended for the treatment of behavioural symptoms of dementia because it may cause sudden weakness or numbness of the face, arms or legs, slurred speech or problems with your vision.

Taking other medicines

You should make sure you have told your doctor or pharmacist about any other medicines you are taking, including any you have bought without a prescription. If you answer yes to any of the following questions, talk to your doctor before taking this medicine:
- If you have had any medicine for high blood pressure, antidepressants, sedatives, or keep your eyes open.
- Beta-blockers such as atenolol and propranolol (for irregular heartbeat).
- Anti-diuretics, such as furosemide (for water retention).
- For prevention of malaria.

Taking Risperidone film-coated tablets with food and drink

Risperidone film-coated tablets can be taken before a meal or on an empty stomach. You should be careful how much alcohol you drink, because the combined effect of alcohol and your medicine might make you feel drowsy.

Pregnancy and breast-feeding

You should not take Risperidone film-coated Tablets if you are planning to become pregnant, if you are pregnant or if you are breast-feeding, unless advised by your doctor.

Driving and using machines

These tablets may interfere with activities requiring mental alertness. Take care when using these tablets, as your ability to drive or operate machinery may be affected.

Important information about some of the ingredients of Risperidone film-coated tablets

This product contains lactose. If you have been told by your doctor that you have intolerance to some sugars, talk to your doctor before taking this medicine. The 2mg tablets also contain E110, which may cause an allergic reaction.

3. How to take Risperidone film-coated Tablets

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

You may take your tablets at any time of the day, ideally before a meal or on an empty stomach. Your doctor will tell you how many tablets to take, and when to take them. You may divide your dose into one or two doses daily. Tablets can easily be broken in half to aid swallowing.

Treatment of schizophrenic conditions

Adults: The initial dose on day 1 is 2mg either as a single dose or two separate doses. On the second day, the dosage may be increased to 4mg. Most patients typically benefit from a daily dose of 4 to 6mg.

The maximum daily dose is 16mg.

The elderly: The initial dose is 0.5mg twice a day, and the usual dose is 1 to 2 mg daily.

Children: Not recommended in children under 15 years of age.
Treatment of mania
Adults: Initially 2mg daily, if required the dosage may be increased daily by 1mg up to a maximum of 6mg.
The elderly: The initial dose is 0.5mg twice a day, and the usual dose is 1 to 2mg daily.
Children: Not recommended in children under 15 years of age.

Patients with kidney or liver problems
The initial dose is 0.5mg twice a day, and the usual dose is 1 to 2mg daily. Risperidone should be used cautiously in this group of patients.

If you forget to take Risperidone film-coated Tablets
If you forget to take your tablets, take them as soon as you remember unless it is almost time for the next dose. Do not take a double dose to make up for a forgotten individual dose.

If you take more Risperidone film-coated tablets than you should
If you take more than the recommended number of tablets, contact your doctor or pharmacist immediately. Take this leaflet and the pack of Risperidone film-coated Tablets along with you, if you can.

If you stop taking Risperidone film-coated Tablets
Do not stop taking Risperidone film-coated tablets even if you start feeling better. Continue taking Risperidone film-coated tablets as long as your doctor has advised you. The withdrawal of Risperidone may cause nausea, vomiting, sweating, inability to sleep, and a return of your symptoms (see section 1). 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 film-coated Tablets may cause side effects, although not everybody gets them. Many effects are usually mild and go away when you stop taking the medicine.

Side effects with Risperidone film-coated tablets may include:

Common side effects (less than 1 in 10 people but no more than 1 in 100 people):
- inability to sleep, feelings of agitation or anxiety and headaches.

Less common side effects (less than 1 in 100 people but more than 1 in 1,000 people):
- drowsy, tiredness, dryness, low blood pressure, fast pulse, poor concentration, constipation, stomach upset, nausea or vomiting, abdominal pain, blurred vision, male sexual problems, urinary incontinence, sore or blocked nose, rash and other allergic reactions.
- tremor, rigidity, excess salivaion, slow movements, restlessness, weight gain, irregular periods, male breast enlargement, and abnormal muscle tone, milk production, and blood chemistry.
- stroke or transient ischaemic attacks (temporary reduction in the blood supply to the brain); if you experience sudden weakness or numbness of the face, arms or legs, especially on one side, or instances of slurred speech.

you must seek immediate medical attention

Rare side effects (affecting less than 1 in 1000 people but no more than 1 in 10,000 people):
Excessive thirst and water intoxication, involuntary twitching tongue and facial movement, poor control of body temperature, seizures.

Very rare side effects (affecting less than 1 in 10,000 people but no more than 1 in 1,000,000 people):
High blood sugar levels and loss of control in diabetes, angioedema and benign growths. Seizure, which is usually mild and short lived, has mainly been reported in children and adolescents.

If you suffer from any of these side effects, or if you notice any other side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. How to store your Risperidone film-coated Tablets

Keep out of the reach and sight of children. Do not store above 25°C and keep the tablets in their original package

Do not use Risperidone film-coated Tablets after the expiry date which is stated on the carton after "Expiry." The expiry date refers to the last day of that month.

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 protect the environment.

6. Further information

What Risperidone film-coated Tablets contain
The active substance is Risperidone.
The other ingredients in the tablet are: lactose monohydrate (Section 2 Important information about some of the ingredients of Risperidone film-coated tablets), starch pregelatinised, cellulose microcrystalline, sodium laurylsulphate, silica colloidal anhydrous, talc, magnesium stearate, hypromellose, titanium dioxide (E171) and macrogol 400. Tablet coatings contain:
- 0.5mg tablet: red and yellow iron oxides (E172), and hydroxypropyl methylcellulose.
- 2mg tablet: sunset yellow (E110) and quinoline yellow (E104)
- 3mg tablet: quinoline yellow (E104)
- 4mg tablet: quinoline yellow (E104) and indigo carmine (E132).
- 5mg tablet: hypromellose and FD&C Yellow 45/Ferric oxide Aluminum Lake (E102).

What Risperidone film-coated tablets look like and contents of the pack

Each brown tablet contains equivalent to 0.5mg of Risperidone.
Each white tablet contains equivalent to 1mg of Risperidone.
Each orange tablet contains equivalent to 2mg of Risperidone.
Each yellow tablet contains equivalent to 3mg of Risperidone.
Each green tablet contains equivalent to 4mg of Risperidone.

Your Risperidone Tablets are supplied in boxes containing 20 or 50 tablets for 0.5mg, 20, 28, 50 or 60 tablets for 1mg, 2mg, 3mg and 4mg Risperidone. The 5mg strength is packaged in boxes of 28, 50 or 60 tablets.
UKPAR Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-Coated Tablets

Each film-coated tablet for oral use contains 2mg of risperidone. Also contains sunset yellow (E110) and lactose monohydrate. Please read enclosed leaflet before use. Take as directed by your doctor. Do not store above 25°C. Keep blister in the outer carton.

Risperidone 2mg Film-coated Tablets
Place dispensing label here

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

PL 08553/0255 Dr. Reddy’s Laboratories (UK) Ltd.
6 Rivenlow Rd, Benecroy, HU17 0LD UK

PL 08553/0255-60

Each film-coated tablet for oral use contains 2mg of risperidone. Also contains sunset yellow (E110) and lactose monohydrate. Please read enclosed leaflet before use. Take as directed by your doctor. Do not store above 25°C. Keep blister in the outer carton.

Risperidone 2mg Film-coated Tablets
Place dispensing label here

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

PL 08553/0255 Dr. Reddy’s Laboratories (UK) Ltd.
6 Rivenlow Rd, Benecroy, HU17 0LD UK

50 Tablets

64
Each film-coated tablet for oral use contains 2mg of risperidone. Also contains sunset yellow (E110) and lactose monohydrate. Please read enclosed leaflet before use. Take as directed by your doctor. Do not store above 25°C. Keep blister in the outer carton.

Risperidone 2mg Film-coated Tablets

Place dispensing label here

Risperidone 2mg Film-coated Tablets

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

PL 08553/0256  Dr. Reddy's Laboratories (UK) Ltd., 6 Riverview Rd., Beverley, HU17 0LD, UK