Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg and 6mg
Film-Coated Tablets
PL 14017/0130-5
UKPAR

Table of Contents

Lay Summary Page 2
Scientific discussion Page 3
Steps taken for assessment Page 12
Summary of Product Characteristics
Product Information Leaflet
Labelling
Risperidone Tablets are one of a group of medicines called antipsychotics. They are used to treat conditions which affect the way you think, feel and/or act. These conditions may cause symptoms such as confusion, hallucinations (e.g., hearing, seeing or sensing things which are not there), delusions, unusual suspiciousness (paranoia) and emotional and social withdrawal. People with these conditions may also feel depressed, guilty, anxious or tense. Risperidone Tablets may be taken for both sudden (acute) and long-lasting (chronic) disorders.

In addition, Risperidone Tablets may be used to control the symptoms of mania for people with bipolar disorder.

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, 1, 2, 3, 4 and 6mg Film-Coated Tablets

Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg and 6mg Film-Coated Tablets

PL 14017/0130-5

Scientific Discussion

Table of Contents

Introduction .................................... Page 4
Pharmaceutical assessment .................... Page 5
Preclinical assessment ........................ Page 8
Clinical assessment (including statistical assessment) Page 9
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 0.5mg, 1mg, 2mg, 3mg, 4mg, and 6mg Film-coated Tablets on 16th of October 2007. The products are prescription only medicines.

These applications were submitted as an abridged applications according to Article 10(1) of Directive 2001/83/EC, claiming to be a generic medicinal product of the original products Risperdal 1mg tablets (PL 00242/0186), Risperdal 2mg tablets (PL 00242/0187), Risperdal 3mg tablets (PL 00242/0188) and Risperdal 4mg tablets (PL 00242/0189) first authorised in UK in December 1992 to Janssen-Cilag Ltd.

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

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 Tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

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

They are also 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 Tablets are not licensed for the treatment of behavioural symptoms of dementia.

These applications for Risperidone were submitted at the same time. The bioequivalence study was sufficient to confirm the bioequivalence of the product to the reference product.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

rINN: Risperidone  CAS reg. no. 106266-06-2

Structure

3-\{2-\{4[6-Fluoro-1,2-benzisoxazol-3-yl]piperidin-1-yl\}ethyl\}-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one

C23H27FN4 O2  MW: 410.5

General Properties

Risperidone is a white or almost white powder, practically insoluble in water, freely soluble in methylene, chloride, and sparingly soluble in ethanol (96 per cent). It dissolves in dilute acid solutions. Risperidone is known to show polymorphism. The active substance is the subject of Ph. Eur. monograph.

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. No materials of animal or human origin are used in the production of the active substance.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

All potential known impurities have been identified and characterised.

Active risperidone is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

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

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated, supporting the retest period for the active substance.
DRUG PRODUCT

Other ingredients
Other ingredients consist of pharmaceutical excipients, namely Lactose monohydrate, maize starch, microcrystalline cellulose, povidone, magnesium stearate, colloidal anhydrous silica, sodium laurilsulfate, carnauba wax, OPADRY red (0.5mg) and OPADRY white (1mg, 2mg, 3mg, 4mg, and 6mg).

All excipients used comply with their respective European Pharmacopoeia monograph, with the exception of OPADRY red and OPADRY white which comply with in-House specifications.

Satisfactory specifications and Certificates of Analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The application has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

Dissolution and Impurity profiles
Dissolution and impurity profiles for all strengths of the drug product were found to be generic medicinal products equivalent to those of the reference products.

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
The product is packaged in PVDC-coated PVC blisters, sealed with aluminium foil with package sizes of 20, 28, 56 and 60 tablets per box. Specifications and Certificates of Analysis for all packaging used have been provided. This is satisfactory. All primary product packaging complies with EU legislation regarding contact with food.
Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years with storage condition ‘Store below 30 degree C’ is proposed which is satisfactory.

Conclusion

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

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.
PRECLINICAL ASSESSMENT

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

Risperidone 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 Tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

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

Risperidone 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 Tablets are not licensed for the treatment of behavioural symptoms of dementia

4. DOSE & DOSE SCHEDULE

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

Adults

Risperidone Tablets may be given once or twice daily. All patients, whether acute or chronic, should start with 2 mg/day Risperidone Tablets. 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 Tablets 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 Tablets should be used with caution in this group of patients until further experience is gained.

4.2. b Bipolar Mania:

Adults

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

As with all symptomatic treatments, the continued use of Risperidone Tablets 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 Tablets 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 Tablets 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 Tablets (see Section 4.5 Interaction with other medicinal products and other forms of interaction). It is therefore not recommended to co-administer Risperidone Tablets 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 Tablets.

Method of administration
Oral use.

5. TOXICOLOGY

No new data.

6. CLINICAL PHARMACOLOGY

Risperidone is extensively metabolized in the liver by cytochrome P450 2D6 to a major active metabolite, 9-hydroxyrisperidone, which appears approximately equipotent with risperidone, with respect to receptor binding activity. Consequently, the clinical effect of the drug likely results from the active moiety (the combined concentrations of risperidone plus 9-hydroxyrisperidone). The hydroxylation of risperidone, and hence the concentrations of parent drug and active metabolite, differ substantially in extensive and poor CYP2D6 metabolizers. However, the concentration of the active moiety did not differ substantially between extensive and poor metabolizers, and elimination half-lives were similar in all subjects (20 to 24 hours).

The kinetics of the individual components of the active moiety, risperidone and its 9-hydroxy metabolite, are both dose proportional after doses of risperidone up to 25mg daily. Mean peak plasma concentrations of risperidone and 9-hydroxyrisperidone were reached at about 1 hour and 3 hours, respectively, after drug administration. Food did not affect the extent of absorption.

Bioequivalence study
Test product: Risperidone 1mg tablets
Reference product Risperdal 1mg tablets

A single open label, randomised, two treatment, two period, cross-over, single-dose bioequivalence study is presented in support of this application, comparing risperidone 1mg Tablets of Dexel Ltd., Israel and Risperdal 1mg Tablets of Janssen Cilag Ltd, UK. Healthy adult male and female subjects (including two alternates) were dosed under fasting conditions. The protocol is satisfactory. Sampling schedules were satisfactory for accurate determination of AUC_T, AUC_{inf} and C_{max}.

It is conventional in bioequivalence testing to test the highest dosage form in comparative bioavailability studies and extrapolate from those results to bioequivalence of the lower dosage forms. In this case a low dosage has been tested. The applicant provided an acceptable justification, on ethical and safety grounds, for the use of a low dose in the bioequivalence study.

<table>
<thead>
<tr>
<th>Descriptive Statistics for Pharmacokinetic Parameters of Risperidone</th>
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<tbody>
<tr>
<td></td>
<td>C_{max} (pg/mL)</td>
<td>AUC_T (pg·h/mL)</td>
<td>AUC_{inf} (pg·h/mL)</td>
<td>T_{max} (h)</td>
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<td>Treatment effect p-value</td>
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<td>Ratio of Test/Reference</td>
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<td>100.7</td>
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<td>90% CI of ratio</td>
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<td>102.2–123.62</td>
<td>95.57–119.41^f</td>
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</table>

^a Arithmetic mean
^b Based on data transformed to natural logarithm (except T_{max} and t_{1/2}).
^c Median
^d Range
^e Non-parametric confidence interval

<table>
<thead>
<tr>
<th>Descriptive Statistics for Pharmacokinetic Parameters of 9-Hydroxy-Risperidone</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C_{max} (pg/mL)</td>
<td>AUC_T (pg·h/mL)</td>
<td>AUC_{inf} (pg·h/mL)</td>
<td>T_{max} (h)</td>
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<td>Ratio of Test/Reference</td>
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<td>100.8</td>
<td>101.4</td>
<td>109.5</td>
</tr>
<tr>
<td>90% CI of ratio</td>
<td>94.81–108.17</td>
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<td>96.48–106.60</td>
<td>105.87–161.41^f</td>
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</tbody>
</table>

^a Arithmetic mean
^b Based on data transformed to natural logarithm (except T_{max} and t_{1/2}).
^c Median
^d Range
^e Non-parametric confidence interval
The 90% confidence intervals of $\text{AUC}_T$ and $\text{AUC}_{\text{inf}}$ for risperidone were only just contained in the acceptable range of 80 to 125%, with a point estimate of 12% supra-availability of the test product. In contrast however the AUC ratios for 9-hydroxy-risperidone were close to unity. Some non-linearity of conversion to the active metabolite could be an explanation or there might be no true difference between the parent drug and metabolite as the confidence intervals overlap considerably.

In any event all of the key 90% confidence intervals were completely contained in the acceptable range of 80 to 125% and it is concluded that bioequivalence in accordance with standard criteria has been shown.

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 1mg strength can be extrapolated to the 0.5, 2, 3, 4 and 6mg strength tablets.

7. **EFFICACY**

No new data.

8. **SAFETY**

No new data.

9. **EXPERT REPORTS**

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

10. **PATIENT INFORMATION LEAFLET (PIL)**

This is satisfactory.

11. **LABELLING**

Full colour mock-ups are provided. The labelling is medically satisfactory.

12. **APPLICATION FORM (MAA)**

The MAAs are medically satisfactory.

13. **SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

The SPC is essentially identical to the current approved SPC for the reference product and is satisfactory.
14. DISCUSSION

The requested indications and other SPC details are consistent with current originator SPC. Bioequivalence to the reference product is established.

15. MEDICAL CONCLUSION

Marketing Authorisations may be granted for these preparations.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg, 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
A bioequivalence study was carried out and the test and reference products shown to be bioequivalent for the appropriate pharmacokinetic criteria.

No new or unexpected safety concerns arise from these applications.

The SPC and PIL are satisfactory and consistent with that for the UK reference products.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s product and the reference product 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.
RISPERIDONE 0.5MG, 1MG, 2MG, 3MG, 4MG AND 6MG
FILM-COATED TABLETS

PL 14017/0130-5

**STEPS TAKEN FOR ASSESSMENT**

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<table>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 26th July 2005</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 19th September 2005</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the clinical dossier on 19th July 2006 and quality dossiers on 12th January 2006, 9th October 2006, and 23rd May 2007</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on clinical dossier on the 28th September 2006 and quality dossier on 22nd October 2006, 23rd March 2007 and 14th June 2007</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 16th October 2007</td>
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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
Risperidone 0.5mg
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablets
Red, film-coated, round tablet

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Risperidone 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 Tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia. Risperidone Tablets are also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response. Risperidone 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 Tablets are not licensed for the treatment of behavioural symptoms of dementia (see section 4.4 Special warnings and precautions for use).

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

Adults
Risperidone Tablets may be given once or twice daily. All patients, whether acute or chronic, should start with 2 mg/day Risperidone Tablets. 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 Tablets 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 Tablets should be used with caution in this group of patients until further experience is gained.

4.2. b Bipolar Mania:

Adults

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

As with all symptomatic treatments, the continued use of Risperidone Tablets 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 Tablets 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 Tablets 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 Tablets (see Section 4.5 Interaction with other medicinal products and other forms of interaction). It is therefore not recommended to co-administer Risperidone Tablets 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 Tablets.

Method of administration

Oral use.

4.3 CONTRAINDICATIONS

Risperidone Tablets are contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Elderly patients with dementia

Elderly patients with dementia treated with atypical antipsychotic drugs had an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including risperidone. In placebo-controlled trials with risperidone in this population, the incidence of mortality was 4.0% for risperidone–treated patients compared to 3.1% for placebo-treated patients. The mean age (range) of patients who died was 86 years (67-100).
In these trials treatment with furosemide plus risperidone was associated with a higher incidence of mortality compared to treatment with risperidone or furosemide alone, however, the mechanism for an interaction is unclear. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings. No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

_Cerebrovascular Adverse Events (CAE)_

Risperidone Tablets are 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 tablets (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 Tablets, orthostatic hypotension can occur, especially during the initial dose-titration period. A dose reduction should be considered if hypotension occurs.

Risperidone Tablets 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 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 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 tablets for schizophrenia in children aged less than 15 years has not been formally evaluated.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

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

Carbamazepine has been shown to decrease the plasma levels of the antipsychotic fraction of risperidone. A similar effect might be anticipated with other drugs which stimulate metabolising enzymes in the liver. On initiation of carbamazepine or other hepatic enzyme-inducing drugs, the dosage of Risperidone Tablets should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperidone 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 Tablets. Based on in vitro studies, the same interaction may occur with haloperidol. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. The cholinesterase inhibitor galantamine does not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

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

See section 4.4 (Special warnings and 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. In patients on long-term lithium and older/typical neuroleptic therapy, no significant change
occurred in the pharmacokinetics of lithium after substitution of the concomitant neuroleptic with risperidone.

Food does not affect the absorption of risperidone from the stomach. The effect of food particles in the mouth on absorption from risperidone has not been studied.

4.6 PREGNANCY AND LACTATION

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Risperidone Tablets 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 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 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. 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 Tablets.

Risperidone Tablets 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 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.

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 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 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
Pharmacotherapeutic group: Other antipsychotics
ATC code: N05A X08
Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

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

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

The most important route of metabolism of 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 metabolite 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.

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
Lactose monohydrate
Sodium laurilsulfate
Maize starch
Povidone
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate

Opadry 02B34775 Red which contains:
Hypromellose
Titanium dioxide
Iron oxide red
Macrogol
Carnauba wax

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER
The tablets are packed in PVDC-coated PVC blisters, sealed with aluminium foil.
The blisters are packed in cardboard cartons to contain either 20, 28, 56 or 60 tablets per pack.
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Dexcel-Pharma Limited
1 Cottesbrooke Park
Heartlands Business Park
Daventry, Northamptonshire
NN11 8YL
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 14017/0130

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/10/2007

10 DATE OF REVISION OF THE TEXT
16/10/2007
1 NAME OF THE MEDICINAL PRODUCT
Risperidone 1mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Risperidone 1mg
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablets
White, film coated, round tablets.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Risperidone 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 Tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.
Risperidone Tablets are also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.
Risperidone 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 Tablets are not licensed for the treatment of behavioural symptoms of dementia (see section 4.4 Special warnings and precautions for use).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

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

Adults
Risperidone Tablets may be given once or twice daily. All patients, whether acute or chronic, should start with 2 mg/day Risperidone Tablets. 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 Tablets 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 Tablets should be used with caution in this group of patients until further experience is gained.

4.2. b Bipolar Mania:
Adults
Risperidone should be administered on a once daily schedule, starting with 2 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. A dosing range between 1 and 6 mg per day is recommended.
As with all symptomatic treatments, the continued use of Risperidone Tablets 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 Tablets 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 Tablets 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 Tablets (see Section 4.5 Interaction with other medicinal products and other forms of interaction). It is therefore not recommended to co-administer Risperidone Tablets 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 Tablets.

Method of administration
Oral use.

4.3 CONTRAINDICATIONS
Risperidone Tablets are contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Elderly patients with dementia
Elderly patients with dementia treated with atypical antipsychotic drugs had an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including risperidone. In placebo-controlled trials with risperidone in this population, the incidence of mortality was 4.0% for risperidone–treated patients compared to 3.1% for placebo–treated patients. The mean age (range) of patients who died was 86 years (67-100).
In these trials treatment with furosemide plus risperidone was associated with a higher incidence of mortality compared to treatment with risperidone or furosemide alone, however,
the mechanism for an interaction is unclear. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

*Cerebrovascular Adverse Events (CAE)*

Risperidone Tablets are 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 tablets (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 Tablets, orthostatic hypotension can occur, especially during the initial dose-titration period. A dose reduction should be considered if hypotension occurs.

Risperidone Tablets 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 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 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 tablets for schizophrenia in children aged less than 15 years has not been formally evaluated.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

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

Carbamazepine has been shown to decrease the plasma levels of the antipsychotic fraction of risperidone. A similar effect might be anticipated with other drugs which stimulate metabolising enzymes in the liver. On initiation of carbamazepine or other hepatic enzyme-inducing drugs, the dosage of Risperidone Tablets should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperidone 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 Tablets. 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. Cimetidine and ranitidine do not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

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

See section 4.4 (Special warnings and 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. In patients on long-term lithium and older/typical neuroleptic therapy, no significant change
occurred in the pharmacokinetics of lithium after substitution of the concomitant neuroleptic with risperidone.

Food does not affect the absorption of risperidone from the stomach. The effect of food particles in the mouth on absorption from risperidone has not been studied.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Risperidone Tablets 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 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 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. 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 Tablets.
Risperidone Tablets 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 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.
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 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 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
Pharmacotherapeutic group: Other antipsychotics
ATC code: N05A X08
Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

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

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

The most important route of metabolism of 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 metabolite 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.

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
Lactose monohydrate
Sodium laurilsulfate
Maize starch
Povidone
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate

Opadry Y-1-7000 White which contains:
Hypromellose
Titanium dioxide
Macrogol
Carnauba wax

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER
The tablets are packed in PVDC-coated PVC blisters, sealed with aluminium foil.
The blisters are packed in cardboard cartons to contain either 20, 28, 56 or 60 tablets per pack.
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Dexcel-Pharma Limited
1 Cottesbrooke Park
Heartlands Business Park
Daventry, Northamptonshire
NN11 8YL
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 14017/0131

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/10/2007

10 DATE OF REVISION OF THE TEXT
16/10/2007
1 NAME OF THE MEDICINAL PRODUCT
Risperidone 2mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Risperidone 2mg
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablets
White, film-coated, capsule shaped tablet

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Risperidone 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 Tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.
Risperidone Tablets are also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.
Risperidone 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 Tablets are not licensed for the treatment of behavioural symptoms of dementia (see section 4.4 Special warnings and precautions for use).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
4.2.1 Schizophrenia:
Switching from other antipsychotics: where medically appropriate, gradual discontinuation of the previous treatment while Risperidone Tablets therapy is initiated is recommended. Where medically appropriate when switching patients from depot antipsychotics, consider initiating Risperidone Tablets therapy in place of the next scheduled injection. The need for continuing existing antiparkinson medication should be re-evaluated periodically.
Adults
Risperidone Tablets may be given once or twice daily. All patients, whether acute or chronic, should start with 2 mg/day Risperidone Tablets. 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 Tablets 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 Tablets should be used with caution in this group of patients until further experience is gained.

4.2. b Bipolar Mania:

*Adults*

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

As with all symptomatic treatments, the continued use of Risperidone Tablets 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 Tablets 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 Tablets 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 Tablets (see Section 4.5 Interaction with other medicinal products and other forms of interaction). It is therefore not recommended to co-administer Risperidone Tablets 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 Tablets.

*Method of administration*

Oral use.

4.3 CONTRAINDICATIONS

Risperidone Tablets are contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

*Elderly patients with dementia*

Elderly patients with dementia treated with atypical antipsychotic drugs had an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including risperidone. In placebo-controlled trials with risperidone in this population, the incidence of mortality was 4.0% for risperidone–treated patients compared to 3.1% for placebo-treated patients. The mean age (range) of patients who died was 86 years (67-100).

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

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

**Cerebrovascular Adverse Events (CAE)**

Risperidone Tablets are 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 tablets (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 Tablets, orthostatic hypotension can occur, especially during the initial dose-titration period. A dose reduction should be considered if hypotension occurs.

Risperidone Tablets 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 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 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 tablets for schizophrenia in children aged less than 15 years has not been formally evaluated.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

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

Carbamazepine has been shown to decrease the plasma levels of the antipsychotic fraction of risperidone. A similar effect might be anticipated with other drugs which stimulate metabolising enzymes in the liver. On initiation of carbamazepine or other hepatic enzyme-inducing drugs, the dosage of Risperidone Tablets should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperidone 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 Tablets. Based on in vitro studies, the same interaction may occur with haloperidol. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. The cholinesterase inhibitor galantamine does not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

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

See section 4.4 (Special warnings and 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. In patients on long-term lithium and older/typical neuroleptic therapy, no significant change occurred in the pharmacokinetics of lithium after substitution of the concomitant neuroleptic with risperidone.
Food does not affect the absorption of risperidone from the stomach. The effect of food particles in the mouth on absorption from risperidone has not been studied.

4.6 PREGNANCY AND LACTATION

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Risperidone Tablets 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 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 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. 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 Tablets.

Occasionally, galactorrhea, gynaecomastia, disturbances of the menstrual cycle and amenorrhoea.

Weight gain, oedema and increased hepatic enzyme levels have been observed during treatment with Risperidone 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.

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 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 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

Pharmacotherapeutic group: Other antipsychotics
ATC code: N05A X08

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

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

5.2 PHARMACOKINETIC PROPERTIES

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

The most important route of metabolism of 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 metabolite 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.

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

Lactose monohydrate
Sodium laurilsulfate
Maize starch
Povidone
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate

Opadry Y-1-7000 White which contains:
Hypermellose
Titanium dioxide
Macrogol
Carnauba wax

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER
The tablets are packed in PVDC-coated PVC blisters, sealed with aluminium foil.
The blisters are packed in cardboard cartons to contain either 20, 28, 56 or 60 tablets per pack.
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Dexcel-Pharma Limited
1 Cottesbrooke Park
Heartlands Business Park
Daventry, Northamptonshire
NN11 8YL
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 14017/0132

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/10/2007

10 DATE OF REVISION OF THE TEXT
16/10/2007
1 NAME OF THE MEDICINAL PRODUCT
Risperidone 3mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Risperidone 3mg
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablets
White, film-coated, round tablet

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Risperidone 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 Tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.
Risperidone Tablets are also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.
Risperidone 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 Tablets are not licensed for the treatment of behavioural symptoms of dementia (see section 4.4 Special warnings and precautions for use).

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

Adults
Risperidone Tablets may be given once or twice daily. All patients, whether acute or chronic, should start with 2 mg/day Risperidone Tablets. 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 Tablets 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 Tablets should be used with caution in this group of patients until further experience is gained.

4.2. b Bipolar Mania:

Adults

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

As with all symptomatic treatments, the continued use of Risperidone Tablets 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 Tablets 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 Tablets 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 Tablets (see Section 4.5 Interaction with other medicinal products and other forms of interaction). It is therefore not recommended to co-administer Risperidone Tablets 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 Tablets.

Method of administration

Oral use.

4.3 CONTRAINDICATIONS

Risperidone Tablets are contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Elderly patients with dementia

Elderly patients with dementia treated with atypical antipsychotic drugs had an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including risperidone. In placebo-controlled trials with risperidone in this population, the incidence of mortality was 4.0% for risperidone–treated patients compared to 3.1% for placebo–treated patients. The mean age (range) of patients who died was 86 years (67-100).

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

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

**Cerebrovascular Adverse Events (CAE)**

Risperidone Tablets are 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 tablets (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 Tablets, orthostatic hypotension can occur, especially during the initial dose-titration period. A dose reduction should be considered if hypotension occurs.

Risperidone Tablets 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 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 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 tablets for schizophrenia in children aged less than 15 years has not been formally evaluated.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

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

Carbamazepine has been shown to decrease the plasma levels of the antipsychotic fraction of risperidone. A similar effect might be anticipated with other drugs which stimulate metabolising enzymes in the liver. On initiation of carbamazepine or other hepatic enzyme-inducing drugs, the dosage of Risperidone Tablets should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperidone 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 Tablets. Based on in vitro studies, the same interaction may occur with haloperidol. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. The cholinesterase inhibitor galantamine does not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

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

See section 4.4 (Special warnings and 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. In patients on long-term lithium and older/typical neuroleptic therapy, no significant change occurred in the pharmacokinetics of lithium after substitution of the concomitant neuroleptic with risperidone.
Food does not affect the absorption of risperidone from the stomach. The effect of food particles in the mouth on absorption from risperidone has not been studied.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Risperidone Tablets 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 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 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, bradynessia, akathisia, acute dystonia. If acute in nature, these symptoms are usually mild and are reversible upon dose reduction and/or administration of antiparkinson medication, if necessary. In clinical trials in patients with acute mania risperidone treatment resulted in an incidence of EPS>10%. This is lower than the incidence observed in patients treated with classical neuroleptics.
Occasionally, orthostatic dizziness, hypotension including orthostatic, tachycardia including reflex tachycardia and hypertension have been observed following administration of Risperidone Tablets.
Risperidone Tablets 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 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.
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 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 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
Pharmacotherapeutic group: Other antipsychotics
ATC code: N05A X08
Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

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

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

The most important route of metabolism of 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 metabolite 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.

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
Lactose monohydrate
Sodium laurilsulfate
Maize starch
Povidone
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate

Opadry Y-1-7000 White which contains:
Hypromellose
Titanium dioxide
Macrogol
Carnauba wax

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER
The tablets are packed in PVDC-coated PVC blisters, sealed with aluminium foil.
The blisters are packed in cardboard cartons to contain either 20, 28, 56 or 60 tablets per pack.
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Dexcel-Pharma Limited
1 Cottesbrooke Park
Heartlands Business Park
Daventry, Northamptonshire
NN11 8YL
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 14017/0133

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/10/2007

10 DATE OF REVISION OF THE TEXT
16/10/2007
1 NAME OF THE MEDICINAL PRODUCT
Risperidone 4mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Risperidone 4mg
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablets
White, film-coated, capsule shaped tablet

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Risperidone 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 Tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.
Risperidone Tablets are also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Risperidone 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 Tablets are not licensed for the treatment of behavioural symptoms of dementia (see section 4.4 Special warnings and precautions for use).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

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

Adults
Risperidone Tablets may be given once or twice daily. All patients, whether acute or chronic, should start with 2 mg/day Risperidone Tablets. 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 Tablets 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 Tablets should be used with caution in this group of patients until further experience is gained.

**4.2. b Bipolar Mania:**

**Adults**

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

As with all symptomatic treatments, the continued use of Risperidone Tablets 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 Tablets 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 Tablets 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 Tablets (see Section 4.5 Interaction with other medicinal products and other forms of interaction). It is therefore not recommended to co-administer Risperidone Tablets 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 Tablets.

**Method of administration**

Oral use.

**4.3 CONTRAINDICATIONS**

Risperidone Tablets are contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

**4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

**Elderly patients with dementia**

Elderly patients with dementia treated with atypical antipsychotic drugs had an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including risperidone. In placebo-controlled trials with risperidone in this population, the incidence of mortality was 4.0% for risperidone–treated patients compared to 3.1% for placebo-treated patients. The mean age (range) of patients who died was 86 years (67-100).

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

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

**Cerebrovascular Adverse Events (CAE)**

Risperidone Tablets are 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 tablets (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 Tablets, orthostatic hypotension can occur, especially during the initial dose-titration period. A dose reduction should be considered if hypotension occurs.

Risperidone Tablets 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 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 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 tablets for schizophrenia in children aged less than 15 years has not been formally evaluated.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Possible interactions of risperidone with other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, it should be used with caution in combination with other centrally acting drugs including alcohol.

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

Carbamazepine has been shown to decrease the plasma levels of the antipsychotic fraction of risperidone. A similar effect might be anticipated with other drugs which stimulate metabolising enzymes in the liver. On initiation of carbamazepine or other hepatic enzyme-inducing drugs, the dosage of Risperidone Tablets should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperidone 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 dosage of Risperidone Tablets. Based on in vitro studies, the same interaction may occur with haloperidol. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. The cholinesterase inhibitor galantamine does not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

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

See section 4.4 (Special warnings and 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. In patients on long-term lithium and older/typical neuroleptic therapy, no significant change occurred in the pharmacokinetics of lithium after substitution of the concomitant neuroleptic with risperidone.
Food does not affect the absorption of risperidone from the stomach. The effect of food particles in the mouth on absorption from risperidone has not been studied.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Risperidone Tablets 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 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 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. 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 Tablets.
Risperidone Tablets 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 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.
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 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 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
Pharmacotherapeutic group: Other antipsychotics
ATC code: N05A X08

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

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

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

The most important route of metabolism of 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 metabolite 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.

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
Lactose monohydrate
Sodium laurilsulfate
Maize starch
Povidone
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate

Opadry Y-1-7000 White which contains:
Hypromellose
Titanium dioxide
Macrogol
Carnauba wax

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER
The tablets are packed in PVDC-coated PVC blisters, sealed with aluminium foil.
The blisters are packed in cardboard cartons to contain either 20, 28, 56 or 60 tablets per pack.
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Dexcel-Pharma Limited
1 Cottesbrooke Park
Heartlands Business Park
Daventry, Northamptonshire
NN11 8YL
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 14017/0134

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/10/2007

10 DATE OF REVISION OF THE TEXT
16/10/2007
1  NAME OF THE MEDICINAL PRODUCT
Risperidone 6mg Film-Coated Tablets

2  QUALITATIVE AND QUANTITATIVE COMPOSITION
Risperidone 6mg
For a full list of excipients, see section 6.1.

3  PHARMACEUTICAL FORM
Film-coated tablets
White, film-coated, round tablet

4  CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Risperidone 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 Tablets also alleviate affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.
Risperidone Tablets are also effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.
Risperidone 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 Tablets are not licensed for the treatment of behavioural symptoms of dementia (see section 4.4 Special warnings and precautions for use).

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

Adults
Risperidone Tablets may be given once or twice daily. All patients, whether acute or chronic, should start with 2 mg/day Risperidone Tablets. 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 Tablets 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 Tablets should be used with caution in this group of patients until further experience is gained.

4.2. b Bipolar Mania:

Adults

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

As with all symptomatic treatments, the continued use of Risperidone Tablets 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 Tablets 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 Tablets 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 Tablets (see Section 4.5 Interaction with other medicinal products and other forms of interaction). It is therefore not recommended to co-administer Risperidone Tablets 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 Tablets.

Method of administration

Oral use.

4.3 CONTRAINDICATIONS

Risperidone Tablets are contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Elderly patients with dementia

Elderly patients with dementia treated with atypical antipsychotic drugs had an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including risperidone. In placebo-controlled trials with risperidone in this population, the incidence of mortality was 4.0% for risperidone–treated patients compared to 3.1% for placebo–treated patients. The mean age (range) of patients who died was 86 years (67-100).

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

No consistent pattern for cause of death observed. Nevertheless caution should be exercised and the risks and benefits of the combination of risperidone and furosemide or co-medication with other potent diuretics considered prior to the decision to use. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

**Cerebrovascular Adverse Events (CAE)**

Risperidone Tablets are 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 tablets (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 Tablets, orthostatic hypotension can occur, especially during the initial dose-titration period. A dose reduction should be considered if hypotension occurs.

Risperidone Tablets 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 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 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 tablets for schizophrenia in children aged less than 15 years has not been formally evaluated.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Possible interactions of risperidone with other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, it should be used with caution in combination with other centrally acting drugs including alcohol.

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

Carbamazepine has been shown to decrease the plasma levels of the antipsychotic fraction of risperidone. A similar effect might be anticipated with other drugs which stimulate metabolising enzymes in the liver. On initiation of carbamazepine or other hepatic enzyme-inducing drugs, the dosage of Risperidone Tablets should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperidone 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 Tablets. Based on in vitro studies, the same interaction may occur with haloperidol. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. The cholinesterase inhibitor galantamine does not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

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

See section 4.4 (Special warnings and 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. In patients on long-term lithium and older/typical neuroleptic therapy, no significant change occurred in the pharmacokinetics of lithium after substitution of the concomitant neuroleptic with risperidone.
Food does not affect the absorption of risperidone from the stomach. The effect of food particles in the mouth on absorption from risperidone has not been studied.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Risperidone Tablets 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 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 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. 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 Tablets.
Risperidone Tablets 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 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.
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 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 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
Pharmacotherapeutic group: Other antipsychotics
ATC code: N05A X08
Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the
benzisoxazole-derivatives.
Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic
5-HT2 and dopaminergic D2 receptors. Risperidone binds also to alpha1-adrenergic receptors
and, with lower affinity, to H1-histaminergic and alpha2-adrenergic receptors. Risperidone has
no affinity for cholinergic receptors. Although risperidone is a potent D2 antagonist, that is
considered to improve the positive symptoms of schizophrenia, it causes less depression of
motor activity and induction of catalepsy than classical neuroleptics. Balanced central
serotonin and dopamine antagonism may reduce the tendency to cause extrapyramidal side
effects, and extend the therapeutic activity to the negative and affective symptoms of
schizophrenia.

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

The most important route of metabolism of 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 metabolite 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.

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
Lactose monohydrate
Sodium laurilsulfate
Maize starch
Povidone
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate

Opadry Y-1-7000 White which contains:
Hyromellose
Titanium dioxide
Macrogol
Carnauba wax

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER
The tablets are packed in PVDC-coated PVC blisters, sealed with aluminium foil.
The blisters are packed in cardboard cartons to contain either 20, 28, 56 or 60 tablets per pack.
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Dexcel-Pharma Limited
1 Cottesbrooke Park
Heartlands Business Park
Daventry, Northamptonshire
NN11 8YL
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 14017/0135

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/10/2007

10 DATE OF REVISION OF THE TEXT
16/10/2007
UKPAR Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-Coated Tablets

Risperidone

Read all of this leaflet carefully before you start taking this medicine. It is an important source of information about your medicine and how to take it safely.

- Keep this leaflet. You may need to read it again.
- Tell your doctor or pharmacist 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 Tablets are and what they are used for
2. Before you take Risperidone Tablets
3. How to take Risperidone Tablets
4. Possible side effects
5. How to store Risperidone Tablets
6. Further information

1. WHAT Risperidone TABLETS ARE AND WHAT THEY ARE USED FOR

Risperidone Tablets are one of a group of medicines called antipsychotics. They are used to treat conditions which affect the way you think, feel and/or act. These conditions may cause symptoms such as confusion, hallucinations (e.g. hearing, seeing or sensing things which are not there), delusions, unusual suspicions (paranoia) and emotional and social withdrawal. People with these conditions may also feel depressed, jolly, anxious or tense. Risperidone Tablets may be taken for both sudden (acute) and long-lasting (chronic) disorders.

In addition, Risperidone Tablets may be used to control the symptoms of mania for people with bipolar disorder.

REMEMBER - This medicine has been prescribed for you only.

2. BEFORE YOU TAKE Risperidone TABLETS

Do not take Risperidone Tablets
- If you have ever had an allergic reaction (hypersensitivity) to risperidone or any of the other ingredients of Risperidone Tablets. An allergic reaction may be recognised as a rash, itching, swelling face or lips, or shortness of breath.
- If your age is below 15 years.
- If you are breastfeeding if you are taking Risperidone Tablets.
- Take special care with Risperidone Tablets and ask your doctor for advice:
  - If you are taking or have taken a medicine for Parkinson's disease - you suffer from heart or blood vessel disease, liver or kidney disease, Parkinson's disease, epilepsy or dementia.
  - You have had a stroke or transient ischemic attack (temporary reduction in blood flow to the brain).
  - You should also tell your doctor if you have other risk factors for blood vessel disease, including high blood pressure, diabetes, if you are a smoker or you have a heart disorder called atrial fibrillation.
If you have diabetes or you have a risk of developing diabetes, your doctor may check your blood sugar levels while you are taking Risperidone Tablets (See also "Possible side effects" section).

Your doctor will decide if you can take risperidone and if the dose will need to be altered.

3. TAKING OTHER MEDICINES

Please inform your doctor or your pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription since taking some medicines together can be harmful.

If you are taking any of the following, taking Risperidone Tablets as well may make you feel more drowsy:
- Medicines taken for anxiety or to help you to sleep (tranquilisers)
  - Certain antidepressants
  - Some antihistamines (such as chlorphenamine)

Only take the following medicines while you are on Risperidone Tablets with your doctor's permission:
- A drug called carbamazepine, commonly used to treat epilepsy or facial neuritis (severe pain attacks in the face), may change the effect of Risperidone Tablets, so you should tell your doctor if you start or stop taking this drug, as you may need a different dose of Risperidone Tablets.

Taking Risperidone Tablets with food and drink: You should be careful how much alcohol you drink. The combined effect of Risperidone Tablets and alcohol may make you feel drowsy.

Pregnancy and breast-feeding: If you are pregnant or trying to become pregnant, ask your doctor or pharmacist for advice before taking any medicine.

Tell your doctor if you are breast-feeding. You should not breast feed if you are taking Risperidone Tablets.

Driving and using machines: Risperidone Tablets may affect your alertness. Therefore, do not drive or use any tools or machines until the doctor sees how the tablets affect you.

Important information about some of the ingredients of Risperidone Tablets: This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE Risperidone TABLETS

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

Risperidone Tablets can be taken with or without food. Swallow the correct number of tablets with some liquid.

Your doctor will tell you how many Risperidone Tablets to take and for how long you should continue to take them. This will vary from person to person and your doctor will adjust the number and strength of the tablets to suit you.

For adults and adolescents over 15 years of age with conditions which affect the way they think, feel or act.

The dose will be started gradually over the first days of treatment as follows: Day 1: 2 mg Day 2: 4 mg
This can be taken as a single dose or as half the dose in the morning and half the dose in the evening. However, your doctor may recommend a more gradual increase.

The dosage will then be set to suit your needs but is usually between 4 mg and 6 mg a day. Some patients may require less than 4 mg for a good effect.

For adults and adolescents over 13 years of age with bipolar disorder: If you need to take Risperidone Tablets to help control the symptoms of mania, a starting dose of 2 mg once a day is recommended and your doctor will adjust this if necessary. Most people feel better with doses between 1 and 6 mg per day. Your doctor will tell you what dose suits your particular situation. Your treatment should be regularly reviewed and changed if appropriate.

Important: Do not take more than a total of 16 mg per day.

Risperidone Tablets are only for those aged 18 years and over.

If you are elderly or have a liver or kidney disorder, you should take half the above doses. You will be told how many tablets you need to take.

If you take more Risperidone Tablets than you should: If you take more Risperidone Tablets than you should or if someone else has taken any of your tablets, contact a doctor or hospital immediately. Make sure to allow them your tablets.

If you forget to take Risperidone Tablets: If you miss a tablet, take your next tablet as usual and continue your course. Do not take a double dose to make up for a forgotten tablet.

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

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

Always follow your doctor's instructions carefully.

Always read the label. 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 Tablets can cause side effects, although not everybody gets them. Do not be alarmed by the list of possible side effects. You may not experience any of them. Your doctor has judged that the benefits of Risperidone outweigh the risk of side effects.

Occasionally, the following effects may occur:

- sleepiness, tiredness, dizziness, dizziness, difficulty in concentrating, blurred vision, constipation, indigestion, feeling or being sick (nausea or vomiting), stomach ache, sexual potency problems, leakage of urine, many or blooded nose, liver problems, local skin rash or swelling, or other allergic reactions such as itching, swollen face or lips, or shortness of breath.
- Weight gain or swelling of the ankles.
- Stiffness or transient muscle spasms.
- If you experience sudden weakness or numbness of the face, arms or legs, especially on one side, or instances of slurred speech, seek medical attention.

Occasionally, changes in blood cell count have been reported. Sometimes, the following effects may occur:

- headache, sleeplessness, anxiety or agitation.
- trembling, pronounced muscle stiffness or spasm, stiffness of movement, excess saliva, restlessness or rolling of the eyes can occur but this will usually disappear if your dose of Risperidone Tablets is reduced by your doctor or if your doctor prescribes you an additional medicine.

In some cases, your blood pressure may fall slightly in the early stages of the treatment, resulting in dizziness. This will usually pass off automatically. Sometimes later in the treatment, increased blood pressure may also occur, but this is very rare.

In rare cases:

- Risperidone Tablets may cause a desire to drink large amounts of water.
- You might also experience marked changes in your body temperature or uncontrollable movements, mainly in the face or tongue.
- You may have involuntary trembling (tremor) of the face or hands.
- If any of these occur contact your doctor as soon as possible.

Very rarely:

- Risperidone Tablets might cause fever, faster breathing, sweating, muscle stiffness and reduced consciousness.
- If this occurs, stop taking the tablets and contact a doctor at once.
- In very rare cases, high blood sugar has been reported. So your doctor if you experience symptoms such as excessive thirst or urination.
- If either of these should occur, seek medical attention.

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

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

If your medical affects you in any other way, you should tell your doctor, nurse or pharmacist.

Please also refer to the "Before you take Risperidone Tablets" section above.

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

5. HOW TO STORE Risperidone Tablets

Keep out of the reach of sight and children.

Do not store above 25°C.

Do not take the tablets after the expiry date which is stated on the carton.

The expiry date refers to the last day of that month.

Always return any left-over medicine to your pharmacist. Only keep it if your doctor tells you to.

Medicines should be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Risperidone Tablets contain and their appearance

The active substance is risperidone as follows:

Risperidone 0.5mg Film-Coated Tablets contain 0.5mg Risperidone and are red, film-coated, round tablets.

Risperidone 1mg Film-Coated Tablets contain 1mg Risperidone and are white, film-coated, round tablets.

Risperidone 2mg Film-Coated Tablets contain 2mg Risperidone and are white, film-coated, capsule-shaped tablets.

Risperidone 3mg Film-Coated Tablets contain 3mg Risperidone and are white, film-coated, round tablets.

Risperidone 4mg Film-Coated Tablets contain 4mg Risperidone and are white, film-coated, capsule-shaped tablets.

Risperidone 6mg Film-Coated Tablets contain 6mg Risperidone and are white, film-coated, round tablets.

The other ingredients are:
- Corn flour, monohydrate, sodium lauryl sulphate, maize starch, povidone, microcrystalline cellulose, Colloidal anhydrous silica, magnesium stearate.
- Coating: carrageenan, hypromellose, titanium dioxide (E171), Risperidone 0.5mg FILM-COATED TABLETS also contains red iron oxide (E172).

Risperidone Tablets pack contains 30, 56 or 60 tablets in blister strips. Not all pack sizes may be marketed.

Marketing authorisation holder and manufacturer:

DosePharma Ltd, 1 Cottingham Road, Harlsdown Business Park, Dawby, Northamptonshire NN11 9YL, UK.

This leaflet was last revised in: November 2006.
UKPAR Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-Coated Tablets

Each film-coated tablet contains Risperidone 0.5mg.

Also contains Lactose. See leaflet for further information.

Dosage: For oral use. As directed by your doctor.

Keep out of the reach and sight of children.

Please read the enclosed Patient Information Leaflet before taking this medicine.

Do not store above 30°C.
UKPAR Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-Coated Tablets

Each film-coated tablet contains risperidone 1 mg. Also contains lactose. See section for full details. Do not exceed the recommended dosage. For professional use. Keep out of the reach and sight of children.

Marketing Authorisation Holder: DEXCAL PHARMA LTD, 1 Crofton Business Park, Newlands Business Park, Denbigh, Northamptonshire NN11 4NL, UK.

PL 1407/2013
UKPAR Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-Coated Tablets

Each film-coated tablet contains risperidone 1 mg. Also contains lactose. See label for further information.

Dosage: For oral use. As directed by your doctor.

Keep out of reach of children.

Please read the enclosed Patient Information Leaflet before taking this medicine.

Do not store above 30°C.
Each film-coated tablet contains Risperidone 1 mg. Also contains Lactose. See leaflet for further information.

Dosage: For oral use. As directed by your doctor.

Keep out of the reach and sight of children. Please read the enclosed Patient Information Leaflet before taking this medicine. Do not store above 30°C.
Risperidone 1 mg
Film-Coated Tablets

Each film-coated tablet contains Risperidone 1 mg. Also contains lactose. See leaflet for further information.

Dosage: For use as directed by your doctor.

Keep out of the reach and sight of children.

Please read the enclosed Patient Information Leaflet before taking the medicine.

Do not store above 30°C.