Risperidone 0.5 mg film-coated tablets
PL 00289/0652 and 0658

Risperidone 1 mg film-coated tablets
PL 00289/0653 and 0659

Risperidone 2 mg film-coated tablets
PL 00289/0654 and 0660

Risperidone 3 mg film-coated tablets
PL 00289/0655 and 0661

Risperidone 4 mg film-coated tablets
PL 00289/0656 and 0662

Risperidone 6 mg film-coated tablets
PL 00289/0657 and 0663

UKPAR

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RISPERIDONE 3 MG FILM-COATED TABLETS  
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PL 00289/0656 and 0662

RISPERIDONE 6 MG FILM-COATED TABLETS  
PL 00289/0657 and 0663

LAY SUMMARY

The MHRA granted Teva UK Limited Marketing Authorisations (licences) for the medicinal products Risperidone 0.5mg Film-Coated Tablets (PL 00289/0652 and 0658), Risperidone 1mg Film-Coated Tablets (PL 00289/0653 and 0659), Risperidone 2mg Film-Coated Tablets (PL 00289/0654 and 0660), Risperidone 3mg Film-Coated Tablets (PL 00289/0655 and 0661), Risperidone 4mg Film-Coated Tablets (PL 00289/0656 and 0662) and Risperidone 6mg Film-Coated Tablets (PL 00289/0657 and 0663) on 30th March 2007.

These are prescription-only medicines (POM) for the treatment and prevention of symptoms of sudden (acute) and long lasting (chronic) psychotic disorders, including schizophrenia. These conditions may cause symptoms such as:
- Hallucinations, delusions and thought disturbances
- Emotional and social withdrawal
- Depression, guilt, anxiety, confusion, paranoia
- Unfriendly and aggressive feelings or behaviour.

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

Risperidone belongs to a group of drugs called antipsychotics. It is used to treat conditions that affect the way you feel, think and act.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg, and 6mg Film-Coated Tablets outweighs the risks, hence Marketing Authorisations have been granted.
RISPERIDONE 0.5 MG FILM-COATED TABLETS
PL 00289/0652 and 0658

RISPERIDONE 1 MG FILM-COATED TABLETS
PL 00289/0653 and 0659

RISPERIDONE 2 MG FILM-COATED TABLETS
PL 00289/0654 and 0660

RISPERIDONE 3 MG FILM-COATED TABLETS
PL 00289/0655 and 0661

RISPERIDONE 4 MG FILM-COATED TABLETS
PL 00289/0656 and 0662

RISPERIDONE 6 MG FILM-COATED TABLETS
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-Coated Tablets (PL 00289/0652-63) to Teva UK Limited on 30th March 2007. The products are prescription-only medicines.

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

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

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

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

Risperidone is not licensed for the treatment of behavioural symptoms of dementia.

Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg, and 6mg Film-coated Tablets contain the active ingredient risperidone. Risperidone is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT2 and dopaminergic D2 receptors. Risperidone binds also to alpha1-adrenergic receptors and, with lower affinity, to H1-histaminergic and alpha2 adrenergic receptors.

Risperidone has no affinity for cholinergic receptors. Although Risperidone is a potent D2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extra pyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Risperidone

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

Structure:

![Chemical Structure of Risperidone]

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

A European Pharmacopoeia monograph has been written for active risperidone.

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

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

The active substance is packaged in polyethylene bags, which are sealed and placed in an aluminium laminated bag. Specifications for all packaging have been provided. The primary packaging has been shown to comply with current European regulations concerning contact with food.

Based on the stability data provided, a satisfactory retest period has been set for active risperidone from this source.

DRUG PRODUCT
Other ingredients
All tablets contain lactose monohydrate, sodium laurilsulfate, colloidal anhydrous silica, microcrystalline cellulose, pregelatinised starch, Sodium starch glycolate (Type A), magnesium stearate, hypromellose (E464), titanium dioxide (E171), Macrogol 6000, Macrogol 400. In addition, the 0.5mg, 2mg and 6mg strengths contain red iron oxide (E172) and yellow iron oxide (E172); the 3mg strength contains quinoline.
yellow aluminium lake (E104); and the 4mg strength contains yellow iron oxide (E172), quinoline yellow aluminium lake (E104) and indigocarmine aluminium lake (E132).

All excipients used comply with respective Ph. Eur monographs, with the exception of red iron oxide, yellow iron oxide, quinoline yellow aluminium lake and indigocarmine aluminium lake, which all comply with suitable in-house specifications. Satisfactory certificates of analysis have been provided for all excipients.

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

**Product development**

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

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

**Manufacture**

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

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

**Finished product specification**

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

**Container Closure System**

The finished products are packaged in aluminium/polyvinylidene chloride/polyvinylchloride blisters, which are then placed in cardboard boxes.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. The primary packaging complies with current guidelines regarding materials in contact with foodstuff.

Pack sizes are 20 and 60 tablets for all strengths. Additional pack sizes of 10 tablets are proposed for the 0.5mg strength; 6, 10, 50, 100 and 500 tablets for the 1mg strength; 10, 50, 100 and 500 tablets for the 2mg and 3mg strengths; 10, 30, 50, 100 and 500 tablets for the 4mg strength; and 7, 28, 30, 50 and 100 tablets for the 6mg strength.
The applicant has stated that they are not intending to market all proposed sizes initially and that they commit to submitting packaging for all pack sizes to the MHRA for approval before marketing.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set for all strengths of product with no specific storage instructions. This is satisfactory.

**ADMINISTRATIVE**

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

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

**Labelling**
These are satisfactory.

**Patient Information Leaflet (PIL)**
This is consistent with that for the reference products and is satisfactory. The marketing authorisation holder has provided a commitment to update the marketing authorisation no later than 1st July 2008 with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups.

**MAA Forms**
These are satisfactory.

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

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

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

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

CLINICAL PHARMACOLOGY
The applicant commissioned one single-centre, randomised, single-dose, three-way crossover study in healthy fasted volunteers, comparing the pharmacokinetics of the test product 2 x Risperidone 1mg Film-Coated Tablets versus the reference products 2 x Risperidal 1mg Tablets (UK) and 2 x Risperdal 1mg Tablets (Canada).

The protocol is satisfactory. Sampling schedules were satisfactory for accurate determination of $AUC_T$, $AUC_{inf}$ and $C_{max}$.

The justification for not studying a higher dose, which is usually more discriminating between formulations, is accepted. Higher doses would be likely to give rise to tolerability problems due to postural hypotension and a single-dose study on the lower strength is preferred to a steady-state study titrating up to the highest dose.

The main results for risperidone and the main active metabolite (9-hydroxyrisperidone) are presented below:
The 90% confidence intervals of AUC\textsubscript{T} and AUC\textsubscript{inf} for risperidone and 9-hydroxyrisperidone were well within the acceptable range of 80 to 125%. It is concluded that bioequivalence in accordance with standard criteria has been shown.
EFFICACY
No new data have been provided.

SAFETY
No new data have been provided.

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

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

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

LABELLING
These are satisfactory.

APPLICATION FORMS (MAA)
These are satisfactory.

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

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

The grant of marketing authorisations are recommended for these applications.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Risperidone 2mg Film-Coated Tablets and the reference product Risperidal 2mg 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 2mg strength can be extrapolated to the 0.5, 1, 3, 4 and 6mg strength tablets.

No new or unexpected safety concerns arise from these applications.

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

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with risperidone is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
RISPERIDONE 0.5 MG FILM-COATED TABLETS  
PL 00289/0652 and 0658

RISPERIDONE 1 MG FILM-COATED TABLETS  
PL 00289/0653 and 0659

RISPERIDONE 2 MG FILM-COATED TABLETS  
PL 00289/0654 and 0660

RISPERIDONE 3 MG FILM-COATED TABLETS  
PL 00289/0655 and 0661

RISPERIDONE 4 MG FILM-COATED TABLETS  
PL 00289/0656 and 0662

RISPERIDONE 6 MG FILM-COATED TABLETS  
PL 00289/0657 and 0663

**STEPS TAKEN FOR ASSESSMENT**

<table>
<thead>
<tr>
<th></th>
<th>The MHRA received the marketing authorisation applications on 16(^{th}) December 2003</th>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 23(^{rd}) January 2004</td>
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<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the pharmaceutical dossier on 5(^{th}) October 2004, 10(^{th}) January 2006 and 29(^{th}) June 2006, and relating to the clinical dossier on 7(^{th}) May 2004</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 27(^{th}) April 2005, 22(^{nd}) March 2006 and 22(^{nd}) August 2006 for the pharmaceutical dossier, and 31(^{st}) August 2004 for the clinical dossier.</td>
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<td>5</td>
<td>The applications were determined on 30(^{th}) March 2007</td>
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RISPERIDONE 0.5 MG FILM-COATED TABLETS  
PL 00289/0652 and 0658

RISPERIDONE 1 MG FILM-COATED TABLETS  
PL 00289/0653 and 0659

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RISPERIDONE 4 MG FILM-COATED TABLETS  
PL 00289/0656 and 0662

RISPERIDONE 6 MG FILM-COATED TABLETS  
PL 00289/0657 and 0663

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

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

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 0.5 mg of risperidone

Excipients:
Each tablet contains 81.1 mg of lactose monohydrate (see section 4.4).

For a complete list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Film-coated Tablet.

Brownish-red, round slightly arched tablets, debossed RIS 0.5 and scoreline on one side, plain on the other side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

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

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

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

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

4.2 Posology and method of administration

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

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

Doses above 10 mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extrapyramidal symptoms. Doses above 10 mg/day should only be used in individual patients if the benefit is considered to outweigh the risk. Doses
above 16 mg/day have not been extensively evaluated for safety and therefore should not be used.

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

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

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

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

**Bipolar Mania**

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

As with all symptomatic treatments, the continued use of Risperidone must be evaluated and justified on an ongoing basis.

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

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

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

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

**Method of administration**
Oral use.

### 4.3 Contraindications
Risperidone is contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

### 4.4 Special warnings and precautions for use

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

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

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

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

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

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

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

**Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)**
Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia, characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

**Neuroleptic Malignant Syndrome (NMS)**
Neuroleptic malignant syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels, has been reported to occur with neuroleptics. In this event all antipsychotic drugs including risperidone should be discontinued.
It is recommended to halve both the starting dose and the subsequent dose increments in geriatric patients and in patients with renal or liver insufficiency.

Caution should also be exercised when prescribing Risperidone tablets to patients with Parkinson's disease since, theoretically, it may cause a deterioration of the disease.

**Hyperglycaemia**
Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with risperidone. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

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

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

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

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

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

**4.5 Interaction with other medicinal products and other forms of interaction**
Possible interactions of Risperidone with other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, it should be used with caution in combination with other centrally acting drugs including alcohol.

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

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

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Fluoxetine and paroxetine, CYP2D6 inhibitors, may increase the plasma concentration of risperidone but less so of the active antipsychotic fraction. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of Risperidone. Based on in vitro studies, the same interaction may occur with haloperidol. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. The cholinesterase inhibitor galantamine does not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.
When Risperidone are taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.

See section 4.4 (Special warnings and 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.

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. Therefore, Risperidone should only be used during pregnancy if the benefits outweigh the risks.

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

4.7 Effects on ability to drive and use machines
Risperidone may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

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

Common: insomnia, agitation, anxiety, headache.

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

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

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

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

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

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

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

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

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

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

ATC code: N05AX 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 most important route of metabolism of risperidone is hydroxylation by cytochrome CYP 2D6 to 9-hydroxy-risperidone which has a similar pharmacological activity to risperidone. This hydroxylation is subject to debrisoquine-type genetic polymorphism but this does not affect the active antipsychotic fraction since this consists of risperidone and its active metabolite 9-hydroxyrisperidone. After oral administration, the elimination half-life of the active antipsychotic fraction is 24 hours.

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

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
Silica, colloidal anhydrous
Cellulose, microcrystalline
Starch pregelatinised
Sodium starch glycolate (Type A)
Magnesium stearate
Hypermellose (E464)
Titanium dioxide (E171)
Macrogol 6000
Iron oxide red (E172)
Macrogol 400
Iron oxide yellow (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
No special storage conditions

6.5 Nature and contents of container
Transparent PVC/PVdC blisters with aluminium foil
10, 20 & 60 Film-coated Tablets

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Teva UK Ltd
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
United Kingdom
8  MARKETING AUTHORISATION NUMBER(S)
    PL 00289/0652
    PL 00289/0658

9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
    30/03/2007

10 DATE OF REVISION OF THE TEXT
    30/03/2007
NAME OF THE MEDICINAL PRODUCT
Risperidone 1 mg Film-coated Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 1 mg of risperidone

Excipients:
Each tablet contains 162.2 mg of lactose monohydrate (see section 4.4).
For a complete list of excipients, see 6.1.

PHARMACEUTICAL FORM
Film-coated Tablet.

White, round, slightly arched tablets, debossed RIS 1 and scoreline on one side, plain on the other side.

The tablet can be divided into equal halves.

CLINICAL PARTICULARS

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

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

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

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

4.2 Posology and method of administration

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

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

Doses above 10 mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extrapyramidal symptoms. Doses above 10 mg/day should only be used in individual patients if the benefit is considered to outweigh the risk. Doses above 16 mg/day have not been extensively evaluated for safety and therefore should not be used.
Elderly
A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

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

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

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

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

As with all symptomatic treatments, the continued use of Risperidone must be evaluated and justified on an ongoing basis.

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

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

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

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

Method of administration
Oral use.

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

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

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

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

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

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

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

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)
Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia, characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

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

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

**Hyperglycaemia**

Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with risperidone. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

**Other**

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

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

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

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

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

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

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

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

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

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Fluoxetine and paroxetine, CYP2D6 inhibitors, may increase the plasma concentration of risperidone but less so of the active antipsychotic fraction. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of Risperidone. Based on *in vitro* studies, the same interaction may occur with haloperidol. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. The cholinesterase inhibitor galantamine does not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

When Risperidone are taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.
See section 4.4 (Special warnings and 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.

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. Therefore, Risperidone should only be used during pregnancy if the benefits outweigh the risks.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Common: insomnia, agitation, anxiety, headache.

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

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

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

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

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

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

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

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

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

Withdrawal reactions have been reported in association with antipsychotic drugs (see section 4.4 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. 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
ATC code: N05AX 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-HT\_2 and dopaminergic D\_2 receptors. Risperidone binds also to alpha\_1-adrenergic receptors and, with lower affinity, to H\_1-histaminergic and alpha\_2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D\_2 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 most important route of metabolism of risperidone is hydroxylation by cytochrome CYP 2D6 to 9-hydroxy-risperidone which has a similar pharmacological activity to risperidone. This hydroxylation is subject to debrisoquine-type genetic polymorphism but this does not affect the active antipsychotic fraction since this consists of risperidone and its active metabolite 9-hydroxyrisperidone. After oral administration, the elimination half-life of the active antipsychotic fraction is 24 hours.

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

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
Silica, colloidal anhydrous
Cellulose, microcrystalline
Starch pregelatinised
Sodium starch glycolate (Type A)
Magnesium stearate
Hyromellose (E464)
Titanium dioxide (E171)
Macrogol 6000
Macrogol 400

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
No special storage conditions

6.5 Nature and contents of container
Transparent PVC/PVdC blisters with aluminium foil
6, 10, 20, 50, 60, 100, 100 (5x20) (Hospital Pack) & 500 Film-coated Tablets

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Teva UK Ltd
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/0653
PL 00289/0659
9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   30/03/2007

10 DATE OF REVISION OF THE TEXT
    30/03/2007
NAME OF THE MEDICINAL PRODUCT
Risperidone 2 mg Film-Coated Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 2 mg of risperidone

Excipients:
Each tablet contains 162.2 mg of lactose monohydrate (see section 4.4).
For a complete list of excipients, see 6.1.

PHARMACEUTICAL FORM
Film-coated Tablet.
Tan, round, slightly arched tablets, debossed RIS 2 and scoreline on one side, plain on the other side.
The tablet can be divided into equal halves.

CLINICAL PARTICULARS

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

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

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

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

Posology and method of administration

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

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

Doses above 10 mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extrapyramidal symptoms. Doses above 10 mg/day should only be used in individual patients if the benefit is considered to outweigh the risk. Doses above 16 mg/day have not been extensively evaluated for safety and therefore should not be used.
Elderly
A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

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

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

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

Bipolar Mania

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

As with all symptomatic treatments, the continued use of Risperidone must be evaluated and justified on an ongoing basis.

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

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

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

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

Method of administration
Oral use.

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

4.4 Special warnings and precautions for use

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

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

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

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

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

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

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)
Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia, characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

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

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

**Hyperglycaemia**

Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with risperidone. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

**Other**

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

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

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

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

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

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

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

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

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

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Fluoxetine and paroxetine, CYP2D6 inhibitors, may increase the plasma concentration of risperidone but less so of the active antipsychotic fraction. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of Risperidone. Based on in vitro studies, the same interaction may occur with haloperidol. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. The cholinesterase inhibitor galantamine does not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

When Risperidone are taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.
See section 4.4 (Special warnings and 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.

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. Therefore, Risperidone should only be used during pregnancy if the benefits outweigh the risks.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Common: insomnia, agitation, anxiety, headache.

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

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

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

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

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

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

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

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

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

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

ATC code: N05AX 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 most important route of metabolism of risperidone is hydroxylation by cytochrome CYP 2D6 to 9-hydroxy-risperidone which has a similar pharmacological activity to risperidone. This hydroxylation is subject to debrisoquine-type genetic polymorphism but this does not affect the active antipsychotic fraction since this consists of risperidone and its active metabolite 9-hydroxyrisperidone. After oral administration, the elimination half-life of the active antipsychotic fraction is 24 hours.

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

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
Silica, colloidal anhydrous
Cellulose, microcrystalline
Starch pregelatinised
Sodium starch glycolate (Type A)
Magnesium stearate
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 6000
Iron oxide red (E172)
Macrogol 400
Iron oxide yellow (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
No special storage conditions

6.5 Nature and contents of container
Transparent PVC/PVdC blisters with aluminium foil
10, 20, 50, 60, 100, 100 (5x20) (Hospital Pack) & 500 Film-coated Tablets

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Teva UK Ltd
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
United Kingdom
8 MARKETING AUTHORISATION NUMBER(S)
  PL 00289/0654
  PL 00289/0660

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
  30/03/2007

10 DATE OF REVISION OF THE TEXT
  30/03/2007
1 NAME OF THE MEDICINAL PRODUCT
Risperidone 3 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 3 mg of risperidone

Excipients:
Each tablet contains 241.8 mg of lactose monohydrate (see section 4.4).

For a complete list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Yellow, round, slightly arched tablets, debossed RIS 3 and scoreline on one side, plain on the other side.

The tablet can be divided into equal halves.

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

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

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

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

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

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

Doses above 10 mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extrapyramidal symptoms. Doses above 10 mg/day should only be used in individual patients if the benefit is considered to outweigh the risk. Doses above 16 mg/day have not been extensively evaluated for safety and therefore should not be used.
**Elderly**
A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

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

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

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

**Bipolar Mania**

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

As with all symptomatic treatments, the continued use of Risperidone must be evaluated and justified on an ongoing basis.

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

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

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

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

**Method of administration**
Oral use.

### 4.3 Contraindications
Risperidone is contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

### 4.4 Special warnings and precautions for use

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

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

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

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

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

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

*Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)*
Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia, characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

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

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

**Hyperglycaemia**

Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with risperidone. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

**Other**

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

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

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

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

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

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

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

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

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

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Fluoxetine and paroxetine, CYP2D6 inhibitors, may increase the plasma concentration of risperidone but less so of the active antipsychotic fraction. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of Risperidone. Based on *in vitro* studies, the same interaction may occur with haloperidol. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. The cholinesterase inhibitor galantamine does not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

When Risperidone are taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.
See section 4.4 (Special warnings and 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.

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. Therefore, Risperidone should only be used during pregnancy if the benefits outweigh the risks.

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

4.7 Effects on ability to drive and use machines
Risperidone may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

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

Common: insomnia, agitation, anxiety, headache.

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

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

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

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

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

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

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

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

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

Withdrawal reactions have been reported in association with antipsychotic drugs (see section 4.4 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. 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
ATC code: N05AX 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 most important route of metabolism of risperidone is hydroxylation by cytochrome CYP 2D6 to 9-hydroxy-risperidone which has a similar pharmacological activity to risperidone. This hydroxylation is subject to debrisoquine-type genetic polymorphism but this does not affect the active antipsychotic fraction since this consists of risperidone and its active metabolite 9-hydroxyrisperidone. After oral administration, the elimination half-life of the active antipsychotic fraction is 24 hours.

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

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
Silica, colloidal anhydrous
Cellulose, microcrystalline
Starch pregelatinised
Sodium starch glycolate (Type A)
Magnesium stearate
Hypermellose (E464)
Titanium dioxide (E171)
Macrogol 6000
Macrogol 400
Quinoline yellow aluminium lake (E104)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
No special storage conditions

6.5 Nature and contents of container
Transparent PVC/PVdC blisters with aluminium foil
10, 20, 50, 60, 100, 100 (5x20) (Hospital Pack) & 500 Film-coated Tablets

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Teva UK Ltd
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/0655
PL 00289/0661
<table>
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<th>DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION</th>
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1 NAME OF THE MEDICINAL PRODUCT
Risperidone 4 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 4 mg of risperidone

Excipients:
Each tablet contains 322.4 mg of lactose monohydrate (see section 4.4).
For a complete list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Green, round, slightly arched tablets, debossed RIS 4 and scoreline on one side, plain on the other side.
The tablet can be divided into equal halves.

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

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

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

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

4.2 Posology and method of administration

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

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

Doses above 10 mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extrapyramidal symptoms. Doses above 10 mg/day should only be used in individual patients if the benefit is considered to outweigh the risk. Doses above 16 mg/day have not been extensively evaluated for safety and therefore should not be used.
**Elderly**
A starting dose of 0.5 mg bd is recommended. This dosage can be individually adjusted with 0.5 mg bd increments to 1 to 2 mg bd.

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

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

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

**Bipolar Mania**

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

As with all symptomatic treatments, the continued use of Risperidone must be evaluated and justified on an ongoing basis.

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

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

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

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

**Method of administration**
Oral use.

**4.3 Contraindications**
Risperidone is contraindicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

**4.4 Special warnings and precautions for use**

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

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

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

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

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

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

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)
Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia, characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

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

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

**Hyperglycaemia**

Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with risperidone. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

**Other**

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

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

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

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

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

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

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

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

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

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Fluoxetine and paroxetine, CYP2D6 inhibitors, may increase the plasma concentration of risperidone but less so of the active antipsychotic fraction. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of Risperidone. Based on *in vitro* studies, the same interaction may occur with haloperidol. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. The cholinesterase inhibitor galantamine does not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

When Risperidone are taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.
See section 4.4 (Special warnings and 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.

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. Therefore, Risperidone should only be used during pregnancy if the benefits outweigh the risks.

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

4.7 Effects on ability to drive and use machines
Risperidone may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

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

Common: insomnia, agitation, anxiety, headache.

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

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

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

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

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

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

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

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

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

Withdrawal reactions have been reported in association with antipsychotic drugs (see section 4.4 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. 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
ATC code: N05AX 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 most important route of metabolism of risperidone is hydroxylation by cytochrome CYP 2D6 to 9-hydroxy-risperidone which has a similar pharmacological activity to risperidone. This hydroxylation is subject to debrisoquine-type genetic polymorphism but this does not affect the active antipsychotic fraction since this consists of risperidone and its active metabolite 9-hydroxyrisperidone. After oral administration, the elimination half-life of the active antipsychotic fraction is 24 hours.

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

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
Silica, colloidal anhydrous
Cellulose, microcrystalline
Starch pregelatinised
Sodium starch glycolate (Type A)
Magnesium stearate
Hypermellose (E464)
Titanium dioxide (E171)
Macrogol 6000
Macrogol 400
Iron oxide yellow (E172)
Quinoline yellow aluminium lake (E104)
Indigo carmine aluminium lake (E132)

6.2 **Incompatibilities**
Not applicable

6.3 **Shelf life**
3 years

6.4 **Special precautions for storage**
No special storage conditions

6.5 **Nature and contents of container**
Transparent PVC/PVdC blisters with aluminium foil
10, 20, 30, 50, 60, 100, 100 (5x20) (Hospital Pack) & 500 Film-coated Tablets

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Teva UK Ltd
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
United Kingdom
8 MARKETING AUTHORISATION NUMBER(S)
   PL 00289/0656
   PL 00289/0662

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   30/03/2007

10 DATE OF REVISION OF THE TEXT
    30/03/2007
1 NAME OF THE MEDICINAL PRODUCT
Risperidone 6 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 6 mg of risperidone

Excipients:
Each tablet contains 320.4 mg of lactose monohydrate (see section 4.4).

For a complete list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Tan, round, slightly arched tablets, debossed RIS 6 and scoreline on one side, plain on the other side.

The tablet can be divided into equal halves.

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

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

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

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

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

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

Doses above 10 mg/day generally have not been shown to provide additional efficacy to lower doses and may increase the risk of extrapyramidal symptoms. Doses above 10 mg/day should only be used in individual patients if the benefit is considered to outweigh the risk. Doses above 16 mg/day have not been extensively evaluated for safety and therefore should not be used.
**Elderly**

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

**Children**

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

**Renal and liver disease**

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

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

**Bipolar Mania**

**Adults**

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

As with all symptomatic treatments, the continued use of Risperidone must be evaluated and justified on an ongoing basis.

**Elderly**

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

**Renal and liver disease**

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

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

**Combined use with mood stabilisers**

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

**Method of administration**

Oral use.

### 4.3 Contraindications

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

### 4.4 Special warnings and precautions for use

#### Elderly patients with dementia

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

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

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

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

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

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

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)
Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia, characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

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

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

**Hyperglycaemia**

Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with risperidone. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

**Other**

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

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Fluoxetine and paroxetine, CYP2D6 inhibitors, may increase the plasma concentration of risperidone but less so of the active antipsychotic fraction. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of Risperidone. Based on *in vitro* studies, the same interaction may occur with haloperidol. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. The cholinesterase inhibitor galantamine does not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction. A study of donepezil in non-elderly healthy volunteers also showed no clinically relevant effect on the pharmacokinetics of risperidone and the antipsychotic fraction.

When Risperidone are taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.
See section 4.4 (Special warnings and 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.

### 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. Therefore, Risperidone should only be used during pregnancy if the benefits outweigh the risks.

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

### 4.7 Effects on ability to drive and use machines

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

### 4.8 Undesirable effects

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

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

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

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

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

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

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

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

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

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

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

ATC code: N05AX 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-HT_2 and dopaminergic D_2 receptors. Risperidone binds also to alpha_1-adrenergic receptors and, with lower affinity, to H_1-histaminergic and alpha_2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D_2 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 most important route of metabolism of risperidone is hydroxylation by cytochrome CYP 2D6 to 9-hydroxy-risperidone which has a similar pharmacological activity to risperidone. This hydroxylation is subject to debrisoquine-type genetic polymorphism but this does not affect the active antipsychotic fraction since this consists of risperidone and its active metabolite 9-hydroxyrisperidone. After oral administration, the elimination half-life of the active antipsychotic fraction is 24 hours.

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

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
Silica, colloidal anhydrous
Cellulose, microcrystalline
Starch pregelatinised
Sodium starch glycolate (Type A)
Magnesium stearate
Hyromellose (E464)
Titanium dioxide (E171)
Macrogol 6000
Iron oxide red (E172)
Macrogol 400
Iron oxide yellow (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
No special storage conditions

6.5 Nature and contents of container
Transparent PVC/PVdC blisters with aluminium foil
7, 20, 28, 30, 50, 60, 100 & 100 (5x20) (Hospital Packs) Film-coated Tablets

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Teva UK Ltd
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
United Kingdom
8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/0657
PL 00289/0663

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/03/2007

10 DATE OF REVISION OF THE TEXT
30/03/2007
UKPAR Risperidone 0.5, 1, 2, 3, 4 and 6 mg Film-Coated Tablets

PL 00289/0652-63

RISPERIDONE 0.5, 1, 2, 3, 4 and 6 mg FILM-COATED TABLETS

PACKAGE LEAFLET: INFORMATION FOR THE USER

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

IN THIS LEAFLET:
1. What Risperidone is and what it is used for
2. Before you take Risperidone
3. How to take Risperidone
4. Possible side effects
5. How to store Risperidone
6. Further information

1 WHAT RISPERIDONE IS AND WHAT IT IS USED FOR

Risperidone belongs to a group of drugs called antipsychotics. It is used to treat conditions that affect the way you feel, think and act.
Your medicine is used to treat and prevent symptoms of sudden (acute) and long lasting (chronic) psychotic disorders including schizophrenia. These conditions may cause symptoms such as:
• Hallucinations, delusions and thought disturbances
• Emotional and social withdrawal
• Depression, guilt, anxiety, confusion, paranoia
• Unfriendly and aggressive feelings or behaviour.
In addition, Risperidone may be used to control the symptoms of mania in people with bipolar disorder (manic depressive illness).

2 BEFORE YOU TAKE RISPERIDONE

Do NOT take Risperidone:
• If you are allergic (hypersensitive) to risperidone or any of the other ingredients of this medicine
• If you are taking any other neuroleptic drugs (medicines that are used to treat psychiatric disorders), e.g. haloperidol or chlorpromazine.

Take special care with Risperidone:
Tell your doctor before you start to take this medicine if you have or have had:
• Heart problems, including having an abnormal heart rate or rhythm or stroke. Also, if a member of your family has suffered from any of these problems
• Liver or kidney problems
• Parkinson’s disease
• Epilepsy
• Dementia
• Stroke or ischaemic attack (temporary reduction in blood to the brain)
• Risk factors for blood vessel disease (high blood pressure, diabetes, current smoker or a heart disorder called atrial fibrillation).
Talk to your doctor if you are elderly.

Taking other medicines
Talk to your doctor or pharmacist if you are taking any of the following:
• Drugs used to treat Parkinson’s disease, e.g. levodopa, amantadine
• Carbamazepine (used to treat epilepsy)
• Antidepressants, e.g. clomipramine, fluoxetine and paroxetine
• Drugs known as beta-blockers (used to treat heart problems), e.g. atenolol, propranolol
• Phenothiazines (anti-stress or antipsychotic medicines) e.g. thioridazine, prochlorperazine
• Cimetidine or ranitidine (used to treat stomach/gut ulcers)
• Fluoxetine or other diuretics (‘water tablets’)
• Medicines that affect the levels of salts in your blood for example medicines such as thiazide diuretics (e.g. bendroflumethiazide)
• Medicines that may affect the rhythm of your heart (e.g. pimozide and melflufen).

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

Taking Risperidone with food and drink
Be careful how much alcohol you drink. The combined effect of Risperidone and alcohol may make you feel drowsy.

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

Driving and using machines:
• Risperidone may affect your alertness. You should, therefore, not drive or operate machinery until your doctor decides how the tablets affect you.

Important information about some of the ingredients of Risperidone
• If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3 HOW TO TAKE RISPERIDONE

Always take Risperidone exactly as your doctor has told you.
Check with your doctor or pharmacist if you are not sure.
Risperidone can be taken with or without food. The tablets should be swallowed with a drink of water.

The usual dosage instructions are given below:

Schizophrenia
Adults:
The starting dose is 2 mg on the first day. Your doctor may then increase this to 4 mg on the second day. This may be taken as a single dose or as half a dose in the morning and half in the evening. After this, the usual daily dose is 4-6 mg although some patients may require less than 4 mg.
If you are elderly or have a liver or kidney disorder:
The starting dose is 0.5 mg twice a day on the first day. Your doctor may then gradually increase your dose to 1-2 mg twice a day.

Bipolar mania
Adults:
The usual starting dose is 2 mg once a day on the first day. Your doctor may gradually increase your daily dose to 6 mg.
If you are elderly or have a liver or kidney disorder:
The starting dose is 0.5 mg twice daily. Your doctor may increase this to 1 to 2 mg twice daily.

Children:
Not recommended in children under 15 years old.

If you take more Risperidone than you should
If you (or someone else) swallow a lot of the tablets all together, or if you think a child has swallowed any of the tablets, contact...
your nearest hospital casualty department or your doctor immediately. Overdose may cause drowsiness, low blood pressure (feeling dizzy or faint), fast heart rate, impairment of voluntary movement, e.g. tremors, tics. Changes in muscle tone and slowness of movement have also been reported. Please take this leaflet, any remaining tablets and the container with you to the hospital or doctor so that they know which tablets were consumed.

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

If you stop taking Risperidone
If you suddenly stop taking Risperidone you may experience the following:
• Feeling or being sick, sweating, difficulty in sleeping, muscle stiffness or jerky movements
• Your original medical problem may come back.
These effects are rare but it is advisable to gradually stop taking Risperidone. Always follow your doctor’s instructions.

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

4 POSSIBLE SIDE EFFECTS

Like all medicines, Risperidone can have side effects, although not everybody gets them.

The most common side effects are:
• Difficulty sleeping
• Agitation and anxiety
• Headache.

Less common side effects are:
• Sleepiness, tiredness, feeling dizzy and faint on standing, poor concentration, blurred vision
• Constipation, heartburn/indigestion, nausea, vomiting, abdominal pain
• Continuous painful erection, sexual problems, leakage of urine, runny and itchy nose, rash and other allergic reactions
• Shaking, restlessness, muscle stiffness, sluggish or slow physical movement, changes in muscle tone and the production of excess saliva.

Other side effects include:
• Stroke
• High body temperature, drowsiness, changes in consciousness level and mental responses
• High or low blood pressure and changes in the composition of the blood
• Women may suffer from swollen breasts, milk secretion, an absence of their monthly period or changes in the regularity of their periods
• Men may experience breast swelling
• Weight gain, fluid retention leading to swelling
• Changes in levels of liver enzymes
• Heart problems including abnormal heart rhythms and a fast heart rate
• Sudden unexplained death.

In very rare cases, high blood sugar levels, worsening of existing diabetes and low blood sodium resulting in fits and confusion have been reported.

Tell your doctor or pharmacist if any of the side effects get serious, or if you notice any side effects not listed in this leaflet.

5 HOW TO STORE RISPERIDONE

Keep Risperidone out of the reach and sight of children.
There are no special storage instructions. Do not transfer to another container. Do not use Risperidone after the expiry date shown on the outer packaging.
Medicines should not be disposed of via waste water 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 contains:
• The active ingredient is risperidone.
• Other ingredients are lactose monohydrate, sodium lauril sulfate, hypromellose (E464), macrogol 6000, macrogol 400, colloidal anhydrous silica, microcrystalline cellulose, pregelatinised starch, sodium starch glycolate (Type A) and magnesium stearate. The tablets contain the following colours:
  • 0.5 mg tablets: iron oxide red (E172), iron oxide yellow (E172) and titanium dioxide (E171)
  • 1 mg tablets: iron oxide red (E172) and titanium dioxide (E171)
  • 2 mg tablets: iron oxide red (E172), iron oxide yellow (E172) and titanium dioxide (E171)
  • 3 mg tablets: titanium dioxide (E171) and quinoline yellow aluminium lake (E104)
  • 4 mg tablets: titanium dioxide (E171), quinoline yellow aluminium lake (E104), indigo carmine aluminium lake (E132) and iron oxide yellow (E172)
  • 6 mg tablets: titanium dioxide (E171), iron oxide red (E172) and iron oxide yellow (E172).

What Risperidone looks like and contents of the pack:
• Risperidone 0.5 mg Film-Coated Tablets are brownish-red, round, slightly arched tablets, with “RIS 0.5” and a score line marked on one side and plain on the other side
• Risperidone 1 mg Film-Coated Tablets are white, round, slightly arched tablets with “RIS 1” and a score line marked on one side and plain on the other side
• Risperidone 2 mg Film-Coated Tablets are tan colour, round, slightly arched tablets with “RIS 2” and a score line marked on one side and plain on the other side
• Risperidone 3 mg Film-Coated Tablets are yellow, round, slightly arched tablets with “RIS 3” and a score line marked on one side and plain on the other side
• Risperidone 4 mg Film-Coated Tablets are green, round, slightly arched tablets with “RIS 4” and a score line marked on one side and plain on the other side
• Risperidone 6 mg Film-Coated Tablets are tan colour, round, slightly arched tablets with “RIS 6” and a score line marked on one side and plain on the other side
• The 0.5 mg tablets are available in pack sizes of 10, 20 and 60 film-coated tablets
• The 1 mg tablets are available in pack sizes of 6, 10, 20, 50, 60, 100, 100 (5 x 20 hospital pack) and 500 film-coated tablets
• The 2 mg tablets are available in pack sizes of 10, 20, 50, 60, 100, 100 (5 x 20 hospital pack) and 500 film-coated tablets
• The 3 mg tablets are available in pack sizes of 10, 20, 50, 60, 100, 100 (5 x 20 hospital pack) and 500 film-coated tablets
• The 4 mg tablets are available in pack sizes of 10, 20, 30, 50, 60, 100, 100 (5 x 20 hospital pack) and 500 film-coated tablets
• The 6 mg tablets are available in pack sizes of 7, 20, 28, 30, 50, 60, 100 and 100 (5 x 20 hospital pack) film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
The Marketing Authorisation holder and company responsible for manufacture is TEVA UK Limited, Eastbourne, BN22 9AG.

Distributed by TEVA UK, Leeds, LS27 0JG.

This leaflet was last revised: March 2007
Labels

Please note that representative packaging for each strength is provided only. Packaging for duplicates is not included, but is consistent with the packaging presented.
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UKPAR Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-Coated Tablets

Each tablet contains 3 mg of risperidone. Also includes lactose monohydrate.

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

**Keep out of the reach and sight of children.**

There are no special storage instructions.

Manufacturer:
TEVA UK Limited,
Buckingham, MK12 6NW
Tel: 0800095 2000

Lot 00289/0652-63
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76
Each tablet contains 6 mg of risperidone. Also includes lactose monohydrate.

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

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

There are no special storage instructions.

MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AQ.
PL 00289/0657
60781-1-L T

Risperidone 6 mg Film-Coated Tablets
For Oral Administration

Risperidone 6 mg Film-Coated Tablets
28 Tablets

Risperidone 6 mg Film-Coated Tablets
28 Tablets

47 x 18 x 134 mm