Risperidone 0.5mg Film-coated Tablets
Risperidone 1mg Film-coated Tablets
Risperidone 2mg Film-coated Tablets
Risperidone 3mg Film-coated Tablets
Risperidone 4mg Film-coated Tablets
Risperidone 6mg Film-coated Tablets

PL 17907/0210-5

UK Public Assessment Report

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

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Bristol Laboratories Limited Marketing Authorisations (licences) for the medicinal products, Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets (PL 17907/0210-5) on 17 January 2012. These are prescription-only medicines (POM).

The active ingredient, risperidone, belongs to a group of medicines called “anti-psychotics”. It is used to treat the following:

- Schizophrenia, where you may see, hear or feel things that are not there, believe things that are not true or feel unusually suspicious, or confused.
- Mania, where you may feel very excited, elated, agitated, enthusiastic or hyperactive. Mania occurs in an illness called “bipolar disorder”.
- Short-term treatment (up to 6 weeks) of long-term aggression in people with Alzheimer’s dementia, who harm themselves or others. Alternative (non-drug) treatments should have been used previously.
- Short-term treatment (up to 6 weeks) of long-term, aggression in intellectually disabled children (at least 5 years of age) and adolescents with conduct disorder.

Based on the data submitted by Bristol Laboratories Limited, Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets were considered to be generic versions of the UK reference products, Risperdal 0.5, 1, 2, 3, 4 and 6mg Film-coated tablets (PL 00242/0347, 0186-9 and 0317, Janssen-Cilag Limited).

No new or unexpected safety concerns arose from these applications. It was judged that the benefits of Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.
Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets

PL 17907/0210-5

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Bristol Laboratories Limited Marketing Authorisations for the medicinal products, Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets (PL 17907/0210-5) on 17 January 2012. These are prescription-only medicines (POM).

These are generic applications for Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets, submitted under Article 10(1) of Directive 2001/83/EC, as amended. The applications refer to the UK products, Risperdal 0.5, 1, 2, 3, 4 and 6 mg film-coated tablets (PL 00242/0347, 0186-9 and 0317), licensed to Janssen-Cilag Limited on 30 June 2000 (PL 00242/0347), 08 December 1992 (PL 00242/0186-9) and 15 July 1999 (PL 00242/0317). The UK reference products have been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired.

Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets are indicated for the following:

- treatment of schizophrenia
- treatment of moderate to severe manic episodes associated with bipolar disorders
- short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others
- short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with sub-average intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours require pharmacologic treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment programme, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of conduct disorder of children and adolescents.

Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 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, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical antipsychotics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.
The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Risperidone 2mg Film-coated Tablets, to that of the reference product, Risperdal 2 mg film-coated tablets (Janssen-Cilag Limited). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

The MHRA considers that the pharmacovigilance system described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

An Environmental Risk Assessment (ERA) was not required for these applications. These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the products.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Risperidone

Nomenclature:

INN: Risperidone

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

Structure:

![structure](image)

Molecular formula: C_{23}H_{27}FN_{4}O_{2}

Molecular weight: 410.5 g/mol

CAS No: 106266-06-2

Physical form: White to off-white powder

Solubility: Practically insoluble in water, sparingly soluble in ethanol, freely soluble in methylene chloride

The active substance, risperidone, is the subject of a European Pharmacopeia (Ph. Eur) monograph.

All aspects of the manufacture and control of risperidone are supported by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). The certificate is accepted as confirmation of the suitability of risperidone for inclusion in these medicinal products.
MEDICINAL PRODUCT

Description and Composition

Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets are presented as film-coated tablets with specified markings. The tablets have a score line, which is only to facilitate breaking for ease of swallowing and not to divide into equal doses. Full descriptions of the individual tablets may be found by referring to the SmPCs or patient information leaflet. Each tablet contains 0.5, 1, 2, 3, 4 or 6 mg of the active ingredient, risperidone.

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, microcrystalline cellulose (E460), maize starch, pregelatinised starch, sodium lauryl sulphate, colloidal anhydrous silica and magnesium stearate making up the tablet cores; and hypromellose (E 464), purified talc (E 555B), titanium dioxide (E 171) and macrogol 6000 (E 490) making up the film-coating. The film-coatings additionally contain red iron oxide (E172) for the 0.5 mg strength tablets, sunset yellow (E110) for the 2 mg strength tablets, quinoline yellow (E104) for the 3 mg strength tablets, quinoline yellow (E104) and indigo carmine (E132) for the 4 mg strength tablets and sunset yellow (E110) and quinoline yellow (E104) for the 6 mg strength tablets. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective Ph. Eur monographs, with the exception of the colorants, red iron oxide (E172), sunset yellow (E110), quinoline yellow (E104) and indigo carmine (E132), which comply with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate has been confirmed as being of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The objective was to develop stable, generic, film-coated tablet formulations of risperidone 0.5, 1, 2, 3, 4 and 6mg, bioequivalent to the reference products, Risperdal 0.5, 1, 2, 3, 4 and 6 mg film-coated tablets (PL 00242/0347, 0186-9 and 0317, Janssen-Cilag Limited).

Comparative dissolution and impurity data were provided for batches of the test and appropriate reference products. The dissolution and impurity profiles were satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.
In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and the results were satisfactory. The validation data demonstrate consistency of the manufacturing process.

**Finished product specifications**

Finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**

Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets are licensed for marketing in polyvinylchloride (PVC)-aluminium foil blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 20 tablets (0.5 mg), 20 and 60 tablets (1 mg), 60 tablets (2, 3 and 4 mg) and 28 tablets (6 mg).

Satisfactory specifications and Certificates of Analysis for all packaging components have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support the applied shelf-life of 3 years. Storage instructions are ‘Do not store above 25°C. Store in the original package’.

**Quality Overall Summary**

A satisfactory quality overall summary is provided and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**

The approved Summaries of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The PIL user-testing report has been evaluated and is accepted. It supports the readability of the package leaflet. The labelling fulfils the statutory requirements for Braille.

**Conclusion**

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets from a pharmaceutical point of view.
NON-CLINICAL ASSESSMENT

These abridged applications, submitted under Article 10(1) of Directive 2001/83/EC, as amended, are for Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets, products claiming to be generic versions of the UK reference products, Risperdal 0.5, 1, 2, 3, 4 and 6 mg film-coated tablets (PL 00242/0347, 0186-9 and 0317, Janssen-Cilag Limited).

No new non-clinical data have been supplied with these applications and none are required for applications of this type. A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the expert has been supplied.

There are no objections to approval of these products from a non-clinical point of view.
CLINICAL ASSESSMENT

BACKGROUND
Risperidone is classed as a newer atypical antipsychotic. The antipsychotic effect of risperidone is believed to be connected to its antagonism of dopamine D2 and serotonin 5-HT2 receptors. Risperidone, as other atypical antipsychotics, enhances prolactine release. Blockade of motor activity and catalepsy can occur with higher doses.

Risperidone is used for treatment of psychotic symptoms in psychotic and affective disorders and behavioural disturbances in dementia and learning disability.

INDICATIONS
Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets are indicated for the following:

- treatment of schizophrenia
- treatment of moderate to severe manic episodes associated with bipolar disorders
- short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others
- short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with sub-average intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours require pharmacologic treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment programme, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of conduct disorder of children and adolescents.

The indications are consistent with those for the reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION
Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY
The toxicology of risperidone is well-known. No new data have been submitted and none are required for applications of this type.
CLINICAL PHARMACOLOGY

Pharmacodynamics

The clinical pharmacology of risperidone is well-known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

Pharmacokinetics - Bioequivalence studies

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Risperidone 2mg Film-coated Tablets, to that of the reference product, Risperdal 2 mg film-coated tablets (Janssen-Cilag Limited, UK). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis were provided for the test and reference products.

This was an open-label, randomised, two-period, two-sequence, two-treatment, single-dose crossover bioequivalence study conducted in healthy adult human male subjects under fasting conditions. A single 2 mg dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 11 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose and at specified time points up to 96.0 hours after administration of test or reference product. Plasma levels of risperidone were quantified by a validated LC/MS-MS method.

The primary pharmacokinetic parameters for this study were C_{max}, AUC(0-t) and AUC(0-\infty). Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) of the ratio of the test and reference products fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed C_{max}, AUC(0-t) and AUC(0-\infty) for risperidone.

Results:

An appropriate number of subjects completed the study and were included in the pharmacokinetic evaluation and statistical analysis.

Safety - There were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below:
Summary pharmacokinetic data for risperidone for a randomised, open-label, 2-way, single-dose crossover study; healthy subjects, dosed fasted; t=96 hours, washout period: 11 days

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± Standard Deviation</th>
<th>90% CI (Parametric)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Reference Product (X)</td>
<td>Test Product (Y)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>11.34 ± 4.38</td>
<td>11.17 ± 4.72</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.h/ml)</td>
<td>56.13 ± 33.24</td>
<td>57.48 ± 38.03</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng.h/ml)</td>
<td>61.42 ± 37.66</td>
<td>62.52 ± 42.97</td>
</tr>
</tbody>
</table>

**Conclusion on Bioequivalence**

The results of the bioequivalence study show that the test and reference products are bioequivalent under fasting conditions, as the confidence intervals for C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>0-∞</sub> for risperidone fall within the acceptance criteria ranges of 80-125%.

Satisfactory justification is provided for a bio-waiver for Risperidone 0.5, 1, 3, 4 and 6mg Film-coated Tablets. As Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets meet the criteria 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 2 mg strength can be extrapolated to the 0.5, 1, 3, 4 and 6 mg strength tablets.

**Efficacy**

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of risperidone is well-established from its extensive use in clinical practice.

**Safety**

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of risperidone is well-known.

**Clinical Overview**

A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

**Product Information:**

**Summary of Product Characteristics (SmPC)**

The approved SmPCs are consistent with those of the UK reference products and are acceptable.
**Patient Information Leaflet**

The final PIL is in line with the approved SmPCs and is satisfactory.

**Labelling**

The labelling is satisfactory.

**CONCLUSIONS**

Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was, therefore, recommended.
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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Risperidone 2mg Film-coated Tablets and the UK reference product, Risperdal 2 mg film-coated tablets (Janssen-Cilag Limited).

As Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets meet the criteria 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 2 mg strength were extrapolated to the 0.5, 1, 3, 4 and 6 mg strength tablets, and omission of further bioequivalence studies on the other strengths can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs are consistent with those for the reference products and are satisfactory.

A mock-up PIL has been provided. The package leaflet is in line with the SmPCs and is satisfactory. The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant’s Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets are generic versions of the UK reference products, Risperdal 0.5, 1, 2, 3, 4 and 6 mg film-coated tablets (PL 00242/0347, 0186-9 and 0317, Janssen-Cilag Limited).

Extensive clinical experience with risperidone is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets

PL 17907/0210-5

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation applications on 06 February 2009.

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 15 April 2009.

3 Following assessment of the applications the MHRA requested further information relating to the clinical dossier on 04 June 2009 and 26 August 2011; and further information relating to the quality dossier on 08 July 2009, 01 September 2010 and 04 March 2011.

4 The applicant responded to the MHRA’s requests, providing further information for the clinical sections on 17 August 2010 and 16 November 2011; and further information for the quality sections on 17 August 2010, 09 September 2010 and 27 May 2011.

5 The applications were approved on 17 January 2012.
Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets

PL 17907/0210-5

STEPS TAKEN AFTER AUTHORISATION

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets (PL 17907/0210-5) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

Risperidone 0.5mg Film-coated Tablets.
Risperidone 1mg Film-coated Tablets.
Risperidone 2mg Film-coated Tablets.
Risperidone 3mg Film-coated Tablets.
Risperidone 4mg Film-coated Tablets.
Risperidone 6mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.5mg Risperidone as active ingredient.
Each 0.5 mg film-coated tablet contains 56.50 mg Lactose Monohydrate.

Each film-coated tablet contains 1mg Risperidone as active ingredient.
Each 1 mg film-coated tablet contains 113 mg Lactose Monohydrate.

Each film-coated tablet contains 2mg Risperidone as active ingredient.
Each 2 mg film-coated tablet contains 112 mg Lactose Monohydrate and 0.08mg sunset yellow (E 110).

Each film-coated tablet contains 3mg Risperidone as active ingredient.
Each 3 mg film-coated tablet contains 168 mg Lactose Monohydrate.

Each film-coated tablet contains 4mg Risperidone as active ingredient.
Each 4 mg film-coated tablet contains 224 mg Lactose Monohydrate.

Each film-coated tablet contains 6mg Risperidone as active ingredient.
Each 6 mg film-coated tablet contains 108 mg Lactose Monohydrate and 0.018mg Sunset yellow (E110).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablets

Red coloured, caplet, biconvex tablets with “0.5” embossed on one side and “B/L” embossed on other side.

White coloured, caplet, biconvex tablets with “1” embossed on one side and “B/L” embossed on other side.

Orange coloured, caplet, biconvex tablets with “2” embossed on one side and “B/L” embossed on other side.

Yellow coloured, caplet, biconvex tablets with “3” embossed on one side and “B/L” embossed on other side.

Green coloured, caplet, biconvex tablets with “4” embossed on one side and “B/L” embossed on other side.

Yellow coloured, caplet, biconvex tablets with “6” embossed on one side and “B/L” embossed on other side.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

RISPERIDONE is indicated for the treatment of schizophrenia.

RISPERIDONE is indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders.

RISPERIDONE is indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.

RISPERIDONE is indicated for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with sub average intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours require pharmacologic treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment programme, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of conduct disorder of children and adolescents.

4.2 Posology and method of administration

Schizophrenia

Adults

Risperidone may be given once daily or twice daily.

Patients should start with 2 mg/day risperidone. The dosage may be increased on the second day to 4 mg. Subsequently, the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6 mg. In some patients, a slower titration phase and a lower starting and maintenance dose may be appropriate.

Doses above 10 mg/day have not demonstrated superior efficacy to lower doses and may cause increased incidence of extrapyramidal symptoms. Safety of doses above 16 mg/day has not been evaluated, and is therefore not recommended.

Elderly

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

Paediatric population

Risperidone is not recommended for use in children below age 18 with schizophrenia due to a lack of data on efficacy.

Manic episodes in bipolar disorder

Adults

Risperidone should be administered on a once daily schedule, starting with 2 mg risperidone. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. Risperidone can be administered in flexible doses over a range of 1 to 6 mg per day to optimize each patient's level of efficacy and tolerability. Daily doses over 6 mg risperidone have not been investigated in patients with manic episodes.
As with all symptomatic treatments, the continued use of Risperidone must be evaluated and justified on an ongoing basis.

**Elderly**

A starting dose of 0.5 mg twice daily is recommended. This dosage can be individually adjusted with 0.5 mg twice daily increments to 1 to 2 mg twice daily. Since clinical experience in elderly is limited, caution should be exercised.

**Paediatric population**

Risperidone is not recommended for use in children below age 18 with bipolar mania due to a lack of data on efficacy.

**Persistent aggression in patients with moderate to severe Alzheimer's dementia**

A starting dose of 0.25 mg twice daily is recommended. This dosage can be individually adjusted by increments of 0.25 mg twice daily, not more frequently than every other day, if needed. The optimum dose is 0.5 mg twice daily for most patients. Some patients, however, may benefit from doses up to 1 mg twice daily.

Risperidone should not be used more than 6 weeks in patients with persistent aggression in Alzheimer's dementia. During treatment, patients must be evaluated frequently and regularly, and the need for continuing treatment reassessed.

**Conduct disorder**

*Children and adolescents from 5 to 18 years of age*

For subjects ≥50 kg, a starting dose of 0.5 mg once daily is recommended. This dosage can be individually adjusted by increments of 0.5 mg once daily not more frequently than every other day, if needed. The optimum dose is 1 mg once daily for most patients. Some patients, however, may benefit from 0.5 mg once daily while others may require 1.5 mg once daily. For subjects <50 kg, a starting dose of 0.25 mg once daily is recommended. This dosage can be individually adjusted by increments of 0.25 mg once daily not more frequently than every other day, if needed. The optimum dose is 0.5 mg once daily for most patients. Some patients, however, may benefit from 0.25 mg once daily while others may require 0.75 mg once daily.

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

Risperidone is not recommended in children less than 5 years of age, as there is no experience in children less than 5 years of age with this disorder.

**Renal and hepatic impairment**

Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than in adults with normal renal function. Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone.

Irrespective of the indication, starting and consecutive dosing should be halved, and dose titration should be slower for patients with renal or hepatic impairment.

Risperidone should be used with caution in these groups of patients.

**Method of administration**

Risperidone is for oral use. Food does not affect the absorption of Risperidone.

Upon discontinuation, gradual withdrawal is advised. Acute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotic medicines (see section 4.8). Recurrence of psychotic
symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported.

Switching from other antipsychotics.
When medically appropriate, gradual discontinuation of the previous treatment while Risperidone therapy is initiated is recommended. Also, if medically appropriate, when switching patients from depot antipsychotics, initiate Risperidone therapy in place of the next scheduled injection. The need for continuing existing anti-Parkinson medicines should be re-evaluated periodically.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Elderly patients with dementia

Increased mortality in elderly people with dementia
In a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including Risperidone, elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo. In placebo-controlled trials with oral Risperidone in this population, the incidence of mortality was 4.0% for Risperidone treated patients compared to 3.1% for placebo-treated patients. The odds ratio (95% exact confidence interval) was 1.21 (0.7, 2.1). The mean age (range) of patients who died was 86 years (range 67-100). Data from two large observational studies showed that elderly people with dementia who are treated with conventional antipsychotics are also at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

Concomitant use with furosemide
In the Risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus Risperidone (7.3%; mean age 89 years, range 75-97) when compared to patients treated with Risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus Risperidone was observed in two of the four clinical trials. Concomitant use of Risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination or co-treatment with other potent diuretics should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with Risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CVAE)
An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The pooled data from six placebo-controlled studies with RISPERIDONE in mainly elderly patients (>65 years of age) with dementia showed that CVAEs (serious and non-serious, combined) occurred in 3.3% (33/1009) of patients treated with Risperidone and 1.2% (8/712) of patients treated with placebo. The odds ratio (95% exact confidence interval) was 2.96 (1.34, 7.50). The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. RISPERIDONE should be used with caution in patients with risk factors for stroke.
The risk of CVAEs was significantly higher in patients with mixed or vascular type of dementia when compared to Alzheimer's dementia. Therefore, patients with other types of dementias than Alzheimer's should not be treated with Risperidone.

Physicians are advised to assess the risks and benefits of the use of Risperidone in elderly patients with dementia, taking into account risk predictors for stroke in the individual patient. Patients/caregivers should be cautioned to immediately report signs and symptoms of potential CVAEs such as sudden weakness or numbness in the face, arms or legs, and speech or vision problems. All treatment options should be considered without delay, including discontinuation of Risperidone.

Risperidone should only be used short term for persistent aggression in patients with moderate to severe Alzheimer's dementia to supplement non-pharmacological approaches which have had limited or no efficacy and when there is potential risk of harm to self or others.

Patients should be reassessed regularly, and the need for continuing treatment reassessed.

**Orthostatic hypotension**

Due to the alpha-blocking activity of Risperidone, (orthostatic) hypotension can occur, especially during the initial dose-titration period. Clinically significant hypotension has been observed postmarketing with concomitant use of Risperidone and antihypertensive treatment. Risperidone should be used with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended (see section 4.2). A dose reduction should be considered if hypotension occurs.

**Tardive dyskinesia/extrapyramidal symptoms (TD/EPS)**

Medicines 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. The onset of extrapyramidal symptoms is a risk factor for tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics should be considered.

**Neuroleptic malignant syndrome (NMS)**

Neuroleptic Malignant Syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels has been reported to occur with antipsychotics. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, all antipsychotics, including Risperidone, should be discontinued.

**Parkinson's disease and dementia with Lewy bodies**

Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including Risperidone, to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB). Parkinson's Disease may worsen with Risperidone. Both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medicinal products; these patients were excluded from clinical trials. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

**Hyperglycaemia and diabetes mellitus**

Hyperglycaemia, diabetes mellitus and exacerbation of pre-existing diabetes have been reported during treatment with Risperidone. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Association with ketoacidosis has been reported very rarely, and rarely with diabetic coma. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any atypical antipsychotic, including Risperidone should be monitored for symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus should be monitored regularly for worsening of glucose control.
Weight gain
Significant weight gain has been reported with Risperidone use. Weight should be monitored regularly.

Hyperprolactinaemia
Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. Risperidone should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours.

QT prolongation
QT prolongation has very rarely been reported postmarketing. As with other antipsychotics, caution should be exercised when Risperidone is prescribed in patients with known cardiovascular disease, family history of QT prolongation, bradycardia, or electrolyte disturbances (hypokalaemia, hypomagnesaemia), as it may increase the risk of arrhythmogenic effects, and in concomitant use with medicines known to prolong the QT interval.

Seizures
RISPERIDONE should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Priapism
Priapism may occur with RISPERIDONE treatment due to its alpha-adrenergic blocking effects.

Body temperature regulation
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines. Appropriate care is advised when prescribing RISPERIDONE to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g. exercising strenuously, exposure to extreme heat, receiving concomitant treatment with anticholinergic activity, or being subject to dehydration.

Venous thromboembolism
Cases of Venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with RISPERIDONE and preventative measures undertaken.

Children and adolescents
Before Risperidone is prescribed to a child or adolescent with conduct disorder they should be fully assessed for physical and social causes of the aggressive behaviour such as pain or inappropriate environmental demands.

The sedative effect of Risperidone should be closely monitored in this population because of possible consequences on learning ability. A change in the time of administration of Risperidone could improve the impact of the sedation on attention faculties of children and adolescents.

Risperidone was associated with mean increases in body weight and body mass index (BMI). Changes in height in the long-term open-label extension studies were within expected age-appropriate norms. The effect of long-term Risperidone treatment on sexual maturation and height has not been adequately studied.

Because of the potential effects of prolonged hyperprolactinemia on growth and sexual maturation in children and adolescents, regular clinical evaluation of endocrinological status
should be considered, including measurements of height, weight, sexual maturation, monitoring of menstrual functioning, and other potential prolactin-related effects.

During treatment with Risperidone regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.

For specific posology recommendations in children and adolescents see Section 4.2.

**Excipients**

The film-coated tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

For 2mg and 6mg strengths only: It contain sunset yellow (E110), may cause allergic reactions.

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

As with other antipsychotics, caution is advised when prescribing risperidone with medicinal products known to prolong the QT interval, e.g., class 1a antiarrhythmics (e.g., quinidine, dysopiramid, procainamide), class III antiarrhythmics (e.g., amiodarone, sotalol), tricyclic antidepressant (i.e., amitriptyline), tetracyclic antidepressants (i.e., maprotiline), some antihistaminics, other antipsychotics, some antimalarials (i.e., chinice and mefloquine), and with medicines causing electrolyte imbalance (hypokalaemia, hypomagnesiaemia), bradycardia, or those which inhibit the hepatic metabolism of risperidone. This list is indicative and not exhaustive.

**Potential for Risperidone to affect other medicinal products**

Risperidone should be used with caution in combination with other centrally-acting substances notably including alcohol, opiates, antihistamines and benzodiazepines due to the increased risk of sedation.

*Risperidone* may antagonise the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.

Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment.

*Risperidone* does not show a clinically relevant effect on the pharmacokinetics of lithium, valproate, digoxin or topiramate.

**Potential for other medicinal products to affect Risperidone**

Carbamazepine has been shown to decrease the plasma concentrations of the active antipsychotic fraction of risperidone. Similar effects may be observed with e.g. rifampicin, phenytoin and phenobarbital which also induce CYP 3A4 hepatic enzyme as well as P-glycoprotein. When carbamazepine or other CYP 3A4 hepatic enzyme/P-glycoprotein (P-gp) inducers are initiated or discontinued, the physician should re-evaluate the dosing of *Risperidone*.

Fluoxetine and paroxetine, CYP 2D6 inhibitors, increase the plasma concentration of risperidone, but less so of the active antipsychotic fraction. It is expected that other CYP 2D6 inhibitors, such as quinidine, may affect the plasma concentrations of risperidone in a similar way. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of *Risperidone*.

Verapamil, an inhibitor of CYP 3A4 and P-gp, increases the plasma concentration of risperidone.
Galantamine and donepezil do not show a clinically relevant effect on the pharmacokinetics of risperidone and on the active antipsychotic fraction.

Phenothiazines, tricyclic antidepressants, and some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. 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 combined use of psychostimulants (e.g., methylphenidate) with Risperidone in children and adolescents did not alter the pharmacokinetics and efficacy of Risperidone.

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

Concomitant use of oral Risperidone with paliperidone is not recommended as paliperidone is the active metabolite of risperidone and the combination of the two may lead to additive active antipsychotic fraction exposure.

### 4.6 Fertility, pregnancy and lactation

#### Pregnancy

Neonates exposed to antipsychotics (including Risperidone) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently newborns should be monitored carefully. Risperidone was not teratogenic in animal studies but other types of reproductive toxicity were seen (see section 5.3). Therefore, Risperidone should not be used during pregnancy unless clearly necessary. If discontinuation during pregnancy is necessary, it should not be done abruptly.

#### Lactation

In animal studies, risperidone and 9-hydroxy-risperidone are excreted in the milk. It has been demonstrated that risperidone and 9-hydroxy-risperidone are also excreted in human breast milk in small quantities. There are no data available on adverse reactions in breast-feeding infants. Therefore, the advantage of breast-feeding should be weighed against the potential risks for the child.

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

Risperidone can have minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects (see section 4.8). Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

### 4.8 Undesirable effects

The most frequently reported adverse drug reactions (ADRs) (incidence ≥10%) are: Parkinsonism, headache, and insomnia.

The following are all the ADRs that were reported in clinical trials and postmarketing. The following terms and frequencies are applied: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), and not known (cannot be estimated from the available clinical trial data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse Drug Reactions by System Organ Class and Frequency
Investigations

**Common**
- Blood prolactin increased
- Weight increased

**Uncommon**
- Electrocardiogram QT prolonged, Electrocardiogram abnormal
- Blood glucose increased, Transaminases increased, White blood cell count decreased
- Body temperature increased, Eosinophil count increased, Haemoglobin decreased, Blood creatine phosphokinase increased

**Rare**
- Body temperature decreased

Cardiac disorders

**Common**
- Tachycardia

**Uncommon**
- Atrioventricular block, Bundle branch block, Atrial fibrillation, Sinus bradycardia, Palpitations

Blood and lymphatic system disorders

**Uncommon**
- Anaemia, Thrombocytopenia

**Rare**
- Granulocytopenia

**Not known**
- Agranulocytosis

Nervous system disorders

**Very common**
- Parkinsonism, Headache

**Common**
- Akathisia, Dizziness, Tremor, Dystonia, Somnolence, Sedation, Lethargy, Dyskinesia

**Uncommon**
- Unresponsive to stimuli, Loss of consciousness, Syncope, Depressed level of consciousness, Cerebrovascular accident, Transient ischaemic attack, Dysarthria, Disturbance in attention, Hypersomnia, Dizziness postural, Balance disorder, Tardive dyskinesia, Speech disorder, Coordination abnormal, Hypoaesthesia

**Rare**
- Neuroleptic malignant syndrome, Diabetic coma, Cerebrovascular disorder, Cerebral ischaemia, Movement disorder

Eye disorders

**Common**
- Vision blurred

**Uncommon**
- Conjunctivitis, Ocular hyperaemia, Eye discharge, Eye swelling, Dry eye, Lacrimation increased, Photophobia

**Rare**
- Visual acuity reduced, Eye rolling, Glaucoma

Ear and labyrinth disorders

**Uncommon**
- Ear pain, Tinnitus

Respiratory, thoracic and mediastinal disorders

**Common**
- Dyspnoea, Epistaxis, Cough, Nasal congestion, Pharyngolaryngeal pain

**Uncommon**
- Wheezing, Pneumonia aspiration, Pulmonary congestion, Respiratory disorder, Rales, Respiratory tract congestion, Dysphonia

**Rare**
- Sleep apnea syndrome, Hyperventilation

Gastrointestinal disorders

**Common**
- Vomiting, Diarrhoea, Constipation, Nausea, Abdominal pain, Dyspepsia, Dry mouth, Stomach discomfort

**Uncommon**
- Dysphagia, Gastritis, Faecal incontinence, Faecaloma

**Rare**
- Intestinal obstruction, Pancreatitis, Lip swelling, Cheilitis

Renal and urinary disorders

**Common**
- Enuresis

**Uncommon**
- Urinary retention, Dysuria, Urinary incontinence, Pollakiuria

Skin and subcutaneous tissue disorders

**Common**
- Rash, Erythema

**Uncommon**
- Angioedema, Skin lesion, Skin disorder, Pruritus, Acne, Skin discolouration, Alopecia, Seborrhoeic dermatitis, Dry skin, Hyperkeratosis

**Rare**
- Dandruff
Musculoskeletal and connective tissue disorders
- **Common**: Arthralgia, Back pain, Pain in extremity
- **Uncommon**: Muscular weakness, Myalgia, Neck pain, Joint swelling, Posture abnormal, Joint stiffness, Musculoskeletal chest pain
- **Rare**: Rhabdomyolysis

Endocrine disorders
- **Rare**: Inappropriate antidiuretic hormone secretion

Metabolism and nutrition disorders
- **Common**: Increased appetite, Decreased appetite
- **Uncommon**: Diabetes mellitus, Anorexia, Polydipsia, Hyperglycaemia
- **Rare**: Hypoglycaemia
- **Very rare**: Diabetic ketoacidosis
- **Not known**: Water intoxication

Infections and infestations
- **Common**: Pneumonia, Influenza, Bronchitis, Upper respiratory tract infection, Urinary tract infection
- **Uncommon**: Sinusitis, Viral infection, Ear infection, Tonsillitis, Cellulitis, Otitis media, Eye infection, Localised infection, Acarodermatitis, Respiratory tract infection, Cystitis, Onychomycosis
- **Rare**: Otitis media chronic

Vascular disorders
- **Uncommon**: Hypotension, Orthostatic hypotension, Flushing

General disorders and administration site conditions
- **Common**: Pyrexia, Fatigue, Peripheral oedema, Asthenia, Chest pain
- **Uncommon**: Face oedema, Gait disturbance, Feeling abnormal, Sluggishness, Influenza like illness, Thirst, Chest discomfort, Chills
- **Rare**: Generalised oedema, Hypothermia, Drug withdrawal syndrome, Peripheral coldness

Immune system disorders
- **Uncommon**: Hypersensitivity
- **Rare**: Drug hypersensitivity
- **Not known**: Anaphylactic reaction

Hepatobiliary disorders
- **Rare**: Jaundice

Reproductive system and breast disorders
- **Uncommon**: Amenorrhoea, Sexual dysfunction, Erectile dysfunction, Ejaculation disorder, Galactorrhoea, Gynaecomastia, Menstrual disorder, Vaginal discharge
- **Not known**: Priapism

Psychiatric disorders
- **Very common**: Insomnia
- **Common**: Anxiety, Agitation, Sleep disorder
- **Uncommon**: Confusional state, Mania, Libido decreased, Listless, Nervousness
- **Rare**: Anorgasmia, Blunted affect

Pregnancy, puerperium and perinatal conditions
- **Not known**: Drug withdrawal syndrome neonatal (see 4.6)

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a Hyperprolactinemia can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhoea, galactorrhoea.

b Extrapyramidal disorder may occur: Parkinsonism (salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies,
muscle tightness, akinesia, nuchal rigidity, muscle rigidity, parkinsonian gait, and glabellar reflex abnormal), akathisia (akathisia, restlessness, hyperkinesia, and restless leg syndrome), tremor, dyskinesia (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia. Dystonia includes dystonia, muscle spasms, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm and trismus. Tremor includes tremor and parkinsonian rest tremor. It should be noted that a broader spectrum of symptoms are included, that do not necessarily have an extrapyramidal origin.

In placebo-controlled trials diabetes mellitus was reported in 0.18% in risperidone-treated subjects compared to a rate of 0.11% in placebo group. Overall incidence from all clinical trials was 0.43% in all risperidone-treated subjects.

The following is a list of additional ADRs associated with risperidone that have been identified as ADRs during clinical trials investigating the long-acting injectable risperidone formulation but were not determined to be ADRs in the clinical trials investigating oral Risperidone. This table excludes those ADRs specifically associated with the formulation or injection route of administration of Risperidone.

Additional Adverse Drug Reactions Reported with long-acting injectable risperidone but not with oral risperidone by System Organ Class:

**Investigations**
Weight decreased, Gamma-glutamyltransferase increased, Hepatic enzyme increased

**Cardiac Disorders**
Bradycardia

**Blood and Lymphatic Disorders**
Neutropenia

**Nervous System Disorders**
Paresthesia, Convulsion

**Eye Disorders**
Blepharospasm

**Ear and Labyrinth Disorders**
Vertigo

**Gastrointestinal Disorders**
Toothache, Tongue spasm

**Skin and Subcutaneous Tissue Disorders**
Eczema

**Musculoskeletal, Connective Tissue, and Bone Disorders**
Buttock pain

**Infections and Infestations**
Lower respiratory tract infection, Infection, Gastroenteritis, Subcutaneous abscess

**Injury and Poisoning**
Fall

**Vascular Disorders**
Hypertension

**General Disorders and Administration Site Conditions**
Pain
Psychiatric Disorders
Depression

Class effects
As with other antipsychotics, very rare cases of QT prolongation have been reported postmarketing with risperidone. Other class-related cardiac effects reported with antipsychotics which prolong QT interval include ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia, sudden death, cardiac arrest and Torsades de Pointes.

Venous thromboembolism
Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis, have been reported with antipsychotic drugs (frequency unknown).

Weight gain
The proportions of Risperidone and placebo-treated adult patients with schizophrenia meeting a weight gain criterion of ≥7% of body weight were compared in a pool of 6- to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for Risperidone (18%) compared to placebo (9%). In a pool of placebo-controlled 3-week studies in adult patients with acute mania, the incidence of weight increase of ≥7% at endpoint was comparable in the Risperidone (2.5%) and placebo (2.4%) groups, and was slightly higher in the active-control group (3.5%).

In a population of children and adolescents with conduct and other disruptive behaviour disorders, in long-term studies, weight increased by a mean of 7.3 kg after 12 months of treatment. The expected weight gain for normal children between 5-12 years of age is 3 to 5 kg per year. From 12-16 years of age, this magnitude of gaining 3 to 5 kg per year is maintained for girls, while boys gain approximately 5 kg per year.

Additional information on special populations
Adverse drug reactions that were reported with higher incidence in elderly patients with dementia or paediatric patients than in adult populations are described below:

Elderly patients with dementia
Transient ischaemic attack and cerebrovascular accident were ADRs reported in clinical trials with a frequency of 1.4% and 1.5%, respectively, in elderly patients with dementia. In addition, the following ADRs were reported with a frequency ≥5% in elderly patients with dementia and with at least twice the frequency seen in other adult populations: urinary tract infection, peripheral oedema, lethargy, and cough.

Paediatric patients
The following ADRs were reported with a frequency ≥5% in paediatric patients (5 to 17 years) and with at least twice the frequency seen in clinical trials in adults: somnolence/sedation, fatigue, headache, increased appetite, vomiting, upper respiratory tract infection, nasal congestion, abdominal pain, dizziness, cough, pyrexia, tremor, diarrhoea, and enuresis.

4.9 Overdose
Symptoms
In general, reported signs and symptoms have been those resulting from an exaggeration of the known pharmacological effects of risperidone. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, QT-prolongation and convulsions have been reported. Torsade de Pointes has been reported in association with combined overdose of risperidone and paroxetine.

In case of acute overdose, the possibility of multiple drug involvement should be considered.

Treatment
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 only when drug intake was less than one hour before. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to Risperidone Tablets. Therefore appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, an anticholinergic medicinal product should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antipsychotics, ATC code: N05AX08

Mechanism of action
Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 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, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical antipsychotics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

Pharmacodynamic effects

Schizophrenia
The efficacy of risperidone in the short-term treatment of schizophrenia was established in four studies, 4- to 8-weeks in duration, which enrolled over 2500 patients who met DSM-IV criteria for schizophrenia. In a 6-week, placebo-controlled trial involving titration of risperidone in doses up to 10 mg/day administered twice daily, risperidone was superior to placebo on the Brief Psychiatric Rating Scale (BPRS) total score. In an 8-week, placebo-controlled trial involving four fixed doses of risperidone (2, 6, 10, and 16 mg/day, administered twice daily), all four risperidone groups were superior to placebo on the Positive and Negative Syndrome Scale (PANSS) total score. In an 8-week, dose comparison trial involving five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day administered twice daily), the 4, 8, and 16 mg/day risperidone dose groups were superior to the 1 mg risperidone dose group on PANSS total score. In a 4-week, placebo-controlled dose comparison trial involving two fixed doses of risperidone (4 and 8 mg/day administered once daily), both risperidone dose groups were superior to placebo on several PANSS measures, including total PANSS and a response measure (>20% reduction in PANSS total score). In a longer-term trial, adult outpatient’s predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medicinal product were randomised to risperidone 2 to 8 mg/day or to haloperidol for 1 to 2 years of observation for relapse. Patients receiving risperidone experienced a significantly longer time to relapse over this time period compared to those receiving haloperidol.

Manic episodes in bipolar disorder
The efficacy of risperidone monotherapy in the acute treatment of manic episodes associated with bipolar I disorder was demonstrated in three double-blind, placebo-controlled monotherapy studies in approximately 820 patients who had bipolar I disorder, based on DSM-IV criteria. In the three studies, risperidone 1 to 6 mg/day (starting dose 3 mg in two studies and 2 mg in one study) was shown to be significantly superior to placebo on the pre-specified primary endpoint, i.e., the change from baseline in total Young Mania Rating Scale (YMRS) score at Week 3. Secondary efficacy outcomes were generally consistent with the primary outcome. The percentage of patients with a decrease of ≥50% in total YMRS score from baseline to the 3-week endpoint was significantly higher for risperidone than for placebo. One of the three studies included a haloperidol arm and a 9-week double-blind maintenance
phase. Efficacy was maintained throughout the 9-week maintenance treatment period. Change from baseline in total YMRS showed continued improvement and was comparable between risperidone and haloperidol at Week 12.

The efficacy of risperidone in addition to mood stabilisers in the treatment of acute mania was demonstrated in one of two 3-week double-blind studies in approximately 300 patients who met the DSM-IV criteria for bipolar I disorder. In one 3-week study, risperidone 1 to 6 mg/day starting at 2 mg/day in addition to lithium or valproate was superior to lithium or valproate alone on the pre-specified primary endpoint, i.e., the change from baseline in YMRS total score at Week 3. In a second 3-week study, risperidone 1 to 6 mg/day starting at 2 mg/day, combined with lithium, valproate, or carbamazepine was not superior to lithium, valproate, or carbamazepine alone in the reduction of YMRS total score. A possible explanation for the failure of this study was induction of risperidone and 9-hydroxy-risperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxy-risperidone. When the carbamazepine group was excluded in a post-hoc analysis, risperidone combined with lithium or valproate was superior to lithium or valproate alone in the reduction of YMRS total score.

Persistent aggression in dementia
The efficacy of risperidone in the treatment of Behavioural and Psychological Symptoms of Dementia (BPSD), which includes behavioural disturbances, such as aggressiveness, agitation, psychosis, activity, and affective disturbances was demonstrated in three double-blind, placebo-controlled studies in 1150 elderly patients with moderate to severe dementia. One study included fixed risperidone doses of 0.5, 1, and 2 mg/day. Two flexible-dose studies included risperidone dose groups in the range of 0.5 to 4 mg/day and 0.5 to 2 mg/day, respectively. Risperidone showed statistically significant and clinically important effectiveness in treating aggression and less consistently in treating agitation and psychosis in elderly dementia patients (as measured by the Behavioural Pathology in Alzheimer's Disease Rating Scale [BEHAVE-AD] and the Cohen-Mansfield Agitation Inventory [CMAI]). The treatment effect of risperidone was independent of Mini-Mental State Examination (MMSE) score (and consequently of the severity of dementia); of sedative properties of risperidone; of the presence or absence of psychosis; and of the type of dementia, Alzheimer’s, vascular, or mixed. (See also section 4.4)

Conduct disorder
The efficacy of risperidone in the short-term treatment of disruptive behaviours was demonstrated in two double-blind placebo-controlled studies in approximately 240 patients 5 to 12 years of age with a DSM-IV diagnosis of disruptive behaviour disorders (DBD) and borderline intellectual functioning or mild or moderate mental retardation/learning disorder. In the two studies, risperidone 0.02 to 0.06 mg/kg/day was significantly superior to placebo on the pre-specified primary endpoint, i.e., the change from baseline in the Conduct Problem subscale of the Nisonger-Child Behaviour Rating Form (N-CBRF) at Week 6.

5.2 Pharmacokinetic properties
Risperidone is metabolised to 9-hydroxy-risperidone, which has a similar pharmacological activity to risperidone (see Biotransformation and Elimination).

Absorption
Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) compared with a solution. The absorption is not affected by food and thus risperidone can be given with or without meals. Steady-state of risperidone is reached within 1 day in most patients. Steady-state of 9-hydroxy-risperidone is reached within 4-5 days of dosing.

Distribution
Risperidone is rapidly distributed. The volume of distribution is 1-2 l/kg. In plasma, risperidone is bound to albumin and alpha1-acid glycoprotein. The plasma protein binding of risperidone is 90% that of 9-hydroxy-risperidone is 77%.
**Biotransformation and elimination**

Risperidone is metabolised by CYP 2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxy-risperidone form the active antipsychotic fraction. CYP 2D6 is subject to genetic polymorphism. Extensive CYP 2D6 metabolisers convert risperidone rapidly into 9-hydroxy-risperidone, whereas poor CYP 2D6 metabolisers convert it much more slowly. Although extensive metabolisers have lower risperidone and higher 9-hydroxy-risperidone concentrations than poor metabolisers, the pharmacokinetics of risperidone and 9-hydroxy-risperidone combined (i.e., the active antipsychotic fraction), after single and multiple doses, are similar in extensive and poor metabolisers of CYP 2D6.

Another metabolic pathway of risperidone is N-dealkylation. *In vitro* studies in human liver microsomes showed that risperidone at clinically relevant concentration does not substantially inhibit the metabolism of medicines metabolised by cytochrome P450 isozymes, including CYP 1A2, CYP 2A6, CYP 2C8/9/10, CYP 2D6, CYP 2E1, CYP 3A4, and CYP 3A5. One week after administration, 70% of the dose is excreted in the urine and 14% in the faeces. In urine, risperidone plus 9-hydroxy-risperidone represent 35-45% of the dose. The remainder is inactive metabolites. After oral administration to psychotic patients, risperidone is eliminated with a half-life of about 3 hours. The elimination half-life of 9-hydroxy-risperidone and of the active antipsychotic fraction is 24 hours.

**Linearity**

Risperidone plasma concentrations are dose-proportional within the therapeutic dose-range.

**Elderly, hepatic and renal impairment**

A single-dose study showed on average a 43% higher active antipsychotic fraction plasma concentrations, a 38% longer half-life and a reduced clearance of the active antipsychotic fraction by 30% in the elderly. Higher active antipsychotic fraction plasma concentrations and a reduced clearance of the active antipsychotic fraction by on average 60% were observed in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency, but the mean free fraction of risperidone in plasma was increased by about 35%.

**Paediatric patients**

The pharmacokinetics of risperidone, 9-hydroxy-risperidone and the active antipsychotic fraction in children are similar to those in adults.

**Gender, race and smoking habits**

A population pharmacokinetic analysis revealed no apparent effect of gender, race or smoking habits on the pharmacokinetics of risperidone or the active antipsychotic fraction.

**5.3 Preclinical safety data**

In (sub) chronic toxicity studies, in which dosing was started in sexually immature rats and dogs, dose-dependant effects were present in male and female genital tract and mammary gland. These effects were related to the increased serum prolactin levels, resulting from the dopamine D₂-receptor blocking activity of risperidone. In addition, tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Risperidone was not teratogenic in rat and rabbit. In rat reproduction studies with risperidone, adverse effects were seen on mating behaviour of the parents, and on the birth weight and survival of the offspring. In rats, intrauterine exposure to risperidone was associated with cognitive deficits in adulthood. Other dopamine antagonists, when administered to pregnant animals, have caused negative effects on learning and motor development in the offspring.

In a toxicity study in juvenile rats, increased pup mortality and a delay in physical development was observed. In a 40-week study with juvenile dogs, sexual maturation was delayed. Based on AUC, long bone growth was not affected in dogs at 3.6-times the maximum human exposure in adolescents (1.5 mg/day); while effects on long bones and sexual maturation were observed at 15 times the maximum human exposure in adolescents.
Risperidone was not genotoxic in a battery of tests. In oral carcinogenicity studies of risperidone in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were seen. These tumours can be related to prolonged dopamine D2 antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown. In vitro and in vivo, animal models show that at high doses risperidone may cause QT interval prolongation, which has been associated with a theoretically increased risk of torsade de pointes in patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

**Tablet core**
- Lactose monohydrate
- Cellulose microcrystalline (E 460)
- Maize starch
- Starch pregelatinised
- Sodium Lauryl Sulphate
- Silica, Colloidal anhydrous
- Magnesium Stearate

**Film-coating**
- Hypromellose (E 464)
- Purified Talc (E 555B)
- Titanium dioxide (E 171)
- Macrogol – 6000 (E 490)

Film-coating for 0.5mg strength additionally contains: Red Iron Oxide (E 172)

Film-coating for 2mg strength additionally contains: Sunset yellow (E 110)

Film-coating for 3mg strength additionally contains: Quinoline yellow (E 104)

Film-coating for 4mg strength additionally contains: Quinoline yellow (E 104) and Indigo carmine (E 132)

Film-coating for 6mg strength additionally contains: Sunset yellow (E 110) and Quinoline yellow (E 104)

6.2 Incompatibilities

None

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

<table>
<thead>
<tr>
<th>Strength</th>
<th>Container</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5mg</td>
<td>PVC / Al blister, pack size of 20 tablets</td>
</tr>
<tr>
<td>1mg</td>
<td>PVC / Al blister, pack size of 20 and 60 tablets</td>
</tr>
<tr>
<td>2, 3 and 4mg</td>
<td>PVC / Al blister, pack size of 60 tablets</td>
</tr>
<tr>
<td>6mg</td>
<td>PVC / Al blister, pack size of 28 tablets</td>
</tr>
</tbody>
</table>
6.6 Special precautions for disposal
None

7 MARKETING AUTHORISATION HOLDER
BRISTOL LABORATORIES LIMITED
Unit 3, Canalside, Northbridge Road
Berkhamsted, Herts, HP4 1EG

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0210
PL 17907/0211
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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/01/2012

10 DATE OF REVISION OF THE TEXT
17/01/2012
PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

RISPERIDONE 0.5MG, 1MG, 2MG, 3MG, 4MG AND 6MG FILM-COATED TABLETS

Read all of this leaflet carefully before you start taking this medicine. Even if you have used this medicine or a similar product before, you should read this leaflet carefully as the information may have changed.

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

In this leaflet:
1. What Risperidone Tablets are and what they are used for
2. What you need to know before you take Risperidone Tablets
3. How to take Risperidone Tablets
4. Possible side effects
5. How to store Risperidone Tablets
6. Contents of the pack and other information

1. What Risperidone Tablets are and what they are used for

Risperidone belongs to a group of medicines called “antipsychotics”.

It is used to treat the following:
- Schizophrenia, where you may see, hear or feel things that are not there, believe things that are not true or feel unusually suspicious, or confused
- Mania, where you may feel very excited, elated, agitated, enthusiastic or hyperactive. Mania occurs in an illness called “bipolar disorder”
- Short-term treatment (up to 6 weeks) of long-term aggression in people with Alzheimer’s dementia, who harm themselves or others. Alternative (non drug) treatments should have been used previously
- Short-term treatment (up to 6 weeks) of long-term aggression in intellectually disabled children (at least 5 years of age) and adolescents with conduct disorder.

2. What you need to know before you take Risperidone Tablets

Do not take Risperidone if you:
- are allergic (hypersensitive) to risperidone or any of the other ingredients (these are listed in Section 6, Further Information).

Warnings and precautions
Check with your doctor or pharmacist before taking Risperidone if you:
- have a heart problem. Examples include an irregular heart rhythm, or if you are prone to low blood pressure or if you are using medicines for your blood pressure. It may cause low blood pressure. Your dose may need to be adjusted
- have ever experienced involuntary movements of the tongue, mouth and face
- have ever had a condition whose symptoms include high temperature, muscle stiffness, sweating or a lowered level of consciousness (also known as Neuroleptic Malignant Syndrome)
- know of any factors which would favour you having a stroke, such as high blood pressure, cardiovascular disorder or blood vessel problems in the brain
- have Parkinson’s disease or dementia
- are diabetic
- have epilepsy
- are a man and you have ever had a prolonged or painful erection, if you experience this while taking Risperidone, contact your doctor straight away
- have problems controlling your body temperature or overheating
- have kidney problems
- have liver problems
- have an abnormally high level of the hormone prolactin in your blood or if you have a tumour, which is possibly dependent on prolactin.
- or someone else in your family has a history of blood clots, as antipsychotics have been associated with formation of blood clots.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Risperidone.

Risperidone may cause you to gain weight. Significant weight gain may adversely affect your health. Your doctor should regularly measure your body weight.

As diabetes mellitus or worsening of pre-existing diabetes mellitus have been seen with patients taking Risperidone, your doctor should check for signs of high blood sugar. In patients with pre-existing diabetes mellitus blood glucose should be monitored regularly.

Elderly people with dementia:
In elderly patients with dementia, there is an increased risk of stroke. You should not take risperidone if you have dementia caused by stroke.

During treatment with risperidone you should frequently see your doctor. Medical treatment should be sought straight away if you or your carer notice a sudden change in your mental state or sudden weakness or numbness of your face, arms or legs, especially on one side, or slurred speech, even for a short period of time. These may be signs of a stroke.

Children and adolescents
Before treatment is started in conduct disorder, other causes of aggressive behaviour should have been ruled out.

If during treatment with risperidone tiredness occurs, a change in the time of administration might improve attention difficulties.
Other medicines and Risperidone
Tell your doctor or pharmacist if you are taking or have recently taken any other medicine, even those not prescribed, for example, herbal remedies and health supplements from a pharmacy, supermarket or health food shop, as these tablets may interact with this medicine.

The following medicines can affect Risperidone:
- medicines that work on your brain such as to help you calm down (benzodiazepines) or some medicines for pain (opioids), medicines for allergy (some antihistamines), as risperidone may increase the sedative effect of all of these
- medicines that may change the electrical activity of your heart, such as medicines for malaria, heart rhythm problems (such as quinidine), allergies (anti-histamines), some antidepressants or other medicines for mental problems
- medicines that cause a slow heart beat
- medicines that cause low blood potassium (e.g. certain diuretics)
- medicines to treat elevated blood pressure. Risperidone can lower blood pressure
- medicines for Parkinson’s disease (such as levodopa)
- water tablets (diuretics) used for heart problems or swelling of parts of your body due to a build up of too much fluid (such as furosemide or chlorothiazide).

Risperidone taken by itself or with furosemide may have an increased risk of stroke or death in elderly people with dementia.

The following medicines may reduce the effect of risperidone
- rifampicin (a medicine for treating some infectious)
- carbamazepine, phenytoin (medicines for epilepsy)
- pheobarbitual

If you start or stop taking such medicines you may need a different dose of Risperidone.

The following medicines may increase the effect of risperidone
- quinidine (used for certain types of heart disease)
- antidepressants such as paroxetine, fluoxetine, tricyclic antidepressants
- medicines known as beta blockers (used to treat high blood pressure)
- phenothiazines (e.g. used to treat psychosis or to calm down)
- cimetidine, ranitidine (blockers of the acidity of stomach)

If you start or stop taking such medicines you may need a different dose of risperidone. If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Risperidone.

Risperidone with food, drink and alcohol
You can take this medicine with or without food. You should avoid drinking alcohol when taking Risperidone.

Pregnancy, breast-feeding and fertility
- Talk to your doctor before using Risperidone if you are pregnant, trying to become pregnant or breast feeding. Your doctor will decide if you can take it.
- The following symptoms may occur in newborn babies, of mothers that have used Risperidone in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

Ask your doctor or pharmacist for advice before taking any product.

Driving and using machines
- Dizziness, tiredness, and vision problems may occur during treatment with Risperidone. Do not drive or use any tools or machines without talking to your doctor first.

Risperidone contains
- Risperidone tablets contain Lactose. If your doctor has told you that you are intolerant of some sugars, discuss it with them before taking this medicine.
- The 2 mg and 6 mg Risperidone tablets contain a colour called Sunset Yellow (E110) which may cause allergic reactions. Allergy is more common in those people who are allergic to aspirin.

3. How to take Risperidone Tablets
- Always take these tablets exactly as advised by your doctor. Check with doctor or pharmacist if you are not sure.
- Your doctor will tell you how much medicine to take and for how long. This will depend on your condition and varies from person to person.
- The tablets should be swallowed with a drink of water.
- The score line is to only facilitate the breaking for ease of swallowing and not to divide into equal doses.

For the treatment of schizophrenia

Adults
- The usual starting dose is 2 mg per day, this may be increased to 4 mg per day on the second day.
- Your dose may then be adjusted by your doctor depending on how you respond to the treatment.
- Most people feel better with daily doses of 4 to 6 mg.
- This total daily dose can be divided into either one or two doses a day. Your doctor will tell you which is the best for you.

Elderly people
- Your starting dose will normally be 0.5 mg twice a day.
- Your dose may then be gradually increased by your doctor to 1 mg to 2 mg twice a day.
- Your doctor will tell you which is the best for you.

Children and adolescents
- Children and adolescents under 18 years old should not be treated with Risperidone for schizophrenia.
For the treatment of mania

Adults
- Your starting dose will usually be 2 mg once a day.
- Your dose may then be gradually adjusted by your doctor depending on how you respond to the treatment.
- Most people feel better with doses of 1 to 6 mg once a day.

Elderly people
- Your starting dose will usually be 0.5 mg twice a day.
- Your dose may then be gradually adjusted by your doctor to 1 mg to 2 mg twice a day depending on how much you respond to the treatment.

Children and adolescents
- Children and adolescents under 18 years old should not be treated with Risperidone for mania.

For the treatment of long-standing aggression in people with Alzheimer's dementia

Adults (including elderly people)
- Your starting dose will normally be 0.25 mg twice a day.
- Your dose may then be gradually adjusted by your doctor depending on how you respond to the treatment.
- Most people feel better with 0.5 mg twice a day. Some patients may need 1 mg twice a day.
- Treatment duration in patients with Alzheimer's dementia should be not more than 6 weeks.

For the treatment of conduct disorder in children and adolescents

The dose will depend on your child’s weight:
- For children who weigh less than 50 kg:
  - The starting dose will normally be 0.25 mg once a day.
  - The dose may be increased every other day in steps of 0.25 mg per day.
  - The usual maintenance dose is 0.25 mg to 0.75 mg once a day.
- For children who weigh 50 kg or more:
  - The starting dose will normally be 0.5 mg once a day.
  - The dose may be increased every other day in steps of 0.5 mg per day.
  - The usual maintenance dose is 0.5 mg to 1.5 mg once a day.
- Treatment duration in patients with conduct disorder should be not more than 6 weeks.
- Children under 5 years old should not be treated with Risperidone for conduct disorder.

People with kidney or liver problems
Regardless of the disease to be treated, all starting doses and following doses of Risperidone should be halved. Dose increases should be slower in these patients. Risperidone should be used with caution in this patient group.

If you take more Risperidone Tablets than you should
See a doctor straight away. Take the medicine pack with you.
In case of overdose you may feel sleepy or tired, or have abnormal body movements, problems standing and walking, feel dizzy due to low blood pressure, or have abnormal heartbeats or fits.

If you forget to take a dose of Risperidone Tablets
If necessary, take the missed dose when you remember however, if it is almost time for your next dose, skip the missed dose and then take your next dose when it is due.
Do not take a double dose to make up the forgotten dose.

If you stop taking Risperidone Tablets
You should not stop taking this medicine unless told to do so by your doctor. Your symptoms may return. If your doctor decides to stop this medicine, your dose may be decreased gradually over a few days.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

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

Tell your doctor immediately if you:
- Experience blood clots in the veins, especially in the legs (symptoms include swelling, pain, and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty breathing. If you notice any of these symptoms seek medical advice immediately.
- Have dementia and experience a sudden change in your mental state or sudden weakness or numbness of your face, arms or legs, especially on one side, or slurred speech, even for a short period of time. These may be signs of a stroke.
- Experience fever, muscle stiffness, sweating or a lowered level of consciousness (a disorder called “Neuroleptic Malignant Syndrome”). Immediate medical treatment may be needed.
- Are a man and experience prolonged or painful erection. This is called priapism. Immediate medical treatment may be needed.
- Experience involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of risperidone may be needed.

The following side effects may happen:
- Very common: affects more than 1 user in 10
  - Common: affects 1 to 10 users in 100
  - Uncommon: affects 1 to 10 users in 1,000
  - Rare: affects 1 to 10 users in 10,000
  - Very rare: affects less than 1 user in 10,000
- Not known: frequency cannot be estimated from the available data.

Very Common (affects more than 1 user in 10):
- Parkinsonism. This is a medical term that includes many symptoms. Each individual symptom may occur less frequently than 1 in 10 people. Parkinsonism includes: increase in saliva secretion, or watery mouth, muscular skeletal stiffness, drooling.
jerks when bending the limbs, slow, reduced or impaired body movements, no expression on the face, muscle tightness, stiffness, muscle stiffness, small shuffling, hurried steps and lack of normal arm movements when walking, persistent blinking in response to tapping of the forehead (as abnormal reflex)
• Headache, difficulty falling or staying asleep.

Common (affects 1 to 10 users in 100):
• Drowsiness, fatigue, restlessness, inability to sit still, irritability, anxiety, sleepiness, dizziness, poor attention, feeling exhausted, sleep disorder
• Vomiting, diarrhoea, constipation, nausea, increased appetite, abdominal pain or discomfort, sore throat, dry mouth
• Weight increased, increase in body temperature, decreased appetite
• Difficulty breathing, lung infection (pneumonia), flu, infection of the breathing passages, blurred vision, nose congestion, nose bleeding, cough
• Urinary tract infection, bed wetting
• Muscle spasm, involuntary movements of face or arms and legs, joint pain, back pain, swelling of arms and legs, pain in arms and legs
• Rash, skin redness
• Fast breathing heart, chest pain
• Blood prolactin hormone level increased

Uncommon (affects 1 to 10 users in 1000):
• Excessive drinking of water, stool incontinence, thirsty, very hard faeces, hoarseness or voice disorder
• Diabetes mellitus, high blood sugar.
• Lung infection caused by inhaling of food into the breathing passages, bladder infection, pink eye, sinus infection, viral infection, ear infection, toxic infection, infection under the skin, eye infection, stomach infection, eye discharge, yeast infection of nails
• Abnormal electrical conduction of the heart, drop in blood pressure after standing, low blood pressure, feeling dizzy after changing body position, abnormal electric activity tracing of the heart (ECG), abnormal heart rhythm, awareness of heart beating, heart rate increased or decreased
• Urinary incontinence, pain when passing urine, frequent passing of urine
• Confused, disturbance in attention, low level of consciousness, excessive sleep, nervousness, elated mood (mania), lack of energy and interest
• Liver enzymes increased, white blood cell count decreased, low haemoglobin or red blood cell count (anaemia), increase in eosinophils (special white blood cells), blood creatinine phosphokinase increased, decrease in platelets (blood cells that help you stop bleeding)
• Muscle weakness, muscle pain, ear pain, neck pain, joint swelling, abnormal posture, joint stiffness, musculoskeletal chest pain, chest discomfort
• Skin lesion, skin disorder, dry skin, intense itching of skin, acne, hair loss, skin inflammation caused by nates, skin discoloration, thickening of skin, flushing, reduced skin sensitivity to pain or touch, inflammation of oily skin
• No menstruation, sexual dysfunction, erectile dysfunction, ejaculation disorder, breast discharge, enlargement of breast in men, decreased sexual drive, irregular menstruation, vaginal discharge
• Fatigue, guilt disturbance, sluggishness, decreased appetite resulting in malnutrition and low body weight, feeling out of sorts, balance disorder, allergy, oedema, speech disorder, chills, abnormal coordination
• Painful oversensitivity to light, increased blood flow to the eye, eye swelling, dry eye, increase in tears
• Breathing passage disorder, lung congestion, crackly lung noise, congestion of breathing passages, trouble speaking, difficulty swallowing, cough with sputum, coarse/whistling sound during breathing, flu-like illness, sinus congestion
• Unresponsive to stimuli, loss of consciousness, sudden swelling of lips and eyes along with difficulty breathing, sudden weakness or numbness of the face, arms, or legs, especially on one side, or instances of slurred speech that last for less than 24 hours (these are called mini-strokes or strokes), involuntary movements of face, arms, or legs, tingling in ears, face, oedema.
• Inability to urinate or incomplete emptying of the bladder.

Rare (affects 1 to 10 users in 10,000):
• Inability to reach orgasm, menstrual disorder
• Dandruff
• Drug allergy, coldness in arms and legs, lip swelling, lip inflammation
• Glaucoma, reduced visual clarity, eyelid margin crusting, eye rolling
• Lack of emotion
• Change in consciousness with increased body temperature and twitching of muscles, oedema all over the body, drug withdrawal syndrome, decreased body temperature
• Fast shallow breathing, trouble breathing during sleep, chronic cough, dry cough
• Obstruction of intestine
• Reduced blood flow to the brain
• Decrease in white blood cells, inappropriate secretion of the hormone that controls urine volume
• Breakdown of muscle fibers and pain in muscles (rhabdomyolysis), movement disorder
• Coma due to uncontrolled diabetes
• Yellowing of the skin and the eyes (jaundice)
• Inflammation of the pancreas
• Low blood sugar.

Very rare (affects less than 1 user in 10,000):
• Life threatening complications of uncontrolled diabetes.
UKPAR Risperidone 0.5, 1, 2, 3, 4 and 6mg Film-coated Tablets

Unknown frequency of occurrence (frequency cannot be estimated from the available data):
• Severe allergic reaction resulting in difficulty in breathing and shock
• No granulocytes (a type of white blood cell) to help you against infection
• Prolonged and painful erection
• Dangerously excessive intake of water.

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

5. How to store Risperidone Tablets
• Keep the medicine out of the sight and reach of children.
• Do not use the tablets after the expiry date printed on the pack.
• Do not store above 25°C. Store in the original package to protect the tablets from moisture.
• Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Risperidone Tablets contains
• The active substance is risperidone. Each Risperidone film-coated tablet contains either 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg or 6 mg of risperidone.

The other ingredients are:
• Risperidone film-coated tablets:
  Tablet core: Lactose monohydrate, Cellulose microcrystalline (E460), Maize starch, Starch pregelatinised, Sodium Lauryl Sulphate, Silica Colloidal anhydrous, Magnesium Stearate
  Film-Coating: Hypromellose (E464), Purified Talc (E 553B), Titanium dioxide (E 171), Macrogol – 6000 (E 490).

Also Contains:
• Risperidone 0.5 mg film-coated tablets:
  Film-Coating: Red Ferric Oxide (E172)
• Risperidone 2 mg film-coated tablets:
  Film-Coating: Sunset Yellow (E110)
• Risperidone 3 mg film-coated tablets:
  Film-Coating: Quinoline Yellow (E104)
• Risperidone 4 mg film-coated tablets:
  Film-Coating: Quinoline Yellow (E104), Indigo Carmine (E132)
• Risperidone 6 mg film-coated tablets:
  Film-Coating: Quinoline Yellow (E104), Sunset Yellow (E110)

What the tablets looks like and contents of the pack:
• Risperidone 0.5 mg Film-coated tablets as Red coloured, caplet, biconvex tablets with “0.5” embossed on one side and “B/L” embossed on other side.
• Risperidone 1 mg Film-coated tablets as White coloured, caplet, biconvex tablets with “1” embossed on one side and “B/L” embossed on other side.
• Risperidone 2 mg Film-coated tablets as Orange coloured caplet, biconvex tablets with “2” embossed on one side and “B/L” embossed on other side.
• Risperidone 3 mg Film-coated tablets as Yellow coloured, caplet, biconvex tablets with “3” embossed on one side and “B/L” embossed on other side.
• Risperidone 4 mg Film-coated tablets as Green coloured, caplet, biconvex tablets with “4” embossed on one side and “B/L” embossed on other side.
• Risperidone 6 mg Film-coated tablets as Yellow coloured, caplet, biconvex tablets with “6” embossed on one side and “B/L” embossed on other side.
• Risperidone 0.5 mg Tablets are packed in blister pack of 20 tablets.
• Risperidone 1mg Tablets are packed in blister pack of 20 and 60 tablets.
• Risperidone 2mg, 3mg & 4mg Tablets are packed in blister pack of 60 tablets.
• Risperidone 6mg Tablets are packed in blister pack of 28 tablets.

Marketing Authorisation Holder and Manufacturer:
Name and address: Bristol Laboratories Ltd., Unit 3, Canal side, Northbridge Road, Berkhamsted, Hertfordshire, HP4 1EJ, United Kingdom.
Telephone: 0044 (0)1442 209922
Fax: 0044 (0)1442 873717
E-mail: info@bristol-labs.co.uk

Risperidone 0.5mg film-coated Tablets; PL 17907/0210
Risperidone 1mg film-coated Tablets; PL 17907/0211
Risperidone 2mg film-coated Tablets; PL 17907/0212
Risperidone 3mg film-coated Tablets; PL 17907/0213
Risperidone 4mg film-coated Tablets; PL 17907/0214
Risperidone 6mg film-coated Tablets; PL 17907/0215

This leaflet was last revised in November 2011.

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LABELLING

Risperidone 0.5mg Film-coated Tablets - PL 17907/0210

Carton
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Risperidone 1mg Film-coated Tablets - PL 17907/0211

Carton – pack size 20
Carton – pack size 60
Risperidone 2mg Film-coated Tablets - PL 17907/0212

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

Braille

Blister foil
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