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

PL 36390/0044-9

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency granted STD Chemicals Limited, Marketing Authorisations for the medicinal products, Risperidone 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 6 mg Film-Coated Tablets (PL 36390/0044-49), on 16 June 2011. The products are prescription-only medicines (POM) and are 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
- 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 management (up to 6 weeks) of long-term aggression in intellectually disabled children (at least 5 years of age) and adolescents with conduct disorder

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

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

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted STD Chemicals Limited, Marketing Authorisations for the medicinal products, Risperidone 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg & 6 mg Film-Coated Tablets (PL 36390/0044-49), on 16 June 2011. The products are prescription-only medicines (POM).

These are simple, abridged, ‘informed consent’ applications submitted according to Article 10c of EC Directive 2001/83 (as amended), cross referring to Risperidone 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg & 6 mg Film-Coated Tablets (PL 08137/0160-0165), authorised to Neolab Limited on 19 October 2010.

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

No new data were submitted nor were they necessary for these simple applications, as the data are identical to that of the previously granted cross-reference products, Risperidone 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg & 6 mg Film-Coated Tablets (PL 08137/0160-0165), authorised to Neolab Limited on 19 October 2010.

A Public Assessment Report has been generated for the cross-reference products; Risperidone 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg & 6 mg Film-Coated Tablets (PL 08137/0160-0165).
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 36390/0044-49

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

ACTIVE: Risperidone

COMPANY NAME: STD Chemicals Limited

E.C. ARTICLE: Article 10c of Directive 2001/83/EC

LEGAL STATUS: POM

1. INTRODUCTION

These are simple, informed consent applications for Risperidone 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 6 mg Film-Coated Tablets submitted under Article 10c of Directive 2001/83/EC as amended. The applications cross-refer to Risperidone 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 6 mg Film-Coated Tablets (PL 08137/0160-0165) authorised to Neolab Limited on 19 October 2010. The current applications are considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed names of the products are Risperidone 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 6 mg Film-Coated Tablets. The products have been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

Each tablet contains the active substance, risperidone, the amount specified in the product name.

The finished products are licensed for marketing in blister strips comprising of polyvinylchloride (PVC)/polyethylene (PE)/polyvinylidene chloride (PVdC)/aluminium foil. The blister strips are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons and are available in pack sizes of 60 tablets with the exception of the 0.5 mg and 6mg strength tablets, which are only available in pack sizes of 20 tablets.

The proposed shelf-life is 3 years. Storage conditions for the products are “Store in the original package”. The shelf-life and storage conditions are consistent with the details registered for the cross-reference product.

2.3 Legal status

On approval, the products will be available as prescription-only medicines (POM).

2.4 Marketing authorisation holder/Contact Persons/Company

STD Chemicals Limited, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW, UK.

The Qualified Person (QP) responsible for pharmacovigilance is stated and his curriculum vita has been provided.

2.5 Manufacturers

The proposed manufacturing sites are consistent with those registered for the cross-reference products and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed compositions are consistent with the details registered for the cross-reference products.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specifications are in-line with the details registered for the cross-reference products.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference products.

2.10 TSE Compliance
The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed products. This is consistent with the cross-reference products.

3. EXPERT REPORTS
Satisfactory quality overall summary and curriculum vitae of the expert are provided.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The full description and appearance of each tablet strength, can be found in Section 3 (Pharmaceutical Form) of the Summary of Product Characteristics (SmPCs) and are consistent with that of the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The approved SmPCs are consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET (PIL)/CARTON
PIL
The PIL is satisfactory and in line with the approved SmPCs. It has been prepared according to the Quality Review of Documents (QRD) template and is consistent with the details registered for the cross-reference products.

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.

Carton and label
Mock-ups of the labelling have been provided and are satisfactory. The approved labelling artwork complies with statutory requirements. In line with current legislation the applicant has included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.
7. CONCLUSIONS
The data submitted with these applications are acceptable. Marketing Authorisations were, therefore, granted.
NON-CLINICAL ASSESSMENT

These are simple, abridged, ‘informed consent’ applications made under Article 10c of EC Directive 2001/83 (as amended). These applications are identical to the reference products Risperidone 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg & 6 mg Film-Coated Tablets (PL 08137/0160-0165) authorised to Neolab Limited, therefore, no new non-clinical data have been supplied with these applications and none are required. A non-clinical overview report has been written by a suitably qualified person and is satisfactory. The CV of the non-clinical expert has been supplied.

The marketing authorisation holder has provided adequate justification for not submitting an Environment Risk Assessment (ERA). As these applications are identical to already authorised reference products, it is not expected that the environmental exposure to risperidone will increase following the marketing approval of the proposed products.
CLINICAL ASSESSMENT

These are simple, abridged, ‘informed consent’ applications made under Article 10c of EC Directive 2001/83 (as amended), cross-referring to Risperidone 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg & 6 mg Film-Coated Tablets (PL 08137/0160-0165) authorised to Neolab Limited.

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

The marketing authorisation holder (MAH) has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are identical to already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, 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.

The MAH has provided a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person 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.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for these applications are consistent with those previously assessed for the cross-reference products and as such have been judged to be satisfactory.

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

EFFICACY
These applications are considered identical to the previously granted licences for Risperidone 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg & 6 mg Film-Coated Tablets (PL 08137/0160-0165) authorised to Neolab Limited.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs, PIL and labelling are satisfactory, and consistent with those for the cross-reference products.

PIL user testing has been carried out and is satisfactory.

Mock-ups of the labelling have been provided and are satisfactory. The approved labelling artwork complies with statutory requirements

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products. Extensive clinical experience with risperidone is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
### STEPS TAKEN FOR ASSESSMENT

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<td>The MHRA received the marketing authorisation applications on 28th January 2011.</td>
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<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 15 February 2011.</td>
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<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 15 February 2011.</td>
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<td>The applicant responded to the MHRA’s requests, providing further information on 9th May 2011.</td>
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<td>The applications were determined on 16th June 2011.</td>
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RISPERIDONE 0.5 MG, 1 MG, 2 MG, 3 MG, 4 MG & 6 MG FILM-COATED TABLETS

PL 36390/0044-9

STEPS TAKEN AFTER ASSESSMENT

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SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Risperidone 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg and 6 mg Film-Coated Tablets (PL 36390/0044-49) are as follows:

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
   Each film-coated tablet contains 0.5mg of risperidone.
   Each film-coated tablet contains 69.20 mg lactose monohydrate.

   For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
   Film-coated tablet (tablet).

   The tablets are brown coloured, circular, biconvex film-coated tablets, with ‘0.5’ embossed on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
   Risperidone Tablets are indicated for the treatment of schizophrenia.
   Risperidone Tablets are indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders.
   Risperidone Tablets are 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 Tablets are 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 subaverage 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 Tablets 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 are 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 Tablets 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 Tablets 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 Tablets 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 Tablets must be evaluated and justified on an ongoing basis.

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

**Method of administration**

Risperidone Tablets are for oral use. Food does not affect the absorption of Risperidone Tablets. 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 Tablets therapy is initiated is recommended. Also, if medically appropriate, when switching patients from depot antipsychotics, initiate Risperidone Tablets 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

**Overall mortality**
Elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotics, including Risperidone Tablets. In placebo-controlled trials with Risperidone Tablets in this population, the incidence of mortality was 4.0% for Risperidone Tablets-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).

**Concomitant use with furosemide**
In the Risperidone Tablets 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)**
In placebo-controlled trials in elderly patients with dementia there was a significantly higher incidence (approximately 3-fold increased) of CVAEs, such as stroke (including fatalities) and transient ischaemic attack in patients treated with Risperidone Tablets compared with patients treated with placebo (mean age 85 years; range 73 to 97). The pooled data from six placebo-controlled studies 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 Tablets 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 Tablets 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 Tablets 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 Tablets 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 Tablets, should be discontinued.

**Parkinson's disease and dementia with Lewy bodies**
Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including Risperidone Tablets, 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.

**Hyperglycemia**
Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with Risperidone Tablets. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

**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 Tablets 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 Tablets 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 Tablets 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 Tablets 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.

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

4.5 Interaction with other medicinal products and other forms of interaction
As with other antipsychotics, caution is advised when prescribing risperidone with medicinal products known to prolong the QT interval, e.g., class Ia antiarrhythmics (e.g., quinidine, dyazopiramid, 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 Tablets 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 Tablets 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 Tablets do not show a clinically relevant effect on the pharmacokinetics of lithium, valproate, digoxin or toprimate.

Potential for other medicinal products to affect Risperidone Tablets.
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 Tablets. 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 Tablets.

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 Tablets in children and adolescents did not alter the pharmacokinetics and efficacy of Risperidone Tablets. See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

Concomitant use of oral Risperidone Tablets 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 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of risperidone in pregnant women. According to postmarketing data reversible extrapyramidal symptoms in the neonate were observed following the use of risperidone during the last trimester of pregnancy. 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). The potential risk for humans is unknown. Therefore, Risperidone Tablets 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 Tablets 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

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Blood prolactin increased&lt;sup&gt;a&lt;/sup&gt;, Weight increased</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Body temperature decreased</td>
</tr>
</tbody>
</table>

#### Cardiac disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Tachycardia</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Atrioventricular block, Bundle branch block, Atrial fibrillation, Sinus bradycardia, Palpitations</td>
</tr>
</tbody>
</table>

#### Blood and lymphatic system disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Anaemia, Thrombocytopenia</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Granulocytopenia</td>
</tr>
<tr>
<td><strong>Not known</strong></td>
<td>Agranulocytosis</td>
</tr>
</tbody>
</table>

#### Nervous system disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very common</strong></td>
<td>Parkinsonism&lt;sup&gt;b&lt;/sup&gt;, Headache</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Akathisia&lt;sup&gt;b&lt;/sup&gt;, Dizziness, Tremor&lt;sup&gt;b&lt;/sup&gt;, Dystonia&lt;sup&gt;b&lt;/sup&gt;, Somnolence, Sedation, Lethargy, Dyskinesia&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Neuroleptic malignant syndrome, Diabetic coma, Cerebrovascular disorder, Cerebral ischaemia, Movement disorder</td>
</tr>
</tbody>
</table>

#### Eye disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Vision blurred</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Conjunctivitis, Ocular hyperaemia, Eye discharge, Eye swelling, Dry eye, Lacrimation increased, Photophobia</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Visual acuity reduced, Eye rolling, Glaucoma</td>
</tr>
</tbody>
</table>

#### Ear and labyrinth disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Ear pain, Tinnitus</td>
</tr>
</tbody>
</table>

#### Respiratory, thoracic and mediastinal disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Dyspnoea, Epistaxis, Cough, Nasal congestion, Pharyngolaryngeal pain</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Wheezing, Pneumonia aspiration, Pulmonary congestion, Respiratory disorder, Rales, Respiratory tract congestion, Dysphonia</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Sleep apnea syndrome, Hyperventilation</td>
</tr>
</tbody>
</table>

#### Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Vomiting, Diarrhoea, Constipation, Nausea, Abdominal pain, Dyspepsia, Dry</td>
</tr>
</tbody>
</table>

MHRA-UKPAR – Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg & 6mg Film-Coated Tablets  PL 36390/0044-9
<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>mouth, Stomach discomfort</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td>Dysphagia, Gastritis, Faecal incontinence, Faecaloma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td>Intestinal obstruction, Pancreatitis, Lip swelling, Cheilitis</td>
</tr>
</tbody>
</table>

### Renal and urinary disorders

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Enuresis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td>Dysuria, Urinary incontinence, Pollakiuria</td>
</tr>
</tbody>
</table>

### Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Rash, Erythema</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td>Angioedema, Skin lesion, Skin disorder, Pruritus, Acne, Skin discolouration,</td>
</tr>
<tr>
<td>Alopecia, Seborrhoeic dermatitis, Dry skin, Hyperkeratosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td>Dandruff</td>
</tr>
</tbody>
</table>

### Musculoskeletal and connective tissue disorders

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Arthralgia, Back pain, Pain in extremity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td>Muscular weakness, Myalgia, Neck pain, Joint swelling, Posture abnormal,</td>
</tr>
<tr>
<td>Joint stiffness, Musculoskeletal chest pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
</tr>
</tbody>
</table>

### Endocrine disorders

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td>Inappropriate antidiuretic hormone secretion</td>
</tr>
</tbody>
</table>

### Metabolism and nutrition disorders

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Increased appetite, Decreased appetite</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td>Anorexia, Polydipsia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very rare</strong></td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not known</strong></td>
</tr>
<tr>
<td>Water intoxication</td>
</tr>
</tbody>
</table>

### Infections and infestations

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Pneumonia, Influenza, Bronchitis, Upper respiratory tract infection, Urinary</td>
</tr>
<tr>
<td>tract infection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td>Sinusitis, Viral infection, Ear infection, Tonsillitis, Cellulitis, Otitis media,</td>
</tr>
<tr>
<td>Eye infection, Localised infection, Acarodermatitis, Respiratory tract</td>
</tr>
<tr>
<td>infection, Cystitis, Onychomycosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td>Otitis media chronic</td>
</tr>
</tbody>
</table>

### Vascular disorders

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td>Hypotension, Orthostatic hypotension, Flushing</td>
</tr>
</tbody>
</table>

### General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Pyrexia, Fatigue, Peripheral oedema, Asthenia, Chest pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td>Face oedema, Gait disturbance, Feeling abnormal, Sluggishness, Influenza like</td>
</tr>
<tr>
<td>illness, Thirst, Chest discomfort, Chills</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td>Generalised oedema, Hypothermia, Drug withdrawal syndrome, Peripheral coldness</td>
</tr>
</tbody>
</table>

### Immune system disorders

<table>
<thead>
<tr>
<th>Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td>Hypersensitivity</td>
</tr>
</tbody>
</table>

MHRA-UKPAR – Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg & 6mg Film-Coated Tablets PL 36390/0044-9
<table>
<thead>
<tr>
<th>Rare</th>
<th>Drug hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Anaphylactic reaction</td>
</tr>
</tbody>
</table>

**Hepatobiliary disorders**

| Rare | Jaundice |

**Reproductive system and breast disorders**

<table>
<thead>
<tr>
<th>Uncommon</th>
<th>Amenorrhoea, Sexual dysfunction, Erectile dysfunction, Ejaculation disorder, Galactorrhoea, Gynaecomastia, Menstrual disorder, Vaginal discharge,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Priapism</td>
</tr>
</tbody>
</table>

**Psychiatric disorders**

<table>
<thead>
<tr>
<th>Very common</th>
<th>Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Anxiety, Agitation, Sleep disorder</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Confusional state, Mania, Libido decreased, Listless, Nervousness</td>
</tr>
<tr>
<td>Rare</td>
<td>Anorgasmia, Blunted affect</td>
</tr>
</tbody>
</table>

Note: Hyperprolactinemia can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhoea, galactorrhea.

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, choreathetosis, 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.

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

<table>
<thead>
<tr>
<th>Additional Adverse Drug Reactions reported with injectable risperidone formulation but not with Oral Risperidone Tablets by System Organ Class</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigations</strong></td>
</tr>
<tr>
<td>Weight decreased, Gamma-glutamyltransferase increased, Hepatic enzyme increased</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
</tr>
<tr>
<td>Bradycardia</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic Disorders</strong></td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
</tr>
<tr>
<td>Paresthesia, Convulsion</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
</tr>
<tr>
<td>Blepharospasm</td>
</tr>
<tr>
<td><strong>Ear and Labyrinth Disorders</strong></td>
</tr>
<tr>
<td>Vertigo</td>
</tr>
<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
</tr>
<tr>
<td>Toothache, Tongue spasm</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
</tr>
<tr>
<td>Eczema</td>
</tr>
<tr>
<td>Musculoskeletal, Connective Tissue, and Bone Disorders</td>
</tr>
<tr>
<td>Buttock pain</td>
</tr>
<tr>
<td>Infections and Infestations</td>
</tr>
<tr>
<td>Lower respiratory tract infection, Infection, Gastroenteritis, Subcutaneous abscess</td>
</tr>
<tr>
<td>Injury and Poisoning</td>
</tr>
<tr>
<td>Fall</td>
</tr>
<tr>
<td>Vascular Disorders</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
</tr>
<tr>
<td>Depression</td>
</tr>
</tbody>
</table>

**Class effects**

As with other atypical 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.

**Weight gain**

The proportions of Risperidone Tablets 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 Tablets (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 Tablets (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 Tablets 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, placebo-controlled 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, dose comparison trial involving five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day administered twice-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 outpatients 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-dependent 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. 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 antagonist 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 points in patients.
Lactose monohydrate  
Sodium starch glycolate (Type A)  
Magnesium stearate  

**Film-coating**  
Opadry 03B56826 Brown  
Constituents of Opadry 03B56826 Brown are:  
Hyromellose (E464)  
Titanium dioxide (E171)  
Polyethylene glycol  
Iron Oxide Red (E172).  

6.2 Incompatibilities  
Not applicable.  

6.3 Shelf life  
3 years.  

6.4 Special precautions for storage  
Store in the original package.  
This medicinal product does not require any special storage conditions.  

6.5 Nature and contents of container  
0.025 mm thickness aluminium foil (heat sealable against PVC with VMCH coating).  
PVC/PE/PVdC film.  
Pack size: 20 tablets.  

6.6 Special precautions for disposal  
No special requirements.  

7 MARKETING AUTHORISATION HOLDER  
STD Chemicals Limited,  
Hillbrow House,  
Hillbrow Road,  
Esher,  
Surrey,  
KT10 9NW  

8 MARKETING AUTHORISATION NUMBER(S)  
PL 36390/0044  

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION  
16/06/2011  

10 DATE OF REVISION OF THE TEXT  
16/06/2011  

SUMMARY OF PRODUCT CHARACTERISTICS  

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION  
Each coated tablet contains 1 mg of risperidone.  
Each film-coated tablet contains 69.0 mg lactose monohydrate.  
For a full list of excipients, see Section 6.1.  

3 PHARMACEUTICAL FORM  
Film-coated tablet (tablet).
The tablets are white coloured, round film-coated tablets, with ‘1’ embossed on one side and plain on the other.

4  CLINICAL PARTICULARS

4.1 Therapeutic indications

Risperidone Tablets are indicated for the treatment of schizophrenia.

Risperidone Tablets are indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders.

Risperidone Tablets are 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 Tablets are 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 subaverage 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 Tablets 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 are 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 Tablets 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 Tablets 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 Tablets 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 Tablets must be evaluated and justified on an ongoing basis. Risperidone Tablets are 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 Tablets should be used with caution in these groups of patients.

Method of administration
Risperidone Tablets are for oral use. Food does not affect the absorption of Risperidone Tablets. 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 Tablets therapy is initiated is recommended. Also, if medically appropriate, when switching patients from depot antipsychotics, initiate Risperidone Tablets 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
Overall mortality
Elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotics, including Risperidone Tablets. In placebo-controlled trials with Risperidone Tablets in this population, the incidence of mortality was 4.0% for Risperidone Tablets-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).

Concomitant use with furosemide
In the Risperidone Tablets 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

Elderly patients with dementia

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)
In placebo-controlled trials in elderly patients with dementia there was a significantly higher incidence (approximately 3-fold increased) of CVAEs, such as stroke (including fatalities) and transient ischaemic attack in patients treated with Risperidone Tablets compared with patients treated with placebo (mean age 85 years; range 73 to 97). The pooled data from six placebo-controlled studies 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 Tablets 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 Tablets 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 Tablets 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 Tablets 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 Tablets, should be discontinued.

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

Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including Risperidone Tablets, 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**

Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with Risperidone Tablets. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

**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 Tablets 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 Tablets 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 Tablets 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 Tablets 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.

**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 have 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**

These film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
4.5 Interaction with other medicinal products and other forms of interaction

As with other antipsychotics, caution is advised when prescribing risperidone with medicinal products known to prolong the QT interval, e.g., class Ia antiarrhythmics (e.g., quinidine, dysopiramide, procaainamide), 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 Tablets 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 Tablets 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 Tablets do not show a clinically relevant effect on the pharmacokinetics of lithium, valproate, digoxin or topiramate.

Potential for other medicinal products to affect Risperidone Tablets

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 Tablets.

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 Tablets.

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 Tablets in children and adolescents did not alter the pharmacokinetics and efficacy of Risperidone Tablets. See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

Concomitant use of oral Risperidone Tablets 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 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of risperidone in pregnant women. According to postmarketing data reversible extrapyramidal symptoms in the neonate were observed following the use of risperidone during the last trimester of pregnancy. 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). The potential risk for humans is unknown. Therefore, Risperidone Tablets 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 Tablets can have minor or moderate influence on the ability to drive and use machines due to potential neuronal 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).

<table>
<thead>
<tr>
<th>Adverse Drug Reactions by System Organ Class and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigations</strong></td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Uncommon</td>
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<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
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<td>Not known</td>
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<td><strong>Nervous system disorders</strong></td>
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<tr>
<td>Very common</td>
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<tr>
<td>Common</td>
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<tr>
<td>Uncommon</td>
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MHRA-UKPAR – Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg & 6mg Film-Coated Tablets  PL 36390/0044-9
### Rare
- Neuroleptic malignant syndrome, Diabetic coma, Cerebrovascular disorder, Cerebral ischaemia, Movement disorder

### Eye disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Vision blurred</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Conjunctivitis, Ocular hyperaemia, Eye discharge, Eye swelling, Dry eye, Lacration increased, Photophobia</td>
</tr>
<tr>
<td>Rare</td>
<td>Visual acuity reduced, Eye rolling, Glaucoma</td>
</tr>
</tbody>
</table>

### Ear and labyrinth disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Ear pain, Tinnitus</td>
</tr>
</tbody>
</table>

### Respiratory, thoracic and mediastinal disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Dyspnoea, Epistaxis, Cough, Nasal congestion, Pharyngolaryngeal pain</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Wheezing, Pneumonia aspiration, Pulmonary congestion, Respiratory disorder, Rales, Respiratory tract congestion, Dysphonia</td>
</tr>
<tr>
<td>Rare</td>
<td>Sleep apnea syndrome, Hyperventilation</td>
</tr>
</tbody>
</table>

### Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Vomiting, Diarrhoea, Constipation, Nausea, Abdominal pain, Dyspepsia, Dry mouth, Stomach discomfort</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Dysphagia, Gastritis, Faecal incontinence, Faecaloma</td>
</tr>
<tr>
<td>Rare</td>
<td>Intestinal obstruction, Pancreatitis, Lip swelling, Cheilitis</td>
</tr>
</tbody>
</table>

### Renal and urinary disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Enuresis</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Dysuria, Urinary incontinence, Pollakiuria</td>
</tr>
</tbody>
</table>

### Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Rash, Erythema</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Angioedema, Skin lesion, Skin disorder, Pruritus, Acne, Skin discolouration, Alopecia, Seborrhoeic dermatitis, Dry skin, Hyperkeratosis</td>
</tr>
<tr>
<td>Rare</td>
<td>Dandruff</td>
</tr>
</tbody>
</table>

### Musculoskeletal and connective tissue disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Arthralgia, Back pain, Pain in extremity</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Muscular weakness, Myalgia, Neck pain, Joint swelling, Posture abnormal, Joint stiffness, Musculoskeletal chest pain</td>
</tr>
<tr>
<td>Rare</td>
<td>Rhabdomyolysis</td>
</tr>
</tbody>
</table>

### Endocrine disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Inappropriate antidiuretic hormone secretion</td>
</tr>
</tbody>
</table>

### Metabolism and nutrition disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Increased appetite, Decreased appetite</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Anorexia, Polydipsia</td>
</tr>
<tr>
<td>Very rare</td>
<td>Diabetic ketoacidosis</td>
</tr>
<tr>
<td>Not known</td>
<td>Water intoxication</td>
</tr>
</tbody>
</table>
### Infections and infestations

<table>
<thead>
<tr>
<th>Common</th>
<th>Pneumonia, Influenza, Bronchitis, Upper respiratory tract infection, Urinary tract infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Sinusitis, Viral infection, Ear infection, Tonsillitis, Cellulitis, Otitis media, Eye infection, Localised infection, Acarodermatitis, Respiratory tract infection, Cystitis, Onychomycosis</td>
</tr>
<tr>
<td>Rare</td>
<td>Otitis media chronic</td>
</tr>
</tbody>
</table>

### Vascular disorders

| Uncommon | Hypotension, Orthostatic hypotension, Flushing |

### General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Common</th>
<th>Pyrexia, Fatigue, Peripheral oedema, Asthenia, Chest pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Face oedema, Gait disturbance, Feeling abnormal, Sluggishness, Influenza like illness, Thirst, Chest discomfort, Chills</td>
</tr>
<tr>
<td>Rare</td>
<td>Generalised oedema, Hypothermia, Drug withdrawal syndrome, Peripheral coldness</td>
</tr>
</tbody>
</table>

### Immune system disorders

<table>
<thead>
<tr>
<th>Uncommon</th>
<th>Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Drug hypersensitivity</td>
</tr>
<tr>
<td>Not known</td>
<td>Anaphylactic reaction</td>
</tr>
</tbody>
</table>

### Hepatobiliary disorders

| Rare     | Jaundice |

### Reproductive system and breast disorders

<table>
<thead>
<tr>
<th>Uncommon</th>
<th>Amenorrhoea, Sexual dysfunction, Erectile dysfunction, Ejaculation disorder, Galactorrhoea, Gynaecomastia, Menstrual disorder, Vaginal discharge,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Priapism</td>
</tr>
</tbody>
</table>

### Psychiatric disorders

<table>
<thead>
<tr>
<th>Very common</th>
<th>Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Anxiety, Agitation, Sleep disorder</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Confusional state, Mania, Libido decreased, Listless, Nervousness</td>
</tr>
<tr>
<td>Rare</td>
<td>Anorgasmia, Blunted affect</td>
</tr>
</tbody>
</table>

*Hyperprolactinemia can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhoea, galactorrhea.*

* 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 twiching, 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.

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

<table>
<thead>
<tr>
<th>Additional Adverse Drug Reactions Reported With injectable risperidone formulation but Not With Oral Risperidone Tablets by System Organ Class</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigations</strong></td>
</tr>
<tr>
<td>Weight decreased, Gamma-glutamyltransferase increased, Hepatic enzyme increased</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
</tr>
<tr>
<td>Bradycardia</td>
</tr>
</tbody>
</table>

| 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.

*Weight gain*
The proportions of Risperidone Tablets 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 Tablets (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 Tablets (2.5%) and placebo (2.4%) groups, and was slightly higher in the active-control group (3.3%).

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 Tablets 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 outpatients predominately 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 alpha-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. 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**

Starch.
Cellulose, microcrystalline (E460)
Lactose monohydrate
Sodium starch glycolate (Type A)
Magnesium stearate

**Film-coating:**
Opadry 03B58807 White
Constituents of Opadry 03B58807 White are:
Hypromellose (E464)
Titanium dioxide (E171)
Polyethylene glycol.

6.2 **Incompatibilities**

Not applicable.

6.3 **Shelf life**

3 years.

6.4 **Special precautions for storage**

Store in the original package.
This medicinal product does not require any special storage conditions.

6.5 **Nature and contents of container**

0.025 mm thickness aluminium foil (heat sealable against PVC with VMCH coating).
PVC/PE/PVdC film.

Pack size: 60 tablets.

6.6 **Special precautions for disposal**

No special requirements.

7 **MARKETING AUTHORISATION HOLDER**

STD Chemicals Limited,
Hillbrow House,
Hillbrow Road,
Esher,
Surrey,
KT10 9NW

8 **MARKETING AUTHORISATION NUMBER(S)**

PL 36390/0045
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/06/2011

10 DATE OF REVISION OF THE TEXT
16/06/2011
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Risperidone 2 mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 2 mg of risperidone.

Each film-coated contains 138.0 mg lactose monohydrate and Sunset Yellow (E110).

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet (tablet).

These tablets are orange coloured, round film-coated tablets, with ‘2’ embossed on one side and plain on the other.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Risperidone Tablets are indicated for the treatment of schizophrenia.

Risperidone Tablets are indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders.

Risperidone Tablets are 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 Tablets are 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 subaverage 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 Tablets 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 are 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 Tablets 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 Tablets 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 Tablets 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 Tablets must be evaluated and justified on an ongoing basis.

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

**Method of administration**

Risperidone Tablets are for oral use. Food does not affect the absorption of Risperidone Tablets. 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 Tablets therapy is initiated is recommended. Also, if medically appropriate, when switching patients from depot antipsychotics, initiate Risperidone Tablets 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

Overall mortality
Elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotics, including Risperidone Tablets. In placebo-controlled trials with Risperidone Tablets in this population, the incidence of mortality was 4.0% for Risperidone Tablets-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).

Concomitant use with furosemide
In the Risperidone Tablets 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)

Elderly patients with dementia

No pathological 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)
In placebo-controlled trials in elderly patients with dementia there was a significantly higher incidence (approximately 3-fold increased) of CVAEs, such as stroke (including fatalities) and transient ischaemic attack in patients treated with Risperidone Tablets compared with patients treated with placebo (mean age 85 years; range 73 to 97). The pooled data from six placebo-controlled studies 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 Tablets 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 Tablets 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 Tablets 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 Tablets should be used with caution in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolemic, 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 Tablets, should be discontinued.

Parkinson's disease and dementia with Lewy bodies
Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including Risperidone Tablets, 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.

Hyperglycemia
Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with Risperidone Tablets. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

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 Tablets 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 Tablets 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 Tablets 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 Tablets 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.

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

Risperidone 2 mg Tablets contain the colouring Sunset Yellow which 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 Ia antiarrhythmics (e.g., quinidine, dysopiramid, procainamide), class III antiarrhythmics (e.g., amidarone, sotalol), tricyclic antidepressants (i.e., amitriptyline), tetracyclic antidepressants (i.e., maprotiline), some antihistamines, other antipsychotics, some antimalarials (i.e., chloroquine and mefloquine), and with medicines causing electrolyte imbalance (hypokalaemia, hypomagnesaemia), oedema, or those which inhibit the hepatic metabolism of risperidone. This list is indicative and not exhaustive. Potential for Risperidone Tablets 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 Tablets 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 Tablets does not show a clinically relevant effect on the pharmacokinetics of lithium, valproate, digoxin or topiramate.

Potential for other medicinal products to affect Risperidone Tablets
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 Tablets.
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 Tablets.

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 Tablets in children and adolescents did not alter the pharmacokinetics and efficacy of Risperidone Tablets. See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

Concomitant use of oral Risperidone Tablets 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 Pregnancy and lactation

**Pregnancy**

There are no adequate data from the use of risperidone in pregnant women. According to postmarketing data reversible extrapyramidal symptoms in the neonate were observed following the use of risperidone during the last trimester of pregnancy. 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). The potential risk for humans is unknown. Therefore, Risperidone Tablets 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 Tablets 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.

<table>
<thead>
<tr>
<th>Adverse Drug Reactions by System Organ Class and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigations</strong></td>
</tr>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Blood prolactin increased*, Weight increased</td>
</tr>
</tbody>
</table>

MHRA-UKPAR – Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg & 6mg Film-Coated Tablets PL 36390/0044-9
<table>
<thead>
<tr>
<th>Frequency</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>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</td>
</tr>
<tr>
<td>Rare</td>
<td>Body temperature decreased</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Atrioventricular block, Bundle branch block, Atrial fibrillation, Sinus bradycardia, Palpitations</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Anaemia, Thrombocytopenia</td>
</tr>
<tr>
<td>Rare</td>
<td>Granulocytopenia</td>
</tr>
<tr>
<td>Not known</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Parkinsonism(^b), Headache</td>
</tr>
<tr>
<td>Common</td>
<td>Akathisia(^a), Dizziness, Tremor(^b), Dystonia(^b), Somnolence, Sedation, Lethargy, Dyskinesia(^b)</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Unresponsive to stimuli, Loss of consciousness, Syncope, Depressed level of consciousness, Cerebrovascular accident, Transient ischaemic attack, Dysarthria, Disturbance in attention, Hypersomnina, Dizziness postural, Balance disorder, Tardive dyskinesia, Speech disorder, Coordination abnormal, Hypoaesthesia</td>
</tr>
<tr>
<td>Rare</td>
<td>Neuroleptic malignant syndrome, Diabetic coma, Cerebrovascular disorder, Cerebral ischaemia, Movement disorder</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Vision blurred</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Conjunctivitis, Ocular hyperaemia, Eye discharge, Eye swelling, Dry eye, Lacrimation increased, Photophobia</td>
</tr>
<tr>
<td>Rare</td>
<td>Visual acuity reduced, Eye rolling, Glaucoma</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Ear pain, Tinnitus</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Dyspnoea, Epistaxis, Cough, Nasal congestion, Pharyngolaryngeal pain</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Wheezing, Pneumonia aspiration, Pulmonary congestion, Respiratory disorder, Rales, Respiratory tract congestion, Dysphonia</td>
</tr>
<tr>
<td>Rare</td>
<td>Sleep apnea syndrome, Hyperventilation</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Vomiting, Diarrhoea, Constipation, Nausea, Abdominal pain, Dyspepsia, Dry mouth, Stomach discomfort</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Dysphagia, Gastritis, Faecal incontinence, Faecaloma</td>
</tr>
<tr>
<td>Rare</td>
<td>Intestinal obstruction, Pancreatitis, Lip swelling, Cheilitis</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Common</th>
<th>Enuresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Dysuria, Urinary incontinence, Pollakiuria</td>
</tr>
</tbody>
</table>

**Skin and subcutaneous tissue disorders**

<table>
<thead>
<tr>
<th>Common</th>
<th>Rash, Erythema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Angioedema, Skin lesion, Skin disorder, Pruritus, Acne, Skin discolouration, Alopecia, Seborrhoeic dermatitis, Dry skin, Hyperkeratosis</td>
</tr>
<tr>
<td>Rare</td>
<td>Dandruff</td>
</tr>
</tbody>
</table>

**Musculoskeletal and connective tissue disorders**

<table>
<thead>
<tr>
<th>Common</th>
<th>Arthralgia, Back pain, Pain in extremity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Muscular weakness, Myalgia, Neck pain, Joint swelling, Posture abnormal, Joint stiffness, Musculoskeletal chest pain</td>
</tr>
<tr>
<td>Rare</td>
<td>Rhabdomyolysis</td>
</tr>
</tbody>
</table>

**Endocrine disorders**

| Rare                                | Inappropriate antidiuretic hormone secretion       |

**Metabolism and nutrition disorders**

<table>
<thead>
<tr>
<th>Common</th>
<th>Increased appetite, Decreased appetite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Anorexia, Polydipsia</td>
</tr>
<tr>
<td>Very rare</td>
<td>Diabetic ketoacidosis</td>
</tr>
<tr>
<td>Not known</td>
<td>Water intoxication</td>
</tr>
</tbody>
</table>

**Infections and infestations**

<table>
<thead>
<tr>
<th>Common</th>
<th>Pneumonia, Influenza, Bronchitis, Upper respiratory tract infection, Urinary tract infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Sinusitis, Viral infection, Ear infection, Tonsillitis, Cellulitis, Otitis media, Eye infection, Localised infection, Acarodermatitis, Respiratory tract infection, Cystitis, Onychomycosis</td>
</tr>
<tr>
<td>Rare</td>
<td>Otitis media chronic</td>
</tr>
</tbody>
</table>

**Vascular disorders**

| Uncommon                            | Hypotension, Orthostatic hypotension, Flushing  |

**General disorders and administration site conditions**

<table>
<thead>
<tr>
<th>Common</th>
<th>Pyrexia, Fatigue, Peripheral oedema, Asthenia, Chest pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Face oedema, Gait disturbance, Feeling abnormal, Sluggishness, Influenza like illness, Thirst, Chest discomfort, Chills</td>
</tr>
<tr>
<td>Rare</td>
<td>Generalised oedema, Hypothermia, Drug withdrawal syndrome, Peripheral coldness</td>
</tr>
</tbody>
</table>

**Immune system disorders**

| Uncommon                            | Hypersensitivity                                     |
| Rare                                | Drug hypersensitivity                                |
| Not known                           | Anaphylactic reaction                                |

**Hepatobiliary disorders**

| Rare                                | Jaundice                                            |
### Reproductive system and breast disorders

<table>
<thead>
<tr>
<th>Uncommon</th>
<th>Amenorrhea, Sexual dysfunction, Erectile dysfunction, Ejaculation disorder, Galactorrhoea, Gynaecomastia, Menstrual disorder, Vaginal discharge,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Priapism</td>
</tr>
</tbody>
</table>

### Psychiatric disorders

<table>
<thead>
<tr>
<th>Very common</th>
<th>Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Anxiety, Agitation, Sleep disorder</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Confusional state, Mania, Libido decreased, Listless, Nervousness</td>
</tr>
<tr>
<td>Rare</td>
<td>Anorgasmia, Blunted affect</td>
</tr>
</tbody>
</table>

* Hyperprolactinemia can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhea, galactorrhea.
* 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.

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

<table>
<thead>
<tr>
<th>Additional Adverse Drug Reactions reported with injectable risperidone formulation but not with Oral Risperidone Tablets by System Organ Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
</tr>
<tr>
<td>Weight decreased, Gamma-glutamyltransferase increased, Hepatic enzyme increased</td>
</tr>
</tbody>
</table>

### Cardiac Disorders

<table>
<thead>
<tr>
<th>Bradycardia</th>
</tr>
</thead>
</table>

### Blood and Lymphatic Disorders

<table>
<thead>
<tr>
<th>Neutropenia</th>
</tr>
</thead>
</table>

### Nervous System Disorders

<table>
<thead>
<tr>
<th>Paesthesia, Convulsion</th>
</tr>
</thead>
</table>

### Eye Disorders

<table>
<thead>
<tr>
<th>Blepharospasm</th>
</tr>
</thead>
</table>

### Ear and Labyrinth Disorders

<table>
<thead>
<tr>
<th>Vertigo</th>
</tr>
</thead>
</table>

### Gastrointestinal Disorders

<table>
<thead>
<tr>
<th>Toothache, Tongue spasm</th>
</tr>
</thead>
</table>

### Skin and Subcutaneous Tissue Disorders

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
</table>

MHRA-UKPAR – Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg & 6mg Film-Coated Tablets  PL 36390/0044-9
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.

*Weight gain*

The proportions of Risperidone Tablets 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 Tablets (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 Tablets (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 Tablets 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, placebo-controlled 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 outpatients 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-dependent 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. 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

<table>
<thead>
<tr>
<th>Excipient</th>
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<tbody>
<tr>
<td>Starch</td>
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<tr>
<td>Cellulose, microcellulose (E460)</td>
</tr>
</tbody>
</table>

MHRA-UKPAR – Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg & 6mg Film-Coated Tablets  PL 36390/0044-9 - 53 -
Lactose monohydrate
Sodium starch glycolate (Type A)
Magnesium stearate

Film-coating:
Opadry 03B53353 Orange
Constituents of Opadry 03B53353 Orange are:
Hyromellose (E464)
Titanium dioxide (E171)
Polyethylene glycol
Sunset Yellow (E110)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store in the original package.
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
0.025 mm thickness aluminium foil (heat sealable against PVC with VMCH coating).
PVC/PE/PVdC film.
Pack size: 60 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
STD Chemicals Limited,
Hillbrow House,
Hillbrow Road,
Esher,
Surrey,
KT10 9NW

8 MARKETING AUTHORISATION NUMBER(S)
PL 36390/0046

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/06/2011

10 DATE OF REVISION OF THE TEXT
16/06/2011
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Risperidone 3 mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 3 mg of risperidone.

Each film-coated tablet contains 207.0 mg lactose monohydrate.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet (tablet).

These tablets are yellow coloured, round film-coated tablets, with ‘3’ embossed on one side and plain on the other.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Risperidone Tablets are indicated for the treatment of schizophrenia.

Risperidone Tablets are indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders.

Risperidone Tablets are 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 Tablets are 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 subaverage 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 Tablets 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 are 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 Tablets 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 Tablets 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 Tablets 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 Tablets must be evaluated and justified on an ongoing basis.

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

**Method of administration**

Risperidone Tablets are for oral use. Food does not affect the absorption of Risperidone Tablets. 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 Tablets therapy is initiated is recommended. Also, if medically appropriate, when switching patients from depot antipsychotics, initiate Risperidone Tablets 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

Overall mortality
Elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotics, including Risperidone Tablets. In placebo-controlled trials with Risperidone Tablets in this population, the incidence of mortality was 4.0% for Risperidone Tablets-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).

Concomitant use with furosemide
In the Risperidone Tablets 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) may be associated with an increased risk of mortality. 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)
In placebo-controlled trials in elderly patients with dementia there was a significantly higher incidence (approximately 3-fold increased) of CVAEs, such as stroke (including fatalities) and transient ischaemic attack in patients treated with Risperidone Tablets compared with patients treated with placebo (mean age 85 years; range 73 to 97). The pooled data from six placebo-controlled studies 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 Tablets 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 Tablets 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 Tablets 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 Tablets 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 rhythmic 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 Tablets, should be discontinued.

Parkinson's disease and dementia with Lewy bodies
Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including Risperidone Tablets, 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.

Hyperglycemia
Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with Risperidone Tablets. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

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 Tablets 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 Tablets 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 Tablets 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 Tablets 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.

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

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

Potential for Risperidone Tablets 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 Tablets 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 Tablets do not show a clinically relevant effect on the pharmacokinetics of lithium, valproate, digoxin or topiramate.

Potential for other medicinal products to affect Risperidone Tablets.
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-glycoproteine. 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 Tablets.
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 Tablets.

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 Tablets in children and adolescents did not alter the pharmacokinetics and efficacy of Risperidone Tablets. See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

Concomitant use of oral Risperidone Tablets 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 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of risperidone in pregnant women. According to postmarketing data reversible extrapyramidal symptoms in the neonate were observed following the use of risperidone during the last trimester of pregnancy. 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). The potential risk for humans is unknown. Therefore, Risperidone Tablets 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 Tablets 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 <1/1000), 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.
<table>
<thead>
<tr>
<th>Common</th>
<th>Blood prolactin increased⁺, Weight increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>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</td>
</tr>
<tr>
<td>Rare</td>
<td>Body temperature decreased</td>
</tr>
</tbody>
</table>

**Cardiac disorders**

<table>
<thead>
<tr>
<th>Common</th>
<th>Tachycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Atrioventricular block, Bundle branch block, Atrial fibrillation, Sinus bradycardia, Palpitations</td>
</tr>
</tbody>
</table>

**Blood and lymphatic system disorders**

<table>
<thead>
<tr>
<th>Common</th>
<th>Anaemia, Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Granulocytopenia</td>
</tr>
<tr>
<td>Not known</td>
<td>Agranulocytosis</td>
</tr>
</tbody>
</table>

**Nervous system disorders**

<table>
<thead>
<tr>
<th>Very common</th>
<th>Parkinsonism⁺, Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Akathisia⁺, Dizziness, Tremor⁺, Dystonia⁺, Somnolence, Sedation, Lethargy, Dyskinesia⁺</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Unresponsive to stimuli, Loss of consciousness, Syncope, Depressed level of consciousness, Cerebrovascular accident, Transient ischaemic attack, Dysarthria, Disturbance in attention, Hypersomnias, Dizziness postural, Balance disorder, Tardive dyskinesias, Speech disorder, Coordination abnormal, Hypoaesthesia</td>
</tr>
</tbody>
</table>

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

**Eye disorders**

<table>
<thead>
<tr>
<th>Common</th>
<th>Vision blurred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Conjunctivitis, Ocular hyperaemia, Eye discharge, Eye swelling, Dry eye, Lacrimation increased, Photophobia</td>
</tr>
<tr>
<td>Rare</td>
<td>Visual acuity reduced, Eye rolling, Glaucoma</td>
</tr>
</tbody>
</table>

**Ear and labyrinth disorders**

| Uncommon               | Ear pain, Tinnitus                         |

**Respiratory, thoracic and mediastinal disorders**

<table>
<thead>
<tr>
<th>Common</th>
<th>Dyspnoea, Epistaxis, Cough, Nasal congestion, Pharyngolaryngeal pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Wheezing, Pneumonia aspiration, Pulmonary congestion, Respiratory disorder, Rales, Respiratory tract congestion, Dysphonia</td>
</tr>
</tbody>
</table>

| Rare                   | Sleep apnea syndrome, Hyperventilation                         |

**Gastrointestinal disorders**

<table>
<thead>
<tr>
<th>Common</th>
<th>Vomiting, Diarrhoea, Constipation, Nausea, Abdominal pain, Dyspepsia, Dry mouth, Stomach discomfort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Dysphagia, Gastritis, Faecal incontinence, Faecaloma</td>
</tr>
<tr>
<td>Rare</td>
<td>Intestinal obstruction, Pancreatitis, Lip swelling, Cheilitis</td>
</tr>
</tbody>
</table>
### Renal and urinary disorders
- **Common**: Enuresis
- **Uncommon**: Dysuria, Urinary incontinence, Pollakiuria

### Skin and subcutaneous tissue disorders
- **Common**: Rash, Erythema
- **Uncommon**: Angioedema, Skin lesion, Skin disorder, Pruritus, Acne, Skin discoloration, 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**: Anorexia, Polydipsia
- **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
<table>
<thead>
<tr>
<th><strong>Rare</strong></th>
<th>Jaundice</th>
</tr>
</thead>
</table>

**Reproductive system and breast disorders**

<table>
<thead>
<tr>
<th><strong>Uncommon</strong></th>
<th>Amenorrhoea, Sexual dysfunction, Erectile dysfunction, Ejaculation disorder, Galactorrhoea, Gynaecomastia, Menstrual disorder, Vaginal discharge,</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not known</strong></td>
<td>Priapism</td>
</tr>
</tbody>
</table>

**Psychiatric disorders**

<table>
<thead>
<tr>
<th><strong>Very common</strong></th>
<th>Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Anxiety, Agitation, Sleep disorder</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Confusional state, Mania, Libido decreased, Listless, Nervousness</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Anorgasmia, Blunted affect</td>
</tr>
</tbody>
</table>

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

* 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.

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

### Additional Adverse Drug Reactions Reported With injectable risperidone formulation but not with Oral Risperidone Tablets 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
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.

Weight gain
The proportions of Risperidone Tablets 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 Tablets (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 Tablets (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

4.9.1 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 Tablets and paroxetine.

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

4.9.2 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 outpatients 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 alpha,-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 2C9/10, 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-dependent 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. 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
Starch
Cellulose, microcrystalline (E460)
Lactose monohydrate  
Sodium starch glycolate (Type A)  
Magnesium stearate

Film-coating:  
Opadry 03B52319 Yellow  
Constituents of Opadry 03B52319 Yellow are:  
Hypermellose (E464)  
Titanium dioxide (E171)  
Polyethylene glycol  
Quinoline Yellow (E104)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store in the original package.  
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
0.025 mm thickness aluminium foil (heat sealable against PVC with VMCH coating).  
PVC/PE/PVdC film.  

Pack size: 60 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
STD Chemicals Limited,  
Hillbrow House,  
Hillbrow Road,  
Esher,  
Surrey,  
KT10 9NW

8 MARKETING AUTHORISATION NUMBER(S)
PL 36390/0047

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/06/2011

10 DATE OF REVISION OF THE TEXT
16/06/2011

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Risperidone 4 mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 4 mg of risperidone.  

Each film-coated tablet contains 276.0 mg lactose monohydrate.  

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet (tablet).  

MHRA-UKPAR – Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg & 6mg Film-Coated Tablets  PL 36390/0044-9  - 68 -
The tablets are green coloured, round film-coated tablets, with ‘4’ embossed on one side and plain on the other.

4  CLINICAL PARTICULARS

4.1 Therapeutic indications
Risperidone Tablets are indicated for the treatment of schizophrenia.
Risperidone Tablets are indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders.
Risperidone Tablets are 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 Tablets are 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 subaverage 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 Tablets 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 are 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 Tablets 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 Tablets 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 Tablets 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 Tablets must be evaluated and justified on an ongoing basis.

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

Method of administration
Risperidone Tablets are for oral use. Food does not affect the absorption of Risperidone Tablets. 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 Tablets therapy is initiated is recommended. Also, if medically appropriate, when switching patients from depot antipsychotics, initiate Risperidone Tablets 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

Overall mortality
Elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotics, including Risperidone Tablets. In placebo-controlled trials with Risperidone Tablets in this population, the incidence of mortality was 4.0% for Risperidone Tablets -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).

Concomitant use with furosemide
In the Risperidone Tablets 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)

Elderly patients with dementia
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)
In placebo-controlled trials in elderly patients with dementia there was a significantly higher incidence (approximately 3-fold increased) of CVAEs, such as stroke (including fatalities) and transient ischaemic attack in patients treated with Risperidone Tablets compared with patients treated with placebo (mean age 85 years; range 73 to 97). The pooled data from six placebo-controlled studies 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 Tablets 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 Tablets 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 Tablets 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 Tablets 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 Tablets, should be discontinued.

**Parkinson's disease and dementia with Lewy bodies**
Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including Risperidone Tablets, 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.

**Hyperglycemia**
Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with Risperidone Tablets. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

**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 Tablets 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 Tablets 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 Tablets 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 Tablets 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.

**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-
The effect of long-term risperidone treatment on sexual maturation and height have 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
These film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

As with other antipsychotics, caution is advised when prescribing risperidone with medicinal products known to prolong the QT interval, e.g., class Ia antiarrhythmics (e.g., quinidine, dysopyramide, 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 Tablets 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 Tablets 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 Tablets does not show a clinically relevant effect on the pharmacokinetics of lithium, valproate, digoxin or topiramate.

Potential for other medicinal products to affect Risperidone Tablets.
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 Tablets.

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 Tablets.

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 Tablets in children and adolescents did not alter the pharmacokinetics and efficacy of Risperidone Tablets. See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

Concomitant use of oral Risperidone Tablets 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 Pregnancy and lactation

**Pregnancy**

There are no adequate data from the use of risperidone in pregnant women. According to postmarketing data reversible extrapyramidal symptoms in the neonate were observed following the use of risperidone during the last trimester of pregnancy. 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). The potential risk for humans is unknown. Therefore, Risperidone Tablets 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 Tablets 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.

<table>
<thead>
<tr>
<th>Adverse Drug Reactions by System Organ Class and Frequency</th>
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<tbody>
<tr>
<td><strong>Investigations</strong></td>
</tr>
<tr>
<td>Common</td>
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<tr>
<td>Uncommon</td>
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<tr>
<td>Rare</td>
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<tr>
<td><strong>Cardiac disorders</strong></td>
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<tr>
<td>Common</td>
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<tr>
<td>Uncommon</td>
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<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
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<tr>
<td>Uncommon</td>
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<tr>
<td>Frequency</td>
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</tr>
<tr>
<td>Rare</td>
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<tr>
<td>Very common</td>
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<td>Common</td>
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<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
</tr>
</tbody>
</table>

### Endocrine disorders

| **Rare** | Inappropriate antidiuretic hormone secretion |

### Metabolism and nutrition disorders

| **Common** | Increased appetite, Decreased appetite |
| **Uncommon** | Anorexia, Polydipsia |
| **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 |
Anorgasmia, Blunted affect

* Hyperprolactinemia can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhoea, galactorrhea.

* Extrapyramidal disorder may occur: Parkinsonism (salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked faces, 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.

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

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Weight decreased, Gamma-glutamyltransferase increased, Hepatic enzyme increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Disorders</td>
<td>Braddycardia</td>
</tr>
<tr>
<td>Blood and Lymphatic Disorders</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Paresthesia, Convulsion</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>Blepharospasm</td>
</tr>
<tr>
<td>Ear and Labyrinth Disorders</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Toothache, Tongue spasm</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Eczema</td>
</tr>
<tr>
<td>Musculoskeletal, Connective Tissue, and Bone Disorders</td>
<td>Buttock pain</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>Lower respiratory tract infection, Infection, Gastroenteritis, Subcutaneous abscess</td>
</tr>
<tr>
<td>Injury and Poisoning</td>
<td>Fall</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
</tr>
</tbody>
</table>
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.

Weight gain
The proportions of Risperidone Tablets 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 Tablets (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 Tablets (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 Tablets 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.

MHRA-UKPAR – Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg & 6mg Film-Coated Tablets   PL 36390/0044-9  - 78 -
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 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 outpatients meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 years 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. 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
Starch
Cellulose, microcrystalline (E460)
Lactose monohydrate
Sodium starch glycolate (Type A)
Magnesium stearate

Film-coating:
Opadry 03B51168 Green
Constituents of Opadry 03B51168 Green are:
Hypromellose (E464)
Titanium dioxide (E171)
Polyethylene glycol
Quinolone yellow (E104)
Indigo Carmine (E104).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.
6.4 Special precautions for storage
Store in the original package.
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
0.025 mm thickness aluminium foil (heat sealable against PVC with VMCH coating).
PVC/PE/PVdC film.

Pack size: 60 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
STD Chemicals Limited,
Hillbrow House,
Hillbrow Road,
Esher,
Surrey,
KT10 9NW

8 MARKETING AUTHORISATION NUMBER(S)
PL 36390/0048

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/06/2011

10 DATE OF REVISION OF THE TEXT
16/06/2011
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Risperidone 6 mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 6 mg of risperidone.

Each film-coated tablet contains 274.0 mg lactose monohydrate.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet (tablet).

The tablets are yellow coloured, capsule-shaped, biconvex film-coated tablets, with ‘6’ embossed on one side and plain on the other.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Risperidone Tablets are indicated for the treatment of schizophrenia.

Risperidone Tablets are indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders.

Risperidone Tablets are 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 Tablets are 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 subaverage 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 Tablets 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 are 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 Tablets 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 Tablets 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 Tablets 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 Tablets must be evaluated and justified on an ongoing basis.

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

Method of administration
Risperidone Tablets are for oral use. Food does not affect the absorption of Risperidone Tablets. 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 Tablets therapy is initiated is recommended. Also, if medically appropriate, when switching patients from depot antipsychotics, initiate Risperidone Tablets therapy in place of the next scheduled dose.
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

Overall mortality
Elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotics, including Risperidone Tablets. In placebo-controlled trials with Risperidone Tablets in this population, the incidence of mortality was 4.0% for Risperidone Tablets-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).

Concomitant use with furosemide
In the Risperidone Tablets 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) Elderly patients with dementia

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)
In placebo-controlled trials in elderly patients with dementia there was a significantly higher incidence (approximately 3-fold increased) of CVAEs, such as stroke (including fatalities) and transient ischaemic attack in patients treated with Risperidone Tablets compared to patients treated with placebo (mean age 85 years; range 73 to 97). The pooled data from six placebo-controlled studies 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 Tablets 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 Tablets 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 Tablets 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 Tablets 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 Tablets, should be discontinued.

Parkinson's disease and dementia with Lewy bodies
Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including Risperidone Tablets, 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.

Hyperglycemia
Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with Risperidone Tablets. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

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 Tablets 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 Tablets 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 Tablets 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 Tablets 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.

**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 have 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**

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

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

As with other antipsychotics, caution is advised when prescribing risperidone with medicinal products known to prolong the QT interval, e.g., class Ia antiarrhythmics (e.g., quinidine, disopyramide, 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 Tablets 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 Tablets 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 Tablets does not show a clinically relevant effect on the pharmacokinetics of lithium, valproate, digoxin or topiramate.

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

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 Tablets. 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 Tablets.

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 Tablets in children and adolescents did not alter the pharmacokinetics and efficacy of Risperidone Tablets. See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

Concomitant use of oral Risperidone Tablets 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 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of risperidone in pregnant women. According to postmarketing data reversible extrapyramidal symptoms in the neonate were observed following the use of risperidone during the last trimester of pregnancy. 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). The potential risk for humans is unknown. Therefore, Risperidone Tablets 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 Tablets 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.

<table>
<thead>
<tr>
<th>Adverse Drug Reactions by System Organ Class and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigations</strong></td>
</tr>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Blood prolactin increased†, Weight increased</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td>Electrocardiogram QT prolonged, Electrocardiogram abnormal, Blood glucose increased, Transaminases increased, White blood cell count decreased Body</td>
</tr>
<tr>
<td>Medical System</td>
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<td>-------------------------</td>
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<tr>
<td>Gastrointestinal</td>
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<td>Renal and urinary</td>
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<td>Gastrointestinal</td>
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<td>Renal and urinary</td>
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<td>Blood and lymphatic</td>
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<tr>
<td>system disorders</td>
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<tr>
<td>Nervous system disorders</td>
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<tr>
<td>Very common</td>
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<tr>
<td>Common</td>
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<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Eye disorders</td>
</tr>
<tr>
<td>Common</td>
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<tr>
<td>Uncommon</td>
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<tr>
<td>Rare</td>
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<tr>
<td>Ear and labyrinth</td>
</tr>
<tr>
<td>disorders</td>
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<tr>
<td>Respiratory, thoracic</td>
</tr>
<tr>
<td>and mediastinal disorders</td>
</tr>
<tr>
<td>Common</td>
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<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Rare</td>
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<tr>
<td>Gastrointestinal</td>
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<tr>
<td>Common</td>
</tr>
<tr>
<td>Renal and urinary</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
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<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
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<td><strong>Common</strong></td>
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<tr>
<td><strong>Uncommon</strong></td>
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<tr>
<td><strong>Rare</strong></td>
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<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
</tr>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td><strong>Endocrine disorders</strong></td>
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<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
</tr>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
</tr>
<tr>
<td><strong>Not known</strong></td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
</tr>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
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<tr>
<td><strong>General disorders and administration site conditions</strong></td>
</tr>
<tr>
<td><strong>Common</strong></td>
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<tr>
<td><strong>Uncommon</strong></td>
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<tr>
<td><strong>Rare</strong></td>
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<tr>
<td><strong>Immune system disorders</strong></td>
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<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
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<tr>
<td><strong>Not known</strong></td>
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<tr>
<td><strong>Hepatobiliary disorders</strong></td>
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<tr>
<td><strong>Rare</strong></td>
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<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
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<tr>
<td>Not known</td>
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<tr>
<td><strong>Psychiatric disorders</strong></td>
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<td>Very common</td>
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<td>Common</td>
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<td>Uncommon</td>
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<td>Rare</td>
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* Hyperprolactinemia can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhoea, galactorrhoea.

* Extrapyramidal disorder may occur: Parkinsonism (salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies, muscle tightness, akesiase, mchal 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 paralysus, 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.

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

| **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                                                                 |

MHRA-UKPAR – Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg & 6mg Film-Coated Tablets  PL 36390/0044-9

- 91 -
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.

Weight gain
The proportions of Risperidone Tablets 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 Tablets (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 Tablets (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 Tablets 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 outpatients 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 significantly 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-depdendent 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, intraterne 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. 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

- Starch
- Cellulose, microcrystalline (E460)
- Lactose monohydrate
- Sodium starch glycolate (Type A)
- Magnesium stearate

**Film-coating:**
Opadry 03B52319 Yellow

**Constituents of Opadry 03B52319 Yellow are:**
- Hypromellose (E464)
- Titanium dioxide (E171)
- Polyethylene glycol
- Quinolone yellow (E104)

#### 6.2 Incompatibilities
Not applicable.

#### 6.3 Shelf life
3 years.
6.4 **Special precautions for storage**
Store in the original package.
This medicinal product does not require any special storage conditions.

6.5 **Nature and contents of container**
0.025 mm thickness aluminium foil (heat sealable against PVC with VMCH coating).
PVC/PE/PVdC film.

Pack size: 28 tablets.

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

7 **MARKETING AUTHORISATION HOLDER**
STD Chemicals Limited,
Hillbrow House,
Hillbrow Road,
Esher,
Surrey,
KT10 9NW

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 36390/0049

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
16/06/2011

10 **DATE OF REVISION OF THE TEXT**
16/06/2011
RISPERIDONE 0.5 MG, 1 MG, 2 MG, 3 MG, 4 MG & 6 MG FILM-COATED TABLETS

PL 36390/0044-9

PATIENT INFORMATION LEAFLET

Risperidone Tablets 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg & 6 mg are Film-Coated Tablets which are available in packs of 56 tablets.

What are Risperidone Tablets used for?

Risperidone Tablets are used in the treatment of schizophrenia and as an adjuvant in the treatment of acute exacerbations of bipolar disorder. Risperidone Tablets are also used as an adjuvant in the treatment of symptoms of schizophrenia and bipolar disorder in the elderly, particularly those with cognitive impairments.

How to take Risperidone Tablets

Risperidone Tablets are usually taken with or without food. Do not split tablets.

The usual starting dose is 1 mg per day, which may be increased to 2 mg per day, or 4 mg per day if it is necessary. The maximum dose is 6 mg per day.

If you are already taking another medicine, tell your doctor or pharmacist before you start taking Risperidone Tablets.

What to do if you have a problem

If you experience any symptoms of adverse reactions, tell your doctor or pharmacist immediately.

If you experience any side effects, tell your doctor or pharmacist immediately.

What to do if you are pregnant or breast-feeding

Tell your doctor or pharmacist if you are pregnant or breast-feeding before you start taking Risperidone Tablets.

What to do if you need a blood test

If you need a blood test while you are taking Risperidone Tablets, tell your doctor or pharmacist immediately.

What to do if you need an emergency

If you need an emergency, tell your doctor or pharmacist immediately.

What to do if you need to stop taking Risperidone Tablets

If you need to stop taking Risperidone Tablets, tell your doctor or pharmacist immediately.

What to do if you need to change the dose

If you need to change the dose, tell your doctor or pharmacist immediately.

What to do if you need to change the regimen

If you need to change the regimen, tell your doctor or pharmacist immediately.

What to do if you need to change the treatment

If you need to change the treatment, tell your doctor or pharmacist immediately.

What to do if you need to change the dosage form

If you need to change the dosage form, tell your doctor or pharmacist immediately.

What to do if you need to change the administration route

If you need to change the administration route, tell your doctor or pharmacist immediately.

What to do if you need to change the dosage schedule

If you need to change the dosage schedule, tell your doctor or pharmacist immediately.

What to do if you need to change the frequency of administration

If you need to change the frequency of administration, tell your doctor or pharmacist immediately.

What to do if you need to change the duration of treatment

If you need to change the duration of treatment, tell your doctor or pharmacist immediately.

What to do if you need to change the treatment regimen

If you need to change the treatment regimen, tell your doctor or pharmacist immediately.

What to do if you need to change the treatment dosage form

If you need to change the treatment dosage form, tell your doctor or pharmacist immediately.

What to do if you need to change the treatment administration route

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What to do if you need to change the treatment dosage schedule

If you need to change the treatment dosage schedule, tell your doctor or pharmacist immediately.

What to do if you need to change the treatment duration of administration

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What to do if you need to change the treatment regimen duration

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What to do if you need to change the treatment dosage form duration

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What to do if you need to change the treatment administration route duration

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What to do if you need to change the treatment dosage schedule duration

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If you need to change the treatment dosage form duration duration duration duration duration duration duration, tell your doctor or pharmacist immediately.

What to do if you need to change the treatment administration route duration duration duration duration duration duration duration

If you need to change the treatment administration route duration duration duration duration duration duration duration, tell your doctor or pharmacist immediately.

What to do if you need to change the treatment dosage schedule duration duration duration duration duration duration duration

If you need to change the treatment dosage schedule duration duration duration duration duration duration duration, tell your doctor or pharmacist immediately.

What to do if you need to change the treatment duration of administration duration duration duration duration duration duration duration

If you need to change the treatment duration of administration duration duration duration duration duration duration duration, tell your doctor or pharmacist immediately.

What to do if you need to change the treatment regimen duration duration duration duration duration duration duration duration

If you need to change the treatment regimen duration duration duration duration duration duration duration duration, tell your doctor or pharmacist immediately.

What to do if you need to change the treatment dosage form duration duration duration duration duration duration duration duration

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What to do if you need to change the treatment administration route duration duration duration duration duration duration duration duration

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What to do if you need to change the treatment dosage schedule duration duration duration duration duration duration duration duration

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What to do if you need to change the treatment duration of administration duration duration duration duration duration duration duration duration

If you need to change the treatment duration of administration duration duration duration duration duration duration duration duration, tell your doctor or pharmacist immediately.
How to take Risperidone Tablets

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

Your doctor will tell you how much medication to take and how long you will need to take it. This will depend on your condition and may change from person to person. The amount of medication you should take is an explanation of the dose that is right for you, but should not be used instead of medical advice.

You should swallow the tablets with a drink of water.

If you take more Risperidone Tablets than you should:

See a doctor right away. Take the medicine with you.

If you take less medication than you should:

Take your normal dose. Do not take any extra tablets. Ask your doctor or pharmacist.

If you forget to take Risperidone Tablets:

If you forget to take the medicine, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and continue your usual dose. If you take too many tablets, contact your doctor.

If you stop taking Risperidone Tablets:

Do not stop taking Risperidone Tablets without discussing it with your doctor. Your symptoms may return. If you think the drug does not work, your doctor may prescribe a substitute drug.

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

4. COMBINED USE

Use of other drugs, Risperidone Tablets can cause side effects, although not everyone gets them.

The effects of side effects have been also reported:

Very Common (affects more than 1 in 10)

Common (affects 1 in 10 to 1 in 100)

Uncommon (affects 1 in 100 to 1 in 1000)

Rare (affects 1 in 10,000 to 1 in 100,000)

Very rare (affects less than 1 in 100,000)


5. HOW TO STORE AMPHORIDONE

Keep out of the reach and sight of children. Do not take this medicine after the expiry date (EoA). The expiry date is the last day of that month.

Store your tablets in the original package. This medicinal product does not require any special temperature storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist to dispose of medicines no longer required. These medicines will help to protect the environment.

6. OTHER INFORMATION

What Risperidone Tablets contain:

The active ingredient is risperidone. There are other ingredients as follows: 2.5 mg, 5 mg, 7.5 mg, 10 mg and 15 mg per tablet. The other ingredients are starchmicrocrystalline cellulose (460), dextrose monohydrate, sodium starch glycolate (571), and magnesium stearate.

Risperidone 1.5 mg Tablets also contain: Colour: Brown. Opaque Brown contains Hypromellose (E464), Titanium Dioxide (E171) and Iron Oxide Red (E172). Risperidone 1 mg Tablets also contain: Opacity: White contains Hypromellose (E464), Titanium Dioxide (E171) and Polyethylene Glycol. Risperidone 0.5 mg Tablets also contain: Opacity: Orange contains Hypromellose (E464), Titanium Dioxide (E171) and Polysorbate 80. Risperidone 2 mg Tablets also contain: Opacity: Yellow contains Hypromellose (E464), Titanium Dioxide (E171), Polysorbate 80 and Quinine Sulfate in the ratio 0.0060.

What Risperidone Tablets look like and the contents of the pack:

Risperidone 5 mg Film-Coated Tablets:

Brown coloured, oval, bismuth film-coated tablets with ‘R’ engraved on one side and plain on the other. Available in packs of 30 tablets.

Risperidone 1 mg Film-Coated Tablets:

White coloured, round, film-coated tablets, with ‘R’ embossed on one side and plain on the other. Available in packs of 30 tablets.

Risperidone 2 mg Film-Coated Tablets:

Orange coloured, round, film-coated tablets, with ‘R’ embossed on one side and plain on the other. Available in packs of 50 tablets.

Risperidone 0.5 mg Film-Coated Tablets:

Yellow coloured, oval, bismuth film-coated tablets, with ‘R’ embossed on one side and plain on the other. Available in packs of 30 tablets.

Risperidone 4 mg Film-Coated Tablets:

Green coloured, bismuth film-coated tablets, with ‘R’ embossed on one side and plain on the other. Available in packs of 30 tablets.

Risperidone 5 mg Film-Coated Tablets:

Brown coloured, oval, bismuth film-coated tablets, with ‘R’ embossed on one side and plain on the other. Available in packs of 30 tablets.

Not all pack sizes may be marketed.

Marketing Authorization Holder and Manufacturer:

The Product License holder is STE Chemicals LTD, Mill House, Hilllwood Road, Esher, Surrey, KT10 9BB.

The manufacturer responsible for batch release is Nestlé UK Ltd, 57 High Street, Dunbarton, West, NS10 1DL.

This information is available in alternative formats upon request.

The leaflet last text review in December 2010.
Risperidone 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg & 6 mg Film-Coated Tablets

LABELLING

CARTON

Risperidone 0.5 mg Film-Coated Tablets

Bar code

Each film-coated tablet contains 0.5 mg risperidone.
Also contains: lactose monohydrate.
For oral administration. To be taken as directed by your doctor.
Store in original package.
Please read the enclosed leaflet carefully before use.
Keep out of the reach and sight of children.

Distributor:
Ncolab Ltd, 57 High Street, Odiham, Hants, RG29 1LF.
PL 36390/0044
MA Holder: STD Chemicals Ltd. Hillbrow House,
Hillbrow Road, Esher, Surrey, KT10 9NW.

BLISTER FOIL

Risperidone 0.5mg Film-Coated Tablets
MA Holder: STD Chemicals Ltd.
Code No: XDDA795/XXXX

Risperidone 0.5mg Film-Coated Tablets
MA Holder: STD Chemicals Ltd.
Code No: XDDA795/XXXX

Risperidone 0.5mg Film-Coated Tablets
MA Holder: STD Chemicals Ltd.
Code No: XDDA795/XXXX
Risperidone 1mg Film-Coated Tablets

Each film-coated tablet contains 1 mg risperidone. Also contains lactose monohydrate.

For oral administration.
To be taken as directed by your doctor.
Store in original package.
Please read the enclosed leaflet carefully before use.
Keep out of the reach and sight of children.

Distributor:
Neela Ltd, 57 High Street, Odiham, Hants, RG29 1LF.
PL 3639000045
MA Holder: STD Chemicals Ltd, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW.

BLISTER FOIL
CARTON

Risperidone 2mg Film-Coated Tablets

Each film-coated tablet contains 2 mg risperidone. Also contains lactose monohydrate and Sunset Yellow (E110).

For oral administration.
To be taken as directed by your doctor.
Store in original package.
Please read the enclosed leaflet carefully before use.
Keep out of the reach and sight of children.

BLISTER FOIL

Risperidone 2 mg Film-Coated Tablets
MA Holder: STD Chemicals Ltd
Code No. XXDBUC00XXXX

Risperidone 2 mg Film-Coated Tablets
MA Holder: STD Chemicals Ltd
Code No. XXDBUC00XXXX

Risperidone 2 mg Film-Coated Tablets
MA Holder: STD Chemicals Ltd
Code No. XXDBUC00XXXX
Each film-coated tablet contains 3 mg risperidone. Also contains: lactose monohydrate.

For oral administration.
To be taken as directed by your doctor.
Store in original package.
Please read the enclosed leaflet carefully before use.
Keep out of the reach and sight of children.

Distributor:
Nestlé Ltd, 37 High Street, Oxted, Surrey, RH8 9LG

PL 36390/0044-9

MHRA-UKPAR – Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg & 6mg Film-Coated Tablets  PL 36390/0044-9  - 102 -
Risperidone 4mg Film-Coated Tablets

Each film-coated tablet contains: 4 mg risperidone.
Also contains: lactose monohydrate.

For oral administration.
To be taken as directed by your doctor.
Store in original package.
Please read the enclosed leaflet carefully before use.
Keep out of the reach and sight of children.

Risperidone 4mg Film-Coated Tablets

60 Film-coated Tablets

Distributor:
Novanab Ltd, 57 High Street, Odibam, Hants, RG29 1LF.

PE 36390/0048
MA Holder: STD Chemicals Ltd. Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW.

MHRA-UKPAR – Risperidone 0.5mg, 1mg, 2mg, 3mg, 4mg & 6mg Film-Coated Tablets PL 36390/0044-9