

IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PPA1151/091/001
Case No: 2077692

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Imbat Limited

Unit L2, North Ring Business Park, Santry, Dublin 9

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Risperdal 0.5 mg Tablets

the particulars of which are set out in the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **08/10/2010** until **16/04/2014**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Risperdal 0.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.5 mg risperidone.

Excipients: Also contains lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Product sourced from the United Kingdom:

Brownish-red, oblong tablets marked, Ris / 0.5 on one side and 'JANSSEN' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Risperdal is indicated for the treatment of schizophrenia.

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

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

Risperdal is indicated for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with 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

Risperdal may be given once 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 lower starting maintenance dose may be appropriate.

Doses above 10 mg/day have not been 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 episode in bipolar disorder*Adults*

Risperdal should be administered on a once daily schedule, starting with 2 mg risperidone. Dosage adjustment, 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 Risperdal 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 schizophrenia 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.

Risperdal 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 Risperdal must be regularly evaluated and justified on an ongoing basis.

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

Renal and hepatic impairment

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

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

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

Method of administration

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

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:

Where medically appropriate, gradual discontinuation of the previous treatment while Risperdal therapy is initiated is recommended. Also, if medically appropriate, when switching patients from depot antipsychotics, initiate Risperdal 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 or any of the excipients.

4.4 Special warnings and precautions for useElderly 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 Risperdal. In placebo-controlled trials with Risperdal in this population, the incidence of mortality was 4.0% for Risperdal-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 Risperdal 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 thiazides 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 medication 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 attacks in patients treated with Risperdal 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 patients populations. Risperdal 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 Risperdal 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.

Risperdal 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. Risperdal 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 antagonist 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, including Risperdal, should be discontinued.

Parkinson's disease and dementia with Lewy bodies

Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including Risperdal, 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 Risperdal. 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. Risperdal 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

Risperdal 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 Risperdal 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 RISPERDAL to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g. exercising strenuously, exposure to extreme heat, receiving concomitant treatment with anticholinergic activity, or being subject to dehydration.

Venous thromboembolism (VTE)

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

Children and adolescents

Before risperidone is prescribed to a child or adolescent with conduct disorder they should be fully assessed for physical and social causes of the aggressive behaviour such as pain or inappropriate environmental demands. The sedative effect of risperidone should be closely monitored in this population because of possible consequences on learning ability. A change in the time of administration of risperidone could improve the impact of the sedation on attention faculties of children and adolescents.

Risperidone was associated with mean increases in body weight and body mass index (BMI). Changes in height in the long-term open-label extension studies were within expected age-appropriate norms. The effect of long-term risperidone treatment on sexual maturation and height 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

The 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, procainamide), class III antiarrhythmics (e.g. amiodarone, sotalol), tricyclic antidepressant (i.e. amitriptyline), tetracyclic antidepressants (i.e. maprotiline), some antistaminics, other antipsychotics, some antimalarials (i.e. chinice 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 Risperdal 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.

Risperdal 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.

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

Potential for other medicinal products to affect Risperdal

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 Risperdal.

Fluoxetine and paroxetine, CYP 2D6 inhibitors, may 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 Risperdal.

Verapamil, an inhibitor of CYP 3A4 and P-gp, increase 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 Risperdal in children and adolescents did not alter the pharmacokinetics and efficacy of Risperdal.

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

Concomitant use of oral Risperdal 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, RISPERDAL 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

Risperdal 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 $\geq 10\%$) 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$), very rare ($< 1/10,000$), and not known (cannot be estimated from the available clinical trial data). Within the frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse Drug Reactions by System Organ Class and Frequency	
Investigations	
<i>Common</i>	Blood prolactin increased ^a , Weight increased
<i>Uncommon</i>	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

<i>Rare</i>	Body temperature decreased
Cardiac disorders	
<i>Common</i>	Tachycardia
<i>Uncommon</i>	Atrioventricular block, Bundle branch block, Atrial fibrillation, Sinus bradycardia, Palpitations
Blood and lymphatic system disorders	
<i>Uncommon</i>	Anaemia, Thrombocytopenia
<i>Rare</i>	Granulocytopenia
<i>Not known</i>	Agranulocytosis
Nervous system disorders	
<i>Very common</i>	Parkinsonism ^b , Headache
<i>Common</i>	Akathisia ^b , Dizziness, Tremor ^b , Dystonia ^b , Somnolence, Sedation, Lethargy, Dyskinesia ^b
<i>Uncommon</i>	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, Trandive dyskinesia, Speech disorder, Coordination abnormal, Hypoaesthesia
<i>Rare</i>	Neuroleptic malignant syndrome, Diabetic coma, Cerebrovascular disorder, Cerebral ischaemia, Movement disorder.
Eye disorders	
<i>Common</i>	Vision blurred
<i>Uncommon</i>	Conjunctivitis, Ocular hyperaemia, Eye discharge, Eye swelling, Dry eye, Lacrimation increased, Photophobia
<i>Rare</i>	Visual acuity reduced, Eye rolling, Glaucoma
Ear and labirynth disorders	
<i>Uncommon</i>	Ear pain, Tinnitus
Respiratory, Thoracic and mediastinal disorders	
<i>Common</i>	Dyspnoea, Epistaxis, Cough, Nasal congestion, Pharyngolaryngeal pain
<i>Uncommon</i>	Wheezing, Pneumonia aspiration, Pulmonary congestion, Respiratory disorder, Rales, Respiratory tract congestion, Dysphonia
<i>Rare</i>	Sleep apnea syndrome, Hyperventilation
Gastrointestinal disorders	
<i>Common</i>	Vomiting, Diarrhoea, Constipation, Nausea, Abdominal pain, Dyspepsia, Dry mouth, Stomach discomfort
<i>Uncommon</i>	Dysphagia, Gastritis, Faecal incontinence, Faecaloma
<i>Rare</i>	Intestinal obstruction, Pancreatitis, Lip swelling, Chilitis
Renal and urinary disorders	
<i>Common</i>	Enuresis
<i>Uncommon</i>	Dysuria, Urinary incontinence, Pollakiuria
Skin and subcutaneous tissue disorders	
<i>Common</i>	Rash, Erythema
<i>Uncommon</i>	Andioedema, Skin lesion, Skin disorder, Pruritus, Acne, Skin discolouration, Alopecia, Seborrhoeic dermatitis, Dry skin, Hyperkeratosis
<i>Rare</i>	Dandruff
Musculoskeletal and connective tissue disorders	
<i>Common</i>	Arthralgia, Back pain, Pain in extremity
<i>Uncommon</i>	Muscular weakness, Myalgia, Neck pain, Joint swelling, Posture abnormal, Joint stiffness, Musculoskeletal chest pain

<i>Rare</i>	Rhabdomyolysis
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Endocrine disorders	
<i>Rare</i>	Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	
<i>Common</i>	Increased appetite, Decreased appetite
<i>Uncommon</i>	Anorexia, Polydipsia
<i>Very rare</i>	Diabetic ketoacidosis
<i>Not known</i>	Water intoxication
Infections and infestations	
<i>Common</i>	Pneumonia, Influenza, Bronchitis, Upper respiratory tract infection, Urinary tract infection
<i>Uncommon</i>	Sinusitis, Viral infection, Ear infection, Tonsillitis, Cellulitis, Otitis media, Eye infections, Localised infection, Acarodermatitis, Respiratory tract infection, Cystitis, Onychomycosis
<i>Rare</i>	Otitis media chronic
General disorders and administration site conditions	
<i>Common</i>	Pyrexia, Fatigue, Peripheral oedema, Asthenia, Chest pain
<i>Uncommon</i>	Face oedema, Gait disturbance, Feeling abnormal, Sluggishness, Influenza like illness, Thirst, Chest discomfort, Chills
<i>Rare</i>	Generalised oedema, Hypothermia, Drug withdrawal syndrome, Peripheral coldness
Immune system disorders	
<i>Uncommon</i>	Hypersensitivity
<i>Rare</i>	Drug hypersensitivity
<i>Not known</i>	Anaphylactic reaction
Hepatobiliary disorders	
<i>Rare</i>	Jaundice
Reproductive system and breast disorders	
<i>Uncommon</i>	Amenorrhoea, Sexual dysfunction, Erectile dysfunction, Ejaculation disorder, Galactorrhoea, Gynaecomastia, Menstrual disorder, Vaginal discharge
<i>Not known</i>	Priapism
Psychiatric disorders	
<i>Very common</i>	Insomnia
<i>Common</i>	Anxiety, Agitation, Sleep disorder
<i>Uncommon</i>	Confusional state, Mania, Libido decreased, Listless, Nervousness
<i>Rare</i>	Anorgasmia, Blunted affect

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

^b Extrapyrarnidal 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 spas, 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.

Cases of venous thromboembolism, including pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs – Frequency unknown.

The following is a list of additional ADRs associated with risperidone that have been identified as ADRs during

clinical trials investigation the ling-acting injectable risperidone formulation (RISPERDAL CONSTA) but were not determined to be ADRs in the clinical trials investigation oral Risperdal. This table excludes those ADRs specifically associated with the formulation or injection route of administration of RIPSERDAL CONSTA.

Additional Adverse Drug Reactions Reported With RISPERDAL CONSTA but Not With Oral RISPERDAL by System Organ Class
Investigation
Weight decreased, Gamma-glutamyltransferase increased, Heptaic enzyme increased
Cardiac Disorders
Bradycardia
Blood and Lymphatic Disorders
Neutropenia
Nervous System Disorders
Paresthesia, Convulsion
Eye Disorders
Blepharospasm
Ear and Labyrinth Disorders
Vertigo
Gastrointestinal Disorders
Toothache, Tongue spasm
Skin and Subcutaneous Tissue Disorders
Eczema
Musculoskeletal, Connective Tissue, and Bone Disorders
Buttock pain
Infections and Infestations
Lower respiratory tract infection, Infection, Gastroenteritis, Subcutaneous abscess
Injury and Poisoning
Fall
Vascular Disorders
Hypertension
General Disorders and Administration Site Conditions
Pain
Psychiatric Disorders
Depression

Class effects

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

Weight gain

The proportions of Risperdal and placebo-treated adult patients with schizophrenia meeting a weight gain criterion of $\geq 7\%$ of body weight were compared on a pool of 6- to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for Risperdal (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 $\geq 7\%$ at endpoint was comparable in the Risperdal (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 7.3kg after 12 months of treatment. The expected weight gain for normal children between 5-12 years of age is 3 to 5kg per year. From 12-16 years of age, this magnitude of gaining 3 to 5kg per year is

maintained for girls, while boys gain approximately 5kg per year.

Additional information on special populations

Adverse drug reactions that were reported with higher incidence in elderly patients with dementia or paediatric patients that 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 $\geq 5\%$ in elderly patients with dementia and with at least twice the frequency seen in other adult populations: urinary tract infections, peripheral oedema, lethargy, and cough.

Paediatric patients

The following ADRs were reported with a frequency $\geq 5\%$ 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 Risperdal and paroxetine. In case of acute overdosage, 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 Risperdal. Therefore, appropriate supportive measures should be instituted.

Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, anticholinergic 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 serotonergic 5-HT₂ and dopaminergic D₂ receptors. Risperidone binds also to alpha₁-adrenergic receptors, and, with lower affinity, to H₁-histaminergic and alpha₂-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D₂ antagonist, 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 10mg/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 16mg/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 16mg/day administered twice-daily), the 4, 8, and 16mg/day risperidone dose groups were superior to the 1mg 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 8mg/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 6mg/day (starting dose 3mg in two studies and 2mg 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 \geq 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 6mg/day starting at 2mg/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 6mg/day starting at 2mg/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 2mg/day. Two flexible-dose studies included risperidone dose groups in the range of 0.5 to 4mg/day and 0.5 to 2mg/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

Risperdal orodispersible tablets and oral solution are bio-equivalent to RISPERDAL film-coated tablets. 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 concentrations 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 are 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 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

Lactose
Maize starch
Microcrystalline cellulose
Hypromellose
Magnesium stearate
Colloidal anhydrous silica
Sodium lauryl sulphate
Propylene glycol
Titanium dioxide (E171)
Talc
Red ferric oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The shelf life expiry date of this product is the date shown on the blister strips and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Overlabelled cardboard outer containing blister strips.
Pack size: 20 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Imbat Limited
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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1151/91/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th April 2009

10 DATE OF REVISION OF THE TEXT

October 2010