Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Resdal 2 mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 2 mg risperidone.

Excipients: aspartame (E951), sorbitol (E420).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet.

Round, slightly convex, pink marbled orodispersible tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Resdal is indicated for the treatment of schizophrenia.

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

Resdal 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.

Resdal 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

Resdal orodispersible tablets should not be divided. When administration of 0.25 mg or dose increments of 0.25 mg is necessary another preparation containing risperidone should be used.

<u>Schizophrenia</u>

Adults

Resdal 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

Resdal 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 Resdal 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.

Resdal 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 Resdal must be evaluated and justified on an ongoing basis.

Resdal 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.

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

Method of administration

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

As the orodispersible tablets are fragile, they should not be pushed through the foil as this will cause damage to the tablet. The blister is opened by pulling up the edge of the foil and peeling it off. Then the tablet should be tipped out. The tablet should be taken immediately after removal from the blister. The tablet begins disintegrating within a few seconds when placed on the tongue and the use of water is unnecessary. No attempt should be made to divide the tablet.

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 Resdal therapy is initiated is recommended. Also, if medically appropriate, when switching patients from depot antipsychotics, initiate Resdal 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. In placebo-controlled trials with risperidone in this population, the incidence of mortality was 4.0% for risperidone-treated patients compared to 3.1% for placebo-treated patients. The 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 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 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. {Product name} 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 Resdal 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.

Resdal 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.

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 Resdal and preventive measures undertaken.

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. Resdal 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 Resdal, should be discontinued.

Parkinson’s disease and dementia with Lewy bodies

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

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

Priapism

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

Body temperature regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines. Appropriate care is advised when prescribing Resdal 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

The orodispersible tablets contain aspartame. Aspartame is a source of phenylalaninewhich may be harmful for people with phenylketonuria.
Resdal orosdispersible tablets contain sorbitol also. Patients with hereditary problems of fructose intolerance 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 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 Resdal to affect other medicinal products

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

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

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

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

Potential for other medicinal products to affect Resdal

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 Resdal.

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 Resdal.

Verapamil, an inhibitor of CYP 3A4 and P−gp, increases the plasma concentration of risperidone.

Galantamine and donepezil do not show a clinically relevant effect on the pharmacokinetics of risperidone and on the active antipsychotic fraction.

Phenothiazines, tricyclic antidepressants, and some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction.

The combined use of psychostimulants (e.g., methylphenidate) with risperidone in children and adolescents did not alter the pharmacokinetics and efficacy of risperidone.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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, Resdal 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 breastfeeding should be weighed against the potential risks for the child.

4.7 Effects on ability to drive and use machines

Resdal 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

	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Infections and infestations		Pneumonia, Influenza, Bronchitis, Upper respiratory tract infection, Urinary tract infection	Sinusitis, Viral infection, Ear infection, Tonsillitis, Cellulitis, Otitis media, Eye infection, Localised infection, Acaroder-matitis, Respiratory tract infection, Cystitis, Onychomycosis	Otitis media chronic		
Blood and lymphatic system disorders			Anaemia, Thrombo-cytopenia	Granulocytopenia		Agranulocytosis
Immune system disorders			Hypersensitivity	Drug hypersensitivity		Anaphylactic reaction
Endocrine disorders				Inappropriate antidiuretic hormone secretion		
Metabolism and nutrition disorders		Increased appetite, Decreased appetite	Diabetes mellitus[c], Anorexia, Polydipsia.	Hypoglycemia	Diabetic ketoaci-dosis	Water intoxication
Psychiatric disorders	Insomnia	Anxiety, Agitation, Sleep disorder	Confusional state, Mania, Libido decreased, Listless, Nervousness	Anorgasmia, Blunted affect		

Nervous system disorders	Parkinso-nism[b], Headache	Akathisia[b], Dizziness, Tremor[b], Dystonia[b], Somnolence, Sedation, Lethargy, Dyskinesia[b]	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	Neuroleptic malignant syndrome, Diabetic coma, Cerebrovascular disorder, Cerebral ischaemia, Movement disorder		
Eye disorders		Vision blurred	Conjunctivitis, Ocular hyperaemia, Eye discharge, Eye swelling, Dry eye, Lacrimation increased, Photophobia	Visual acuity reduced, Eye rolling, Glaucoma		
Ear and labyrinth disorders			Ear pain, Tinnitus			
Cardiac disorders		Tachycardia	Atrioventricular block, Bundle branch block, Atrial fibrillation, Sinus bradycardia, Palpitations			
Vascular disorders			Hypotension, Orthostatic hypotension, Flushing			Venous thromboembolism, including pulmonary embolism and deep vein thrombosis
Respira-tory, thoracic and mediastinal disorders		Dyspnoea, Epistaxis, Cough, Nasal congestion, Pharyngo-laryngeal pain	Wheezing, Pneumonia aspiration, Pulmonary congestion, Respiratory disorder, Rales, Respiratory tract congestion, Dysphonia	Sleep apnea syndrome, Hyperventilation		
Gastro-intestinal disorders		Vomiting, Diarrhoea, Constipation, Nausea, Abdominal pain, Dyspepsia, Dry mouth, Stomach discomfort	Dysphagia, Gastritis, Faecal incontinence, Faecaloma	Intestinal obstruction, Pancreatitis, Lip swelling, Cheilitis		
Hepato-biliary disorders				Jaundice		
Skin and subcuta-neous tissue disorders		Rash, Erythema	Angioedema, Skin lesion, Skin disorder, Pruritus, Acne, Skin discolourration, Alopecia, Seborrhoeic dermatitis, Dry skin, Hyperkeratosis	Dandruff		
Musculo-skeletal and connective tissue disorders		Arthralgia, Back pain, Pain in extremity	Muscular weakness, Myalgia, Neck pain, Joint swelling, Posture abnormal, Joint stiffness, Musculo-skeletal chest pain	Rhabdomyolysis		
Renal and urinary disorders		Enuresis	Urinary retention, Dysuria, Urinary incontinence, Pollakiuria,			
Reproduc-tive system and breast disorders			Amenorrhoea, Sexual dysfunction, Erectile dysfunction, Ejaculation disorder, Galactorrhoea, Gynaecomastia, Menstrual disorder, Vaginal discharge			Priapism

General disorders and administra-tion site conditions		Pyrexia, Fatigue, Peripheral oedema, Asthenia, Chest pain	Face oedema, Gait disturbance, Feeling abnormal, Sluggishness, Influenza like illness, Thirst, Chest discomfort, Chills	Generalised oedema, Hypothermia, Drug withdrawal syndrome, Peripheral coldness		
Investigations		Blood prolactin increased[a], Weight increased	Electrocardiogram QT prolonged, Electrocar-diogram abnormal, Blood glucose increased, Transaminases increased, White blood cell count decreased Body temperature increased, Eosinophil count increased, Haemoglobin decreased, Blood creatine phosphokinase increased	Body temperature decreased		

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

[b]Extrapyramidal disorder may occur: Parkinsonism (salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies, muscle tightness, akinesia, nuchal rigidity, muscle rigidity, parkinsonian gait, and glabellar reflex abnormal), akathisia (akathisia, restlessness, hyperkinesia, and restless leg syndrome), tremor, dyskinesia (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia.

Dystonia includes dystonia, muscle spasms, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm and trismus. Tremor includes tremor and parkinsonian rest tremor. It should be noted that a broader spectrum of symptoms are included, that do not necessarily have an extrapyramidal origin.

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

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

Additional adverse drug reactions reported with long-acting injectable risperidone formulation but not with oral risperidone by system organ class

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Investigations
Weight decreased, Gamma−glutamyltransferase increased, Hepatic enzyme increased

Cardiac Disorders
Bradycardia

Blood and Lymphatic Disorders
Neutropenia

Nervous System Disorders
Paresthesia, Convulsion

Eye Disorders
Blepharospasm

Ear and Labyrinth Disorders
Vertigo

Gastrointestinal Disorders
Toothache, Tongue spasm

Skin and Subcutaneous Tissue Disorders
Eczema

Musculoskeletal, Connective Tissue, and Bone Disorders
Buttock pain

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

Injury and Poisoning
Fall

Vascular Disorders
Hypertension

General Disorders and Administration Site Conditions
Pain

Psychiatric Disorders
Depression

Class effects

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

Weight gain

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

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

Additional information on special populations

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

Elderly patients with dementia

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

Paediatric patients

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

4.9 Overdose

Symptoms

In general, reported signs and symptoms have been those resulting from an exaggeration of the known pharmacological effects of risperidone. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, QT−prolongation and convulsions have been reported. Torsade de Pointes has been reported in association with combined overdose of risperidone and paroxetine.
In case of acute overdose, the possibility of multiple drug involvement should be considered.

Treatment

Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if the patient is unconscious) and administration of activated charcoal together with a laxative should be considered only when drug intake was less than one hour before. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to risperidone. 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 $5-HT_2$ and dopaminergic D_2 receptors. Risperidone binds also to alpha1-adrenergic receptors, and, with lower affinity, to H_1−histaminergic and alpha2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D_2 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, placebocontrolled 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

Resdal orodispersible tablets are bio-equivalent to Resdal 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 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 9hydroxy−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, dosedependant 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 D_2−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 D_2 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

Mannitol
Basic butylated methacrylate copolymer
Povidone K25
Microcrystalline cellulose
Low-substituted hydroxypropylcellulose
Aspartame (E951)
Crospovidone
Red iron oxide (E172)
Spearmint flavour
Peppermint flavour (containing in particular sorbitol (E420), levomenthol)
Calcium silicate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Perforated unit dose blister (OPA/Aluminium/PVC/Aluminium).
Pack sizes of 10, 20, 28, 30, 56 and 60 orodispersible tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Niche Generics Limited
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Hitchin
Hertfordshire SG4 0TW
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1063/026/003

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10 DATE OF REVISION OF THE TEXT

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