# Part II

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Risperdal Quicklet 1mg Orodispersible Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 1mg risperidone.

*For full list of excipients, see section 6.1.*

## 3 PHARMACEUTICAL FORM

Orodispersible tablet.

*Product imported from the Netherlands and the UK:*
Light coral, square biconvex tablets, etched “R1”.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

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

Risperdal Quicklet is effective in maintaining clinical improvement in patients who have shown an initial treatment response.

Risperdal Quicklet is also indicated for the treatment of severe behavioural disturbances in patients with dementia in whom symptoms such as aggressiveness (verbal outbursts, physical violence), activity disturbances (agitation, wandering) or psychotic symptoms are prominent and lead to patient suffering, disability potential danger or self harm.

Such patients should be closely monitored and Risperdal Quicklet continued only if the benefits of treatment are considered to outweigh the risks for the individual patient. *(See Section 4.4 Special Warning and Precautions for Use and Section 4.8 Undesirable Effects.)*

Risperdal Quicklet is indicated in the treatment of conduct and other disruptive behaviour disorders in adults with impaired social, academic or occupational functioning, in whom challenging behaviours (e.g. aggression, impulsiveness, and self-injury) are prominent. Risperdal is also indicated for this condition in children and adolescents when conduct disorders are severe.

Risperdal Quicklet is also indicated as adjunctive therapy to mood stabilizers in the acute treatment of manic episodes associated with bipolar disorders.

Treatment of severe disruptive behavioural symptoms in children and adolescents with autism and pervasive developmental disorders.

## 4.2 Posology and method of administration

### 4.2a Schizophrenia

Switching from other antipsychotics:

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

Adults

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

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

Elderly

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

Patients should be monitored and treatment reviewed at regular intervals.

Children

Use of Risperdal for schizophrenia in children ages less than 15 years has not been formally evaluated and experience is limited.

Renal and liver disease

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

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

### 4.2b Behavioural Disturbances in patients with Dementia

The Risperdal Quicklet formulation should not be used for the initial doses in patients with dementia as the tablets must not be divided.

A starting dose of 0.25 mg bd. is recommended. This dosage can be individually adjusted by increments of 0.25 mg bd. every other day. The optimum dose is 0.5 mg bd. for most patients. Some patients, however, may benefit from doses up to 1 mg bd. Once patients have reached their target dose, a once daily dosing regimen can be considered.

Risperdal Quicklet should be used with caution in this group of patients. Treatment should be reviewed regularly and discontinued if no benefit is seen or if intolerance occurs. *(See Section 4.1, Therapeutic Indications, 4.4 Special Warnings and Special Precautions for Use and Section 4.8 Undesirable Effects.)*

### 4.2c Conduct and other disruptive behaviour disorders

For children and adolescents with conduct and other disruptive behaviour disorders, risperidone should be prescribed by physicians with specialist knowledge in this area (e.g. child psychiatrists).

*Patients >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.

*Patients <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 ever 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 evaluated and justified on an ongoing basis.

Risperdal has not been formally evaluated in children ages less than 5 years and experience is limited.

### 4.2.d Bipolar mania – adjunctive therapy

A starting dosage of 2 mg once daily is recommended. This can be individually adjusted by increments of up to 2 mg/day not more frequently than every other day. Most patients will benefit from doses between 2 and 6 mg/day.

Treatment with risperidone should be reviewed regularly and discontinued if no benefit is seen or intolerance occurs.

### 4.2.e. Autism (children aged 5 or over and adolescents)

The dosage of Risperdal should be individualised according to the needs and response of the patient.

Dosing should be initiated at 0.25 mg per day for patients<20kg and 0.5 mg per day for patients ≥20kg.

On Day 4, the dose may be increased by 0.25 mg for patients <20kg and 0.5 mg for patients ≥20kg. This dose should be maintained and response should be assessed at approximately Day 14. Only patients not achieving sufficient clinical response should additional dose increased be considered. Dose increases may proceed at 2-week intervals in increments of 0.25mg for patients<20kg or 0.5mg for patients ≥20kg.

In clinical studies, the maximum dose studied did not exceed a total daily dose of 1.5mg in patients <20kg, 2.5mg in patients ≥20kg, or 3.5mg in patients >45kg.

**Doses of Risperdal® in Pediatric Patients With Autistic Disorder (by total mg/day)**

| *Weight Categories* | *Days 1-3* | *Days 4-14*$^{+}$ | *Increments if Dose Increases are Needed* | *Dose Range* |
|---|---|---|---|---|
| <20kg | 0.25mg | 0.5 mg | +0.25 mg | +0.5 mg |
| ≥20kg | 0.5mg | 1.00 mg | 0.5 mg-1.5 mg at >2 week intervals | 1.0 mg-2.5 mg* at > 2 week intervals |

*Subjects weighing >45kg may require higher doses: maximum dose studied was 3.5mg/day

For prescribers preferring to dose on a mg/kg/day basis the following guidance is provided.

**Doses of Risperdal® in Pediatric Patients With Autistic Disorder (by mg/kg/day)**

| *Weight Categories* | *Days 1-3* | *Days 4-14+* | *Increments if Dose Increases are Needed* | *Dose Range* |
|---|---|---|---|---|
| All | 0.01mg/kg/day | 0.02mg/kg/day | +0.01mg/kg/day | 0.02 mg/kg/day - 0.06mg/kg/day at > 2 week intervals |

Risperdal can be administered once daily or twice daily.

Patients experiencing somnolence may benefit from a switch in dosing from once daily to either once daily at bedtime or twice daily.

Once sufficient clinical response has been achieved and maintained, consideration may be given to gradually lowering the dose to achieve the optimal balance of efficacy and safety. There is insufficient evidence from controlled trials to indicate how long the patient with Autistic Disorder should be treated with Risperdal

Method of administration

Oral use. The Risperdal Quicklet tablet should be placed on the tongue. It begins disintegrating in the mouth within seconds and can be swallowed subsequently with or without water. If taken with food, the mouth should be empty before placing the tablet on the tongue.

As the tablets are fragile, they should not be pushed through the foil as this will cause damage. Open blister by pulling up the edge of the foil and peeling it off, then tip the tablet out. After removal from its blister, the RISPERDAL® QUICKLET® tablet should be consumed immediately as it cannot be stored once removed.

RISPERDAL® QUICKLET® tablets begin disintegrating within seconds when placed on the tongue and the use of water is unnecessary. No attempt should be made to split the tablet.

## 4.3 Contraindications

Risperdal Quicklet is contra-indicated in patients with a known hypersensitivity to the product.

## 4.4 Special warnings and precautions for use

*Elderly patients with dementia*

Overall Mortality

Elderly patients with dementia treated with atypical antipsychotic drugs had an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs, including 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 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. Odds ratio [95% confidence interval] was 1.82 [0.65, 5.14]). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials.

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 should be combination 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, dehydrations was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

*Cerebrovascular Adverse Events (CAE)*

In placebo-controlled trials conducted in elderly patients with dementia there was higher incidence of cerebrovascular adverse events(cerebrovascular accidents and transient ischaemic attacks) including fatalities, in patients (mean age 85 years, range 73-97) treated with Risperdal, compared to patients receiving placebo. Cerebrovascular adverse events (CVAEs) occurred in 3.3% (33/989) of patients treated with risperidone and 1.2% (8/693) of patients treated with placebo.

Prior to treatment, physicians should carefully consider the risk of cerebrovascular adverse events with Risperdal (given the observations in elderly patients with dementia detailed above) before treating any patient with a previous history of CVA/TIA, or vascular co-morbidities such as hypertension and cardiovascular disease. These patients should be closely monitored during treatment and patients/caregivers advised 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. Patients presenting with such symptoms should be promptly evaluated and treatment discontinued, if appropriate.

*Alpha-blocking activity*

Due to the alpha-blocking activity of Risperdal, orthostatic hypotension can occur, especially during the initial dose-titration period. Risperdal should be used with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolaemia or cerebrovascular disease) and the dosage should be gradually titrated as recommended. A dose reduction should be considered if hypotension occurs.

*Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS)*

Drugs 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. It has also been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. Risperdal should therefore have a reduced risk of inducing tardive dyskinesia as compared to classical neuroleptics. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs should be considered.

*Neuroleptic Malignant Syndrome (NMS)*

As with other neuroleptics, rare cases of Neuroleptic Malignant Syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels have been reported. In such an event, all antipsychotic drugs, including Risperdal, should be discontinued.

Physicians should assess the risks versus the benefits when prescribing Risperdal, to patients with Lewy body dementia or Parkinson’s disease since they may be at increased risk of neuroleptic malignant syndrome or a worsening of

Parkinson-like symptoms.

*Hyperglycaemia*

Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in vary 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 *(see also section 4.8 Undesirable effects).*

*Other*

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

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

For posology recommendations in elderly patients, patients with renal and liver disease and patients with dementia, please see recommended doses and dosage schedule.

As with other antipsychotics, patients should be advised to refrain from excessive eating in view of the possibility of weight gain.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medication.

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

Possible interactions of Risperdal Quicklet with other drugs have not been systematically evaluated. Given the primary CNS effects of Risperdal Quicklet it should be used with caution in combination with other centrally acting drugs.

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

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

Topiramate modestly reduces the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance.

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Fluoxetine and paroxetine, CYP2D6 inhibitors, may increase the plasma concentration of risperidone but less so of the active antipsychotic fraction. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of Risperdal. Based on in vitro studies, the same interaction may occur with haloperidol.

Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increased the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction. The cholinesterase inhibitors, galantamine and donezepil, do not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction.

When Risperdal Quicklet is taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.

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

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

The incidence of somnolence was reduced when psychostimulants were used concomitantly.

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

As with Risperdal tablets and liquid, food does not affect the absorption of risperidone from the stomach. The effect of food particles in the mouth on absorption has not been studied.

## 4.6 Pregnancy and lactation

Although, in experimental animals, risperidone did not show direct reproductive toxicity, some indirect, prolactin- and CNS-mediated effects were observed, typically delayed oestrus and changes in mating and nursing behaviour in rats. No teratogenic effect of risperidone was noted in any study. The safety of Risperdal Quicklet for use during human pregnancy has not been established. Therefore, Risperdal Quicklet should only be used during pregnancy if the benefits outweigh the risks.

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

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

Risperdal Quicklet is generally well tolerated and in many instances it has been difficult to differentiate adverse events from symptoms of the underlying disease.

Adverse events observed in association with the use of Risperdal Quicklet include:

*Common:* Insomnia, agitation, anxiety, headache. In children and adolescents, mild and transient sedation has been reported more frequently than in adults.

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

Cerebrovascular adverse events, including cerebrovascular accidents (some of which were fatal), and transient ischaemic attacks, have been reported during treatment with Risperdal. *(See also Section 4.4, Special Warning and Special Precautions for Use.)*

Risperidone has a lower propensity to induce extrapyramidal symptoms than classical neuroleptics. However, in some cases the following extrapyramidal symptoms may occur: tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia. If acute in nature, these symptoms are usually mild and are reversible upon dose reduction and/or administration of antiparkinson medication, if necessary.

Occasionally, orthostatic dizziness, hypotension including orthostatic, tachycardia including reflex tachycardia and hypertension have been observed following administration of Risperdal.

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

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

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

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

The following adverse events have been reported as very common in children and adolescents with conduct disorders: somnolence, headaches, hyperprolactinaemia, weight increase.

Hyperglycaemia and exacerbation of pre-existing diabetes have been reported in very rare cases during risperidone treatment.

## 4.9 Overdose

Overdosages of up to 360 mg have been reported. In general, reported signs and symptoms have been those resulting from an exaggeration of the drug's known pharmacological effects. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose rare cases of QT-prolongation have been reported. In case of acute overdosage, the possibility of multiple drug involvement should be considered.

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

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

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Risperdal Quicklet is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

Risperidone is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-$HT_2$ and dopaminergic $D_2$ receptors.

Risperidone binds also to alpha$_1$-adrenergic receptors and, with lower affinity, to $H_1$-histaminergic and alpha$_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although Risperidone is a potent $D_2$ antagonist, an activity which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical neuroleptics.

Balanced central serotonin and dopamine antagonism may reduce the tendency to cause extrapyramidal side effects, and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

## 5.2 Pharmacokinetic properties

Risperdal Quicklet is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. The absorption is not affected by food and thus Risperdal Quicklet can be given with or without meals.

Risperidone is partly metabolised by cytochrome P-450 IID6 to 9-hydroxy-risperidone which has a similar pharmacological activity to risperidone. Risperidone plus 9-hydroxy-risperidone form the active antipsychotic fraction. Another metabolic pathway of risperidone is N-dealkylation.

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.

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

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 88%, that of 9-hydroxy-risperidone is 77%. 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.

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

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

## 5.3 Preclinical safety data

There are no prclinical data of relevance to the prescriber other than those already provided in other sections of the SPC.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Polacrilex resin
Gelatin
Mannitol (E421)
Glycine
Simeticone
Carbomer
Sodium hydroxide
Aspartame (E951)
Red ferric oxide (E172)
Peppermint oil

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

## 6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package.

## 6.5 Nature and contents of container

Blister packs containing 28 or 56 tablets contained in an outer cardboard carton.

## 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

PCO Manufacturing Ltd.,
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

## 8 Parallel Product Authorisation Number

PPA 0465/078/007

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 March 2006

## 10 DATE OF REVISION OF THE TEXT

October 2008