Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Risperdal 2 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2 mg of risperidone.
Excipients: Lactose, Orange yellow S (E110)
For a full list of excipients, *see Section 6.1*.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Product imported from The UK, Italy, The Netherlands, Belgium and Hungary:
Orange, oblong tablets with a breakline and 'Ris 2' on one side, plain on the other side.

Product imported from Greece:
Orange, oblong tablets with a breakline and 'Ris 2' on one side, 'JANSSEN' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Risperdal 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 also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia.

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

Risperdal is also indicated for the treatment of 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 continued only if the benefits of treatment are considered to outweigh the risks for the individual patient. (*See section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects.)*

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

Risperdal 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.

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 therapy is initiated is

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

Adults:
Risperdal may be given once or twice daily. All patients, whether acute or chronic, should start with 2 mg/day Risperdal. The dosage should 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 dose between 4 and 6 mg/day although in some patients 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 0.5mg bd is recommended. This dosage can be individually adjusted with 0.5mg bd increments to 1 to 2mg bd. Patients should be monitored and treatment reviewed at regular intervals.

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

Renal and liver disease:
A starting dose of 0.5mg bd is recommended. This dosage can be individually adjusted with 0.5mg bd increments to 1 to 2mg bd. Risperdal should be used with caution in this group of patients until further experience is gained.

4.2b Behavioural Disturbances in Patients with Dementia
A starting dose of 0.25mg b.d. is recommended. This dosage can be individually adjusted by increments of 0.25mg b.d. every other day. The optimum dose is 0.5mg b.d. for most patients. Some patients, however, may benefit from doses up to 1mg b.d. Once patients have reached their target dose, a once daily dosing regimen can be considered.

Risperdal 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 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.

4.2d 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 form 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 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 has not been formally evaluated in children aged less than 5 years and experience is limited.

Method of administration
Oral use.

4.3 Contraindications

Risperdal is contra-indicated in patients with a known hypersensitivity to risperidone or any other ingredients in the product.

4.4 Special warnings and precautions for use

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.

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

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.

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.

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

Data from randomized clinical trials conducted in elderly (>65 years) patients with dementia indicate that there is an approximately 3-fold increased risk of cerebrovascular adverse events (including cerebrovascular accidents, some of which were fatal and transient ischaemic attacks) in patients treated with risperidone, compared with 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 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.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Risperdal 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. 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 should be re-evaluated and increased if necessary. Conversely, on discontinuation of such drugs, the dosage of Risperdal should be re-evaluated and decreased if necessary.

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentrations of risperidone but not those of the 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 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, valproate or digoxin.

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.

4.6 Fertility, 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 for use during human pregnancy has not been established. Therefore, risperidone 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 should not breast feed.

4.7 Effects on ability to drive and use machines

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

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

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, headache, 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 360mg 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. 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 is a novel antipsychotic belonging to a new class of antipsychotic agents, the benzisoxazole-derivatives.

Risperdal is selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT2 and dopaminergic D2 receptors. Risperdal binds also to alpha-1-adrenergic receptors and, with lower affinity, to H1-histaminergic and alpha-2-adrenergic receptors. Risperdal has no affinity for cholinergic receptors. Although Risperdal is a potent D2 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 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 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 alpha-1-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

Nothing stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize starch
Microcrystalline cellulose
Hypromellose
Magnesium stearate
Colloidal anhydrous silica

Sodium laurilsulfate
Propylene glycol
Titanium dioxide (E171)
Talc
Orange yellow S (E110)

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 20 or 60 tablets.
Not all pack sizes may be marketed.

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
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 0465/078/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first arthorisation: 21 September 2001

Date of last renewal: 21 September 2006

10 DATE OF REVISION OF THE TEXT

April 2011