PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS S5

PROPRIETARY NAME (and dosage form)

PMI RISPIRIDONE 1 mg/ml (Oral Solution)

COMPOSITION

Each ml of the oral Solution contains 1 mg risperidone.

Preservative: Benzoic acid 0,15 % m/v

Other ingredients: hydrochloric acid, tartaric acid and purified water.

PHARMACOLOGICAL CLASSIFICATION

A.2.6.5 Central nervous system depressants. Miscellaneous structures.

PHARMACOLOGICAL ACTION

Pharmacodynamics

Risperidone is a benzisoxazole antipsychotic with a strong affinity for serotonin type 2 (5-HT_2) receptors and a slightly weaker affinity for dopamine type 2 (D2) receptors. Risperidone also has moderate affinity for the alpha$_1$-adrenergic, alpha$_2$-adrenergic, and H_1-histaminergic receptors. The affinity of risperidone for the serotonin 5-HT_{1A}, 5-HT_{1C} and 5-HT_{1D} receptors are low to moderate while its affinity for dopamine D_1 receptors and the haloperidol-sensitive sigma site is weak. Risperidone has negligible affinity for cholinergic-muscarinic, beta-adrenergic, and serotonin 5-HT_{1B} and 5-HT_3 receptors.

Pharmacokinetics

Absorption and Distribution:

Risperidone is rapidly and extensively absorbed after oral administration, peak plasma concentrations being reached within 1 to 2 hours. Food does not significantly affect the extent of absorption of risperidone. Distribution is rapid and extensive.

Biotransformation:

Risperidone is extensively metabolised in the liver by hydroxylation to its main active metabolite, 9-hydroxyrisperidone. Hydroxylation is mediated by the cytochrome P-450 isoenzyme CYP2D6.

After oral administration to psychotic patients, risperidone's half-life is about 3 hours. The elimination half-life of 9-hydroxyrisperidone and the active psychotic fraction is 24 hours.

Steady state is reached within 1 day for risperidone in most patients and 4 - 5 days for 9-hydroxyrisperidone. Risperidone plasma concentrations is dose proportional within the therapeutic dose range. Risperidone is bound to albumin and alpha, - acid glycoprotein. Plasma protein binding of risperidone is 88 % and 77 % for 9-hydroxyrisperidone. One week after administration 70 % of the dose is excreted in the urine and 14 % in the faeces. In the urine risperidone and 9-hydroxyrisperidone represent 35 – 45 % of the dose. Risperidone showed significantly higher active plasma concentrations and slower elimination in the elderly and in patients with moderately severe renal insufficiency. The plasma concentrations of risperidone were normal in patients with mild to moderate liver insufficiency.

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

INDICATIONS

PMI RISPERIDONE is indicated for:

- Acute and chronic schizophrenic psychoses and related psychosis in which positive symptoms and/or the negative symptoms are prominent. **PMI RISPERIDONE** also alleviates affective symptoms associated with schizophrenia. In patients who have shown an initial treatment response, **PMI RISPERIDONE** is also effective in maintaining the clinical improvement.

- Behavioural disturbances in patients with dementia in whom symptoms such as aggressiveness, activity disturbances or psychotic symptoms are prominent.
- Conduct and other disruptive behaviour disorders in children (aged 5 – 12 years), with subaverage intellectual functioning or mental retardation in whom destructive behaviours are prominent.

CONTRA-INDICATIONS

Hypersensitivity to risperidone or any of the excipients.

Conduct and other disruptive behaviour disorders in children: **PMI RISPERIDONE** is contra-indicated in children under 5 years as efficacy and safety in children under the age of 5 years have not been established.

Lewy body dementia. See “Warnings”.

The safety of **PMI RISPERIDONE** during Pregnancy and Lactation has not been established. See “Pregnancy & Lactation”.

WARNINGS

Hepatic and Renal Impairment

In patients with severe hepatic impairment and renal function metabolism, excretion and protein binding of **PMI RISPERIDONE** may be decreased; reduced dosage is recommended.

Tardive dyskinesia

Tardive dyskinesia (TD), a syndrome consisting of potentially irreversible, involuntary dyskinetic movements may develop in patients treated with **PMI RISPERIDONE**. Although this syndrome of TD appears to be most prevalent in the elderly, especially elderly females, it is impossible to predict at the onset of treatment which patients are likely to develop TD. See “Special Precautions”.

Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS) is a potentially fatal symptom complex that has been reported in association with the use of **PMI RISPERIDONE**. Clinical manifestations of NMS are hyperthermia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, cardiac arrhythmias and diaphoresis). Additional signs may include elevated creatine phosphokinase (CPK) levels, myoglobinuria (rhabdomyolysis), and acute renal failure. See "Special Precautions".

Concomitant use with furosemide

Caution is advised in patients treated with furosemide due to possible dehydration. See "Interactions".

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis and hyperosmolar coma or death, has been reported in patients treated with **PMI RISPERIDONE**.

Patients with an established diagnosis of diabetes mellitus who are started on **PMI RISPERIDONE** should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with **PMI RISPERIDONE** should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with **PMI RISPERIDONE** should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when **PMI RISPERIDONE** was discontinued. However, some patients required continuation of anti-diabetic treatment despite discontinuation of **PMI RISPERIDONE**.

Cerebrovascular Adverse Events

Cerebrovascular adverse events (CAE), including cerebrovascular accidents and transient ischaemic attacks, have been reported during treatment with **PMI RISPERIDONE**.

In placebo-controlled clinical trials in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events, including cerebrovascular accidents and

transient ischaemic attacks, in patients treated with **PMI RISPERIDONE** compared to patients receiving placebo (mean age 85 years; range 73 – 97 years).

Dementia associated with Parkinson's disease and senile dementia

Doctors should weigh the risks versus the benefits when prescribing **PMI RISPERIDONE** to patients with Parkinson's Disease or Dementia with Lewy bodies (DLB) since these groups may be at risk of Neuroleptic Malignant Syndrome (NMS) as well as having an increased

sensitivity to antipsychotic medications such as **PMI RISPERIDONE**. Manifestations of this increased sensitivity can include confusion, obtundation and postural instability with frequent falls, in addition to extrapyramidal symptoms.

In addition, in clinical trials, elderly **PMI RISPERIDONE** treated patients had a higher mortality than placebo treated elderly patients.

The risk of using **PMI RISPERIDONE** in combination with other medicines has not been systematically evaluated. Given the primary CNS depressive effects of **PMI RISPERIDONE**, it should be used with caution in combination with alcohol and other centrally acting medicines. **PMI RISPERIDONE** may antagonise the effect of levodopa and other dopamine agonists.

Alpha-blocking activity

Due to the alpha-blocking activity of **PMI RISPERIDONE**, (orthostatic) hypotension can occur, especially during the initial dose-titration period. **PMI RISPERIDONE** should be used with caution in patients with known cardiovascular disease, and the dosage should be gradually titrated, as recommended. A dose reduction should be considered if hypotension occurs.

Other

Seizures have been reported after treatment with **PMI RISPERIDONE**. Caution is recommended when treating patients with epilepsy.

Risperidone may exacerbate Parkinson's disease and may lower the seizure threshold. **PMI RISPERIDONE** should therefore be administered with caution to epileptic patients and patients with Parkinson's disease.

INTERACTIONS

Chronic administration of carbamazepine may increase the clearance of risperidone, thereby decreasing the plasma levels of the active antipsychotic fraction of **PMI RISPERIDONE** by

about 50 %. On discontinuation of carbamazepine or hepatic enzyme inducers, the dosage of **PMI RISPERIDONE** should be re-evaluated and decreased if necessary. Chronic administration of clozapine may decrease the clearance of **PMI RISPERIDONE** resulting in increased plasma levels.

Cimetidine and ranitidine increased the bioavailability of **PMI RISPERIDONE**, but only marginally that of the active psychotic fraction.

PMI RISPERIDONE may antagonise the effect of levodopa and other dopamine agonists (bromocriptine and pergolide).

Lithium: C_{max} and AUC of lithium were non significantly increased, but T_{max} of lithium was increased from 2,4 hours to 3,0 hours.

Concomitant use of alcohol or other centrally nervous system (CNS) depression-producing medication may have additive CNS depressant effects.

Furosemide: In placebo controlled trials in elderly patients with dementia, there was a higher mortality in patients treated with furosemide and **PMI RISPERIDONE** when compared to patients treated with **PMI RISPERIDONE** alone. Caution is advised in these patients. Dehydration was an overall risk for mortality and should be carefully avoided in these patients.

Fluoxetine and paroxetine may increase the plasma concentration of the anti-psychotic fraction by raising the concentration of risperidone; when either fluoxetine or paroxetine is initiated or discontinued, the doctor should re-evaluate the **PMI RISPERIDONE** dosing.

Valproate: T_{max} of valproate increased from 1,3 hours to 2,0 hours.

Venlafaxine**:** **PMI RISPERIDONE** AUC increased and **PMI RISPERIDONE** clearance decreased, but no effect on 9-hydroxyrisperidone and the active moiety.

Potential hypotensive effects of hypotension-producing medication may enhance the hypotensive effects of **PMI RISPERIDONE**. There may be an increased risk of QT prolongation when **PMI RISPERIDONE** is given with other drugs that are known to cause this effect.

Phenothiazines and some beta-blockers may increase the plasma concentration of risperidone but not that of the anti-psychotic fraction.

When **PMI RISPERIDONE** is taken together with other highly protein-bound medicines (e.g. diazepam, warfarin, digitoxin, imipramine and propranolol), there is no clinically relevant displacement of either agent from the plasma proteins.

PREGNANCY AND LACTATION

Safety of **PMI RISPERIDONE** in pregnancy or lactating women has not been established. Risperidone and 9-hydroxyrisperidone are excreted in human breast milk. Reversible extrapyramidal symptoms, including hypertonia, hypotonia, jitteriness, tremor, muscle rigidity, twitching and convulsions, feeling disorder and withdrawal symptoms have been observed in neonates following postmarketing use of risperidone during the last trimester of pregnancy.

DOSAGE AND DIRECTIONS FOR USE

Schizophrenia:

*Switching from other antipsychotics to **PMI RISPERIDONE***

When, when switching patients from depot antipsychotics, initiate **PMI RISPERIDONE** therapy in place of the next scheduled injection. The need for continuing existing medically appropriate, gradual discontinuation of the previous treatment is recommended. Also if medically appropriate anti-Parkinson medications should be re-evaluated periodically.

Adults

PMI RISPERIDONE may be given on either a once a day or twice a day schedule.

Patients should start with 2mg/day **PMI RISPERIDONE**; this may be increase to 4mg/day on the second day.

From then on, the dosage can be maintained unchanged, or further individualised, if needed.

Most patients will benefit from daily doses of between 4 mg/day to 8 mg/day. Doses above 6 mg/day (when administered twice daily) were associated with more extrapyramidal symptoms and other adverse effects and are not generally recommended. In some patients, particularly with first episode acute psychosis, a slower titration phase and a lower starting and maintenance dose may be appropriate.

Doses above 10 mg/day have not been shown to be superior in efficacy to lower doses and may cause an increased incidence of side-effects such as extrapyramidal symptoms. Dosages above 10 mg/day should only be considered if the benefits outweigh the risk. The maximum total daily dose is 16 mg/day. A benzodiazepine may be added to **PMI RISPERIDONE** if additional sedation is required.

***Hepatic and renal function impairment*:**

Clinical experience is lacking in these patient populations and **PMI RISPERIDONE** should therefore be administered with caution. It is recommended to halve both the starting dose and the subsequent dose increments.

Elderly patients

A starting dose of 0,5 mg twice daily is recommended. The dose can be individually adjusted with increments of 0,5 mg twice daily to 1 – 2 mg twice daily.

Children

Not for children under 15 years as efficacy and safety in children under the age of 15 have not been demonstrated in schizophrenia.

Behavioural disturbances in patients with dementia:

A starting dose of 0,25 mg twice daily is recommended. This dosage can be individually increased 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. However, some patients may benefit from doses up to 1 mg twice daily.

Once patients have reached their target dose, a once-daily dosing regimen can be considered.

The continued use of **PMI RISPERIDONE** must be evaluated and justified on an ongoing basis.

Conduct and other disruptive behaviour disorders in children 5 – 12 years of age:

Subjects < 50 kg

A starting dose of 0,01 mg/kg once daily is recommended. This dosage can be individually adjusted by increments of 0,01 mg/kg once daily, not more frequently than every other day, if needed. The recommended maintenance dose is 0,02 – 0,04 mg/kg once daily. The mean dose is 0,03 mg/kg once daily.

The continued use of **PMI RISPERIDONE** must be evaluated and justified on an ongoing basis.

Experience is lacking in children under the age of 5 years. See “Contra-indications”.

DIRECTIONS FOR OPENING THE BOTTLE AND USING THE PIPETTE

1. Push the plastic screw cap down while turning it counter clockwise. Remove the unscrewed cap.

2. Insert the pipette in to the bottle. While holding down the barrel, pull the plunger up to the level that corresponds with the dosage required for administration.

3. While holding the plunger, remove the pipette from the bottle.

4. Empty the pipette into any non-alcoholic drink, except for tea, by sliding the plunger down.

5. Close the bottle and rinse the pipette.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side effects:

In some instances it has been difficult to differentiate adverse events from symptoms of the underlying psychosis.

- **Blood and the lymphatic system disorders**

Less frequent : Thrombocytopenic purpura. Decrease in neutrophil or thrombocyte counts.

Nervous system disorders

Frequent: Akathisia (restlessness or need to keep moving); anxiety and nervousness; agitation; dizziness; dystonic extrapyramidal effects (muscle spasm of face, neck and back, twitching movements, weakness of arms or legs); parkinsonian extrapyramidal effects (difficulty in peaking or swallowing, loss of balance control, trembling and shaking of hands and fingers); somnolence; insomnia; asthenia; fatigue; lassitude; drowsiness; sedation; headache; increased dream activity; increased duration of sleep; impaired concentration.

Less frequent: Anorexia; hyper- or hypothermia; mania or hypomania; tardive dyskinesia*; neuroleptic malignant syndrome (NMS)**; polydipsia; seizure; tardive dystonia, cerebrovascular accident.

- **Eye disorders**

Frequent: Changes in vision (including disturbances of accommodation and blurred vision).

- **Cardiac disorders**

Less frequent: Cardiovascular effects including orthostatic hypotension, orthostatic dizziness, hypotension or hypertension, palpitations, chest pain, reflex tachycardia or tachycardia; cardiovascular adverse events including stroke and transient ischaemic attacks.

- **Respiratory, thoracic and mediastinal disorders**

Frequent: Dyspnoea; cough; decreased salivation or dryness of mouth; pharyngitis; rhinitis; upper respiratory tract infection.

Frequency not known: Apnoea.

- **Gastrointestinal disorders**

Frequent: Constipation, diarrhoea; dyspepsia; vomiting; nausea.

Less frequent: Abdominal pain.

- **Skin and subcutaneous tissue disorders**

Frequent: Skin rash or itching.

Less frequent: Dry skin; increased pigmentation, increased sweating, photosensitivity; seborrhoea.

- **Renal and urinary disorders**

Frequent: Micturition disturbances or polyuria.

Incidence not known: Urinary incontinence, water intoxication, either due to polydipsia or the syndrome of inappropriate secretion of the antidiuretic hormone (SIADH); hyponatraemia.

- **Psychiatric disorders**

Frequent: Mood or mental changes, including aggressive behaviour, agitation, difficulty in concentration and memory problems.

- **Reproductive system and breast disorders**

Frequent: Sexual and erectile dysfunction or decrease libido; dysmenorrhoea or menorrhagia.

Less frequent: Amenorrhea; galactorhoea; priapism; gynaecomastia.

- **Musculoskeletal disorders**

Less frequent: Back pain; arthralgia.

- **Metabolic disorders**

Frequent: Weight gain.

The following has been reported, but the frequency is unknown: Hyperglycaemia and exacerbation or pre-existing diabetes mellitus.

- **General disorders**

The following has been reported, but the frequency is unknown: Anaphylactic reaction; angioedema.

Special Precautions:

The starting dose and subsequent dose increments should be halved in geriatric patients and in patients with renal or liver insufficiency.

* Tardive dyskinesia (TD) may develop in patients treated with conventional neuroleptics and consists of potentially irreversible, involuntary dyskinetic movements. It is impossible to predict at the onset of treatment which patients are likely to develop the TD syndrome, although it appears to be most prevalent in the elderly, especially elderly females. The occurrence of Parkinsonian side-effects may be a predictor for the development of TD.

** Neuroleptic Malignant Syndrome (NMS) is a potentially fatal symptom complex that has been reported in association with antipsychotic medicines, including risperidone. Clinical manifestations of NMS are hyperthermia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, cardiac arrhythmias and diaphoresis). Additional signs may include elevated creatine phosphokinase (CPK) levels, myoglobinuria (rhabdomyolysis), and acute renal failure.

Important considerations in the differential diagnosis of NMS include:

- Central anticholinergic toxicity, heat stroke, medicine fever and primary central nervous system pathology.
- Identifying cases where the clinical presentation includes both serious medical illnesses (e.g. pneumonia, systemic infection etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS).

The management of NMS should include:

1. Immediate discontinuation of all antipsychotic medicines and other drugs not essential to concurrent therapy;
2. Intensive symptomatic treatment and medical monitoring; and
3. Treatment of any concomitant serious medical problems for which treatments are available.

There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic medicine treatment after recovery of NMS, the potential reintroduction of medicine therapy should be carefully considered.

The patient should be carefully monitored, since recurrences of NMS have been reported.

The risk-benefit should be considered when the patient has breast cancer as prolactin-dependent cancer may be exacerbated.

PMI RISPERIDONE should be used with caution in patients with known cardiovascular disease since orthostatic hypotension may occur due to the alpha-blocking activity of **PMI RISPERIDONE**, especially during the dose-titration period. The dose should be gradually titrated as recommended. A dose reduction should be considered if hypotension occurs.

Caution is advised when treating patients with Parkinson disease since **PMI RISPERIDONE** may, theoretically, cause a deterioration of the disease. Caution is also recommended in patients with a history of developing cerebrovascular disease.

Patients should refrain from excessive eating in view of the possibility of weight gain.

PMI RISPERIDONE's antiemetic effect may mask signs and symptoms of the following conditions: brain tumour, intestinal obstruction, medication overdose or Reye's syndrome.

Effects on ability to drive and use machines:

PMI RISPERIDONE may impair mental alertness and therefore patients should be advised not to operate machinery or drive until their individual susceptibility has been determined.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms of acute overdosage include drowsiness, extrapyramidal symptoms, sedation, hypotension, seizures and tachycardia. Electrocardiogram abnormalities, especially QT-

prolongation have been reported in rare cases. Reported signs and symptoms have been those resulting from an exaggeration of the medicine's known pharmacological effects.

In the case of acute overdosage, the possibility of multiple medicine involvement should be considered.

Treatment:

There is no specific antidote for risperidone. Treatment is symptomatic and supportive.

Establish and maintain a clear airway and ensure adequate oxygenation and ventilation

Gastric lavage (after intubation, if the patient is unconscious) should be considered. Activated charcoal may be administered with a laxative.

Cardiovascular monitoring should be initiated immediately to detect arrhythmias.

Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. For treatment of severe extrapyramidal symptoms an anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

IDENTIFICATION

Clear colourless solution free from foreign particles.

PRESENTATION

30 ml; 60 ml, 100 ml or 120 ml Amber glass bottle (USP Type III) with white Light Density Polyethylene/Polypropylene child resistant, tamper evident cap. Additionally a 4 ml dosing pipette is supplied in each pack consisting of a polystyrene plunger, Light Density Polyethylene barrel and piston, Light Density Polyethylene protective sheath (dosing pipette holder) and Polyethylene wiper. The dosing pipette is CE "Conformite Europeene" marked. The bottle and dosing pipette are packed in an outer cardboard container

STORAGE INSTRUCTIONS

Store at 25 ºC or below. Do not freeze.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

43/2.6.5/0691

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd

Corner Birch Road & Bluegum Avenue,

Anchorville,

Lenasia, 1827

South Africa

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