PROFESSIONAL INFORMATION

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

PMI RISPERIDONE 1 mg/ml (Oral Solution)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of the oral Solution contains 1 mg risperidone.

Preservative: Benzoic acid 0,15 % m/v

Sugar free

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Clear colourless solution free from foreign particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

PMI RISPERIDONE 1 mg/ml is indicated for:

- Acute and chronic schizophrenic psychoses and related psychosis in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness) and/or the negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. PMI RISPERIDONE 1 mg/ml also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia. In patients who have shown an initial treatment response, PMI RISPERIDONE 1 mg/ml 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.
- Mania in bipolar disorder. These episodes are characterised by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgment, including disruptive or aggressive behaviours.
- 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.

4.2 Posology and method of administration

Schizophrenia:

Switching from other antipsychotics to PMI RISPERIDONE 1 mg/ml

When switching patients from depot antipsychotics, initiate PMI RISPERIDONE 1 mg/ml 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 1 mg/ml may be given on either a once a day or twice a day schedule.

Patients should start with 2 mg/day PMI RISPERIDONE 1 mg/ml; this may be increase to 4 mg/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 1 mg/ml if additional sedation is required.

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

Clinical experience is lacking in these patient populations and PMI RISPERIDONE 1 mg/ml should therefore be administered with caution. Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than normal adults. Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone. It is recommended to halve both the starting dose and the subsequent dose increments and dose titration should be slower for patients with renal or hepatic impairment.

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.

Mania in bipolar disorders

PMI RISPERIDONE 1 mg/ml should be administered on a once daily schedule, starting with 2 or 3 mg. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. Efficacy was demonstrated in flexible doses over a range of 1 to 6 mg per day. The continued use of PMI RISPERIDONE 1 mg/ml must be evaluated and justified on an ongoing basis.

Experience is lacking in bipolar mania in children and adolescents less than 18 years of age.

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 1 mg/ml 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 1 mg/ml must be evaluated and justified on an ongoing basis.

Experience is lacking in children under the age of 5 years.

Method of administration

PMI RISPERIDONE 1 mg/ml is for oral use. Food does not affect the absorption of risperidone.

4.3 Contraindications

- Hypersensitivity to risperidone or any of the excipients listed in section 6.1.
- Conduct and other disruptive behaviour disorders in children: PMI RISPERIDONE 1 mg/ml is contra-indicated in children under 5 years as efficacy and safety in children under the age of 5 years have not been established.
- Parkinson's disease and Lewy body dementia (see section 4.4).
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4.4 Special warnings and precautions for use

Elderly patients with dementia (see section 4.5)

Before prescribing, medical practitioners are advised to carefully assess the risks and benefits of the use of atypical antipsychotics in elderly patients with dementia, taking into account risk predictions for stroke in the individual patient (e.g. hypertension, diabetes, current smoking, atrial fibrillation, and age > 80 years).

Where the use of antipsychotics in the elderly is considered essential, the lowest effective dose should be used. These patients should be carefully monitored to avoid or reduce hypotension, gait disturbances, oversedation and complications associated with hyperglycaemia.

Risperidone, such as in PMI RISPERIDONE 1 mg/ml is not indicated in elderly patients with dementia exhibiting behavioural disturbances.

Increased mortality in elderly people with dementia

Elderly patients with dementia treated with atypical antipsychotic medicines have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic medicines, including risperidone. In placebo-controlled trials with oral risperidone in this population, the incidence of mortality was 4,0 % for risperidone-treated patients compared to 3,1 % for placebo-treated patients. The mean age (range) of patients who died was 86 years (range 67 to 100).

Hepatic and Renal Impairment

In patients with severe hepatic impairment and renal function metabolism, excretion and protein binding of PMI RISPERIDONE 1 mg/ml may be decreased; reduced dosage is recommended (see section 4.2).

Tardive dyskinesia / extrapyramidal symptoms (TD/EPS)

Tardive dyskinesia (TD), a syndrome consisting of potentially irreversible, rhythmical involuntary dyskinetic movements predominantly of the tongue and/or face, may develop in patients treated with PMI RISPERIDONE 1 mg/ml. 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.

The occurrence of extrapyramidal symptoms may be a predictor for the development of TD.

The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of the antipsychotic administered to the patient increase. However, the syndrome can develop, although less commonly, after relatively brief periods of treatment at low doses. There is no known treatment for an established case of TD. The syndrome may remit partially or completely if the antipsychotic medicine treatment is withdrawn.

PMI RISPERIDONE 1 mg/ml treatment itself, however, may suppress the signs and symptoms of TD, thereby masking the underlying process. The effect of symptom suppression upon the long-term course of TD is unknown. In view of these considerations, PMI RISPERIDONE 1 mg/ml should be prescribed in a manner that is most likely to minimise the risk of TD. PMI RISPERIDONE 1 mg/ml should be reserved for patients who appear to be obtaining substantial benefit from the medicine. In such patients the smallest dose and the shortest duration of treatment should be sought. The benefit for continued treatment should be reassessed periodically. If signs and symptoms of TD appear in a patient on antipsychotics,

PMI RISPERIDONE 1 mg/ml discontinuation should be considered. However, some patients may require treatment despite the presence of this syndrome.

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 1 mg/ml. Clinical manifestations of NMS are hyperthermia, muscle rigidity, altered mental status (including catatonic signs), evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, cardiac arrhythmias and diaphoresis) and elevated serum creatine phosphokinase levels.

Additional signs may include elevated creatine phosphokinase (CPK) levels, myoglobinuria (rhabdomyolysis), and acute renal failure. In this event, PMI RISPERIDONE 1 mg/ml should be discontinued.

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.

A dose-dependent increase in plasma prolactin concentration may occur. Possible associated manifestations are: galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and amenorrhoea. Premenopausal

women who develop secondary amenorrhoea of greater than six months duration should receive appropriate preventative therapy to avoid hypo-oestrogenic bone loss. The risk-benefit should be considered when the patient has breast cancer as prolactin-dependent cancer may be exacerbated.

Parkinson's disease/Lewy Body dementia and NMS

Patients with Parkinson's disease or Dementia with Lewy Bodies (DLB) have an increased risk of Neuroleptic Malignant Syndrome (NMS) as well as having an increased sensitivity to antipsychotic medications (see section 4.3). Manifestation 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 patients were shown to have a higher mortality than placebo treated elderly patients (see section 4.3).

PMI RISPERIDONE 1 mg/ml may antagonise the effect of levodopa and other dopamine agonists.

Concomitant use with furosemide

In risperidone placebo-controlled trials in elderly patients with dementia, there was a higher mortality in patients treated with furosemide and risperidone when compared to patients treated with risperidone alone. 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. There was no increased incidence of mortality among patients taking other diuretics as concomitant medicine with risperidone. Caution is advised in patients treated with furosemide and risperidone, such as in PMI RISPERIDONE 1 mg/ml due to possible dehydration (see section 4.5). Dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

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 1 mg/ml. Patients with an established diagnosis of diabetes mellitus who are started on PMI RISPERIDONE 1 mg/ml 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 1 mg/ml should be monitored for symptoms of hyperglycaemia

including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with PMI RISPERIDONE 1 mg/ml should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when PMI RISPERIDONE 1 mg/ml was discontinued. However, some patients required continuation of anti-diabetic treatment despite discontinuation of PMI RISPERIDONE 1 mg/ml.

Cerebrovascular Adverse Events

Cerebrovascular adverse events (CAE), including cerebrovascular accidents and transient ischaemic attacks, have been reported during treatment with PMI RISPERIDONE 1 mg/ml.

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 risperidone compared to patients receiving placebo (mean age 85 years; range 73 – 97 years). Caution is also recommended in patients with a history of developing cerebrovascular disease.

Orthostatic hypotension

Due to the alpha-blocking activity of risperidone such as in PMI RISPERIDONE 1 mg/ml, (orthostatic) hypotension can occur, especially during the initial dose-titration period. PMI RISPERIDONE 1 mg/ml 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.

Seizures

Seizures have been reported after treatment with PMI RISPERIDONE 1 mg/ml. Caution is recommended when treating patients with epilepsy, a history of seizures or other conditions that potentially lower the seizure threshold.

Weight gain

Significant weight gain has been reported. Monitoring weight gain is advisable when PMI RISPERIDONE 1 mg/ml is being used. Patients should refrain from excessive eating in view of the possibility of weight gain.

Antiemetic effect

PMI RISPERIDONE 1 mg/ml antiemetic effect may mask signs and symptoms of the following conditions: brain tumour, intestinal obstruction, medication overdose or Reye's syndrome.

Leukopenia, Neutropenia, and Agranulocytosis

Events of leukopenia, neutropenia and agranulocytosis have been reported with PMI RISPERIDONE 1 mg/ml. Agranulocytosis has been reported during post-marketing surveillance. Patients with a history of a clinically significant low white blood cell count (WBC) or a medicine-induced leukopenia/neutropenia should be monitored during therapy and discontinuation of PMI RISPERIDONE 1 mg/ml should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 X 10^9/L) should discontinue PMI RISPERIDONE 1 mg/ml and have their WBC followed until recovery.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with PMI RISPERIDONE 1 mg/ml. 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 PMI RISPERIDONE 1 mg/ml and preventive measures undertaken.

Hyperprolactinaemia

Hyperprolactinaemia is a common side effect of treatment with risperidone as in PMI RISPERIDONE 1 mg/ml. Evaluation of the prolactin plasma level is recommended in patients with evidence of possible prolactin-related side effects (e.g., gynaecomastia, menstrual disorders, anovulation, fertility disorder, decreased libido, erectile dysfunction, and galactorrhoea).

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. PMI RISPERIDONE 1 mg/ml should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours.

QT Interval

Caution should be exercised when PMI RISPERIDONE 1 mg/ml is prescribed in patients with a history of cardiac dysrhythmias, in patients with congenital long QT syndrome, and in concomitant use with medicines known to prolong the QT interval.

Priapism

Medicines with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with PMI RISPERIDONE 1 mg/ml during post marketing surveillance (see section 4.8).

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature may occur. Appropriate care is advised when prescribing PMI RISPERIDONE 1 mg/ml 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 medication with anticholinergic activity, or being subject to dehydration.

Intraoperative Floppy Iris Syndrome

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, including PMI RISPERIDONE 1 mg/ml. IFIS may increase the risk of eye complications during and after the operation. Current or past use of PMI RISPERIDONE 1 mg/ml should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping PMI RISPERIDONE 1 mg/ml prior to cataract surgery has not been established and must be weighed against the risk of stopping PMI RISPERIDONE 1 mg/ml therapy.

Children and adolescents

Before PMI RISPERIDONE 1 mg/ml 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 PMI RISPERIDONE 1 mg/ml should be closely monitored in this population because of possible consequences on learning ability. A change in the time of administration of PMI RISPERIDONE 1 mg/ml could improve the impact of the sedation on attention faculties of children and adolescents.

Risperidone, as in PMI RISPERIDONE 1 mg/ml was associated with mean increases in body weight and body mass index (BMI). Baseline weight measurement prior to treatment and regular weight monitoring are recommended. 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 has 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.

Results from a small post-marketing observational study showed that risperidone-exposed subjects between the ages of 8 to 16 years were on average approximately 3,0 to 4,8 cm taller than those who received other atypical antipsychotic medicines. This study was not adequate to determine whether exposure to risperidone had any impact on final adult height, or whether the result was due to a direct effect of risperidone on bone growth, or the effect of the underlying disease itself on bone growth, or the result of better control of the underlying disease with resulting increase in linear growth.

During treatment with risperidone, as in PMI RISPERIDONE 1 mg/ml regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.

Excipients

This medicinal product contains 1,50 mg benzoic acid in each ml solution. Benzoic acid may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

4.5. Interaction with other medicines and other forms of interaction

The risk of using PMI RISPERIDONE 1 mg/ml in combination with other medicines has not been systematically evaluated.

Pharmacodynamic-related interactions

Medicines known to prolong the QT interval

Caution is advised when prescribing risperidone with medicines known to prolong the QT-interval, such as antidysrhythmics (e.g., quinidine, disopyramide, procainamide, propafenone, amiodarone, sotalol), tricyclic antidepressant (i.e., amitriptyline), tetracyclic antidepressants (i.e., maprotiline), some antihistamines, other antipsychotics, some antimalarials (i.e., quinine and mefloquine), and with medicines causing electrolyte

imbalance (hypokalaemia, hypomagnesaemia), bradycardia, or those which inhibit the hepatic metabolism of risperidone. This list is indicative and not exhaustive.

Centrally acting medicines and alcohol

Risperidone as in PMI RISPERIDONE 1 mg/ml 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.

Levodopa and dopamine agonists

Risperidone as in PMI RISPERIDONE 1 mg/ml 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.

Psychostimulants

The combined use of psychostimulants (e.g. methylphenidate) with risperidone as in PMI RISPERIDONE 1 mg/ml can lead to extrapyramidal symptoms upon change of either or both treatments (see section 4.4).

Medicines with hypotensive effect

Clinically significant hypotension has been observed post-marketing with concomitant use of risperidone as in PMI RISPERIDONE 1 mg/ml and antihypertensive treatment.

Paliperidone

Concomitant use of oral risperidone as in PMI RISPERIDONE 1 mg/ml 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.

Pharmacokinetic-related interactions

Food does not affect the absorption of risperidone.

Risperidone is mainly metabolised through CYP2D6, and to a lesser extent through CYP3A4. Both risperidone and its active metabolite 9-hydroxyrisperidone are substrates of P-glycoprotein (P-gp).

Substances that modify CYP2D6 activity, or substances strongly inhibiting or inducing CYP3A4 and/or P-gp activity, may influence the pharmacokinetics of the risperidone active antipsychotic fraction.

Strong CYP2D6 inhibitors

Co-administration of risperidone as in PMI RISPERIDONE 1 mg/ml with a strong CYP2D6 inhibitor may increase the plasma concentrations of risperidone, but less so of the active antipsychotic fraction. Higher doses of a strong CYP2D6 inhibitor may elevate concentrations of the risperidone active antipsychotic fraction (e.g., paroxetine, see below). It is expected that other CYP2D6 inhibitors, such as quinidine, may affect the plasma concentrations of risperidone in a similar way. When concomitant paroxetine, quinidine, or another strong CYP2D6 inhibitor, especially at higher doses, is initiated or discontinued, the medical practitioner should re-evaluate the dosing of PMI RISPERIDONE 1 mg/ml.

CYP3A4 and/or P-gp inhibitors

Co-administration of risperidone as in PMI RISPERIDONE 1 mg/ml with a strong CYP3A4 and/or P-gp inhibitor may substantially elevate plasma concentrations of the risperidone active antipsychotic fraction. When concomitant itraconazole or another strong CYP3A4 and/or P-gp inhibitor is initiated or discontinued, the medical practitioner should re-evaluate the dosing of PMI RISPERIDONE 1 mg/ml.

CYP3A4 and/or P-gp inducers

Co-administration of risperidone with a strong CYP3A4 and/or P-gp inducer may decrease the plasma concentrations of the risperidone active antipsychotic fraction. When concomitant carbamazepine or another strong CYP3A4 and/or P-gp inducer is initiated or discontinued, the medical practitioner should re-evaluate the dosing of PMI RISPERIDONE 1 mg/ml. CYP3A4 inducers exert their effect in a time-dependent manner and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least 2 weeks to decline.

Highly protein-bound medicines

When risperidone as in PMI RISPERIDONE 1 mg/ml is taken together with highly protein-bound medicines, there is no clinically relevant displacement of either medicine from the plasma proteins.

When using concomitant medicines, the corresponding label should be consulted for information on the route of metabolism and the possible need to adjust dosage.

Paediatric population

Interaction studies have only been performed in adults. The relevance of the results from these studies in paediatric patients is unknown.

The combined use of psychostimulants (e.g., methylphenidate) with risperidone as in PMI RISPERIDONE 1 mg/ml in children and adolescents did not alter the pharmacokinetics and efficacy of risperidone.

Effect of other medicines on the pharmacokinetics of risperidone

Antibacterials

- Erythromycin, a moderate CYP3A4 inhibitor and P-gp inhibitor, does not change the pharmacokinetics of risperidone as in PMI RISPERIDONE 1 mg/ml and the active antipsychotic fraction.
- Rifampicin, a strong CYP3A4 inducer and a P-gp inducer, decreased the plasma concentrations of the active antipsychotic fraction.

Anticholinesterases

Donepezil and galantamine, both CYP2D6 and CYP3A4 substrates, do not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction.

Antiepileptics

- Carbamazepine, a strong CYP3A4 inducer and a P-gp inducer, has been shown to decrease the plasma concentrations of the active antipsychotic fraction of risperidone. Similar effects may be observed with e.g. phenytoin and phenobarbital (phenobarbitone), which also induce CYP3A4 hepatic enzyme, as well as P-glycoprotein.
- Topiramate modestly reduced the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance.

Antifungals

- Itraconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200 mg/day increased the plasma concentrations of the active antipsychotic fraction by about 70 %, at risperidone doses of 2 to 8 mg/day.

- Ketoconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200 mg/day increased the plasma concentrations of risperidone and decreased the plasma concentrations of 9-hydroxyrisperidone.

Antipsychotics

Phenothiazines may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

Chronic administration of clozapine may decrease the clearance of PMI RISPERIDONE 1 mg/ml resulting in increased plasma levels.

Antivirals

Protease inhibitors: No formal study data are available; however, since ritonavir is a strong CYP3A4 inhibitor and a weak CYP2D6 inhibitor, ritonavir and ritonavir-boosted protease inhibitors potentially raise concentrations of the risperidone active antipsychotic fraction.

Beta blockers

Some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

Calcium channel blockers

Verapamil, a moderate inhibitor of CYP3A4 and an inhibitor of P-gp, increases the plasma concentration of risperidone and the active antipsychotic fraction.

Gastrointestinal medicines

H2-receptor antagonists: Cimetidine and ranitidine, both weak inhibitors of CYP2D6 and CYP3A4, increased the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction.

SSRIs and Tricyclic antidepressants

- Fluoxetine, a strong CYP2D6 inhibitor, increases the plasma concentration of risperidone, but less so of the active antipsychotic fraction. When either fluoxetine is initiated or discontinued; the doctor should re-evaluate the PMI RISPERIDONE 1 mg/ml dosing.
- Paroxetine, a strong CYP2D6 inhibitor, increases the plasma concentrations of risperidone, but, at dosages up to 20 mg/day, less so of the active antipsychotic fraction. However, higher doses of paroxetine may elevate concentrations of the risperidone active antipsychotic fraction. When

paroxetine is initiated or discontinued; the doctor should re-evaluate the PMI RISPERIDONE 1 mg/ml dosing.

- Venlafaxine administered under steady state conditions at 150 mg/day inhibited theCYP2D6-mediated metabolism of risperidone (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32 % increase in risperidone AUC. However, venlafaxine co-administration did not significantly alter the pharmacokinetic profile of the total active antipsychotic fraction.
- Tricyclic antidepressants 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.
- Sertraline, a weak inhibitor of CYP2D6, and fluvoxamine, a weak inhibitor of CYP3A4, at dosages up to 100 mg/day are not associated with clinically significant changes in concentrations of the risperidone active antipsychotic fraction. However, doses higher than100 mg/day of sertraline or fluvoxamine may elevate concentrations of the risperidone active antipsychotic fraction.

Effect of risperidone on the pharmacokinetics of other medicines

Antiepileptics

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

Antipsychotics

Aripiprazole, a CYP2D6 and CYP3A4 substrate: Risperidone tablets or injections did not affect the pharmacokinetics of the sum of aripiprazole and its active metabolite, dehydroaripiprazole.

Digoxin

Risperidone does not show a clinically relevant effect on the pharmacokinetics of digoxin.

Lithium

Risperidone does not show a clinically relevant effect on the pharmacokinetics of lithium.

Concomitant use of PMI RISPERIDONE 1 mg/ml with furosemide

There is increased mortality in elderly patients with dementia concomitantly receiving furosemide and risperidone as in PMI RISPERIDONE 1 mg/ml (see section 4.4).

4.6 Fertility, pregnancy and lactation

Safety of PMI RISPERIDONE 1 mg/ml in pregnancy or lactating women has not been established.

Pregnancy

Neonates exposed to antipsychotic medicines (including risperidone) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms that may vary in severity following delivery. These symptoms in the neonates may include agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder.

Although, in experimental animals, risperidone did not show direct reproductive toxicity, some indirect, prolactin- and CNS-mediated effects were observed. No teratogenic effect of risperidone was noted in any study.

Breastfeeding

Risperidone and 9-hydroxyrisperidone are excreted in human breast milk. Therefore, women receiving PMI RISPERIDONE 1 mg/ml should not breastfeed.

Fertility

As with other drugs that antagonize dopamine D2 receptors, risperidone elevates prolactin levels. Hyperprolactinaemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients.

4.7 Effects on ability to drive and use machines

PMI RISPERIDONE 1 mg/ml may impair mental alertness and therefore patients should be advised not to operate machinery or drive until their individual susceptibility has been determined.

4.8 Undesirable effects

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

Summary of the safety profile

The most frequently reported adverse drug reactions (ADRs) are parkinsonism, sedation/somnolence, headache, and insomnia.

The ADRs that appeared to be dose-related included parkinsonism and akathisia.

Tabulated list of adverse reactions

Table 1: Tabulated list of adverse reactions		
System Organ Class	**Adverse reactions**	**Frequency**
Infections and infestations	Pneumonia, influenza, bronchitis, upper respiratory tract infection, sinusitis, urinary tract infection, ear infection	*Frequent*
	Viral infection, tonsillitis, cellulitis, otitis media, eye infection, localised infections, acarodermatitis, respiratory tract infection, cystitis, onychomycosis, chronic otitis media	*Less frequent*
Blood and lymphatic system disorders	Thrombocytopenic purpura, neutropenia, thrombocytopenia, anaemia, granulocytopenia, white blood cell counts decreased, haematocrit decreased, eosinophil count increased, agranulocytosis	*Less frequent*
Immune system disorders	Hypersensitivity, anaphylactic reaction, angioedema	*Less frequent*
	Medicine hypersensitivity	*Frequency unknown*
Endocrine disorders	Hyperprolactinaemia (which can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhoea, anovulation, galactorrhoea, fertility disorder, decreased libido, erectile dysfunction)	*Frequent*
	Inappropriate secretion of the antidiuretic hormone (SIADH), glucose urine present	*Less frequent*
Metabolism and nutrition disorders	Weight increased, increased appetite, decreased appetite	*Frequent*
	Diabetes mellitus, hyperglycaemia and exacerbation or pre-existing diabetes mellitus, polydipsia, weight decreased, anorexia, blood cholesterol increased, water intoxication,	*Less frequent*

	hypoglycaemia, hyperinsulinemia, blood triglycerides increased, diabetic ketoacidosis	
Psychiatric disorders	Mood or mental changes, including aggressive behaviour, agitation, difficulty in concentration and memory problems, insomnia [(1)], depression, sleep disorder, anxiety	*Frequent*
	Mania or hypomania, confused state, decreased libido, listless, anorgasmia, blunted effect, mania, nightmare, catatonia, somnambulism, sleep related eating disorder, nervousness	*Less frequent*
Nervous system disorders	Akathisia [(1)]; dizziness; dystonia[(1)]; parkinsonism[(1)]; somnolence; asthenia; fatigue; lassitude; drowsiness; sedation/ somnolence; headache; increased dream activity; increased duration of sleep; dyskinesia[(1)], tremor	*Frequent*
	Hyper- or hypothermia; tardive dyskinesia (see section 4.4); neuroleptic malignant syndrome (NMS) (see section 4.4); polydipsia; seizure; tardive dystonia, cerebrovascular accident, cerebral ischaemia, unresponsive to stimuli, loss of consciousness, depressed level of consciousness, transient ischaemic attack, convulsion[(1)], syncope, psychomotor hyperactivity, balance disorder, coordination abnormal, dizziness postural, disturbance in attention, dysarthria, dysgeusia, hypoaesthesia, paraesthesia, cerebrovascular disorder, diabetic coma, head intubation	*Less frequent*
Eye disorders	Changes in vision (including disturbances of accommodation and blurred vision), conjunctivitis	*Frequent*
	Ocular hyperaemia, eye discharge, eye swelling, dry eye, lacrimation increased, photophobia, glaucoma, eye movement disorder, eye rolling, eyelid margin crusting, floppy iris syndrome (intraoperative)	*Less frequent*

	Visual acuity reduced	*Frequency unknown*
Ear and labyrinth disorders	Ear pain, tinnitus, vertigo	*Less frequent*
Cardiac disorders	Tachycardia	*Frequent*
	Atrioventricular block, bundle branch block, sinus bradycardia, palpitations, atrial fibrillation, conduction disorder, electrocardiogram QT prolonged, bradycardia, electrocardiogram abnormal, sinus dysrrhythmia	*Less frequent*
Vascular disorder	Hypertension	*Frequent*
	Hypotension, orthostatic hypotension, flushing, pulmonary embolism, venous thrombosis	*Less frequent*
Respiratory, thoracic and mediastinal disorders	Dyspnoea; cough; pharyngitis; rhinitis; epistaxis, pharyngolaryngeal pain, nasal congestion	*Frequent*:
	Pneumonia aspiration, pulmonary congestion, respiratory tract congestion, rales, wheezing, dysphonia, respiratory disorder, sleep apnoea syndrome, hyperventilation	*Less frequent*
Gastrointestinal disorders	Constipation, diarrhoea; dyspepsia; vomiting; nausea, abdominal pain, dry mouth, abdominal discomfort, toothache	*Frequent*:
	Dysphagia, gastritis, faecal incontinence, faecaloma, flatulence, pancreatitis, intestinal obstruction, swollen tongue, cheilitis, gastroenteritis, ileus	*Less frequent*
Hepato-biliary disorders	Transaminases increased, gamma-glutamyltransferase increased, hepatic enzyme increased, jaundice	Less frequent
Skin and subcutaneous tissue disorders	Skin rash or itching, erythema	*Frequent*:
	Dry skin; increased pigmentation, increased sweating, photosensitivity; seborrhoeic dermatitis, skin lesion, skin disorder, acne, hyperkeratosis, alopecia, urticaria, eczema, pruritus, skin discolouration, drug eruption, dandruff	*Less frequent*

Musculoskeletal and connective tissue disorders	muscle spasms, musculoskeletal pain, back pain, arthralgia, pain in the extremity	*Frequent*
	blood creatine phosphokinase increased, posture abnormal, joint stiffness, joint swelling, muscular weakness, neck pain, rhabdomyolysis	*Less frequent*
Renal and urinary disorders	Micturition disturbances or polyuria, enuresis, urinary incontinence	*Frequent*:
	Dysuria, pollakiuria, either due to polydipsia or hyponatraemia, urinary retention	*Less frequent*
Pregnancy, puerperium, and neonatal conditions	neonatal medicine withdrawal syndrome	*Less frequent*
Reproductive system and breast disorders	Amenorrhea; galactorrhoea; priapism; gynaecomastia, breast pain, breast discomfort, sexual and erectile dysfunction, menstrual disorder [(1)], dysmenorrhoea or menorrhagia, vaginal discharge, ejaculation disorder, menstruation delayed, breast engorgement, breast enlargement, breast discharge	*Less frequent*
General disorders and administration site conditions	Oedema [(1)], pyrexia, chest pain, asthenia, fatigue, pain	*Frequent*
	Face oedema, gait disturbance, gait abnormal, feeling abnormal, sluggishness, influenza like illness, thirst, chest discomfort, chills, body temperature increased, malaise, feeling abnormal, discomfort, medicine withdrawal syndrome, peripheral coldness, hypothermia, body temperature decreased, induration	*Less frequent*
Injury, poisoning and procedural complications	fall	*Frequent*
	procedural pain	*Less frequent*

(1) Extrapyramidal disorder:

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, parkinsonian rest tremor), akathisia (akathisia, restlessness, hyperkinesia, and restless leg syndrome), tremor, dyskinesia (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia. Dystonia includes dystonia, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus. It should be noted that a broader spectrum of symptoms is included, that do not necessarily have an extrapyramidal origin. Insomnia includes: initial insomnia, middle insomnia; Convulsion includes: Grand mal convulsion; Menstrual disorder includes: Menstruation irregular, oligomenorrhoea; Oedema includes: generalised oedema, oedema peripheral, pitting oedema.

Undesirable effects noted with paliperidone formulations

Paliperidone is the active metabolite of risperidone, therefore, the adverse reaction profiles of these compounds (including both the oral and injectable formulations) are relevant to one another. In addition to the above adverse reactions, the following adverse reaction has been noted with the use of paliperidone products and can be expected to occur with risperidone as in PMI RISPERIDONE 1 mg/ml.

Cardiac disorders

Postural orthostatic tachycardia syndrome.

Class effects

Cases of QT-prolongation have been reported post-marketing with risperidone. Other class-related cardiac effects reported with antipsychotics which prolong QT-interval include ventricular dysrhythmia, ventricular fibrillation, ventricular tachycardia, sudden death, cardiac arrest, and Torsades de pointes.

Venous thromboembolism

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis, have been reported with antipsychotic medicines (frequency unknown).

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 to 12 years of age is 3 to 5 kg per year. From 12 to 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

ADRs 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 population

In general, the type of adverse reactions in children is expected to be similar to those observed in adults.

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.

The effect of long-term risperidone treatment on sexual maturation and height has not been adequately studied (see 4.4, subsection “Paediatric population”).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms

Reported signs and symptoms have been those resulting from an exaggeration of the medicine's known pharmacological effects. Symptoms of acute overdosage include drowsiness, extrapyramidal symptoms, sedation, hypotension, seizures, convulsions and tachycardia. Electrocardiogram abnormalities, especially QT-prolongation have been reported. Torsades de pointes has been reported in association with combined overdose of oral risperidone as in PMI RISPERIDONE 1 mg/ml and paroxetine. In the case of acute overdosage, the possibility of multiple medicine involvement should be considered.

Treatment:

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

Activated charcoal may be administered with a laxative.

Cardiovascular monitoring should be initiated immediately and should include continuous electrocardiographic monitoring to detect dysrrhythmias.

Since there is no known antidote if accidental poisoning or overdosage is suspected, appropriate supportive measures should be instituted. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.6.5 Central nervous system depressants. Miscellaneous structures.

Pharmacotherapeutic group: Other antipsychotics, ATC Code: N05AX08

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. It is a dopamine D2-antagonist.

5.2 Pharmacokinetic properties

Absorption

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

Distribution is rapid and extensive.

Biotransformation:

Risperidone is extensively metabolised in the liver by hydroxylation to its main active metabolite, 9-hydroxyrisperidone, which has a similar pharmacological activity to risperidone. Risperidone and 9-hydroxy-risperidone form the active antipsychotic fraction. 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. In patients with severe renal insufficiency the clearance was one third that of normal. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzoic acid

Tartaric Acid

Hydrochloric Acid

Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

An in use shelf-life of 100 days is approved for this product stored at or below 25 ^{0}C

6.4 Special precautions for storage

Store at or below 25 ºC or below. Do not freeze.

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal and other handling

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 into 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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd
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8. REGISTRATION NUMBER

43/2.6.5/0691

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of registration: 11 June 2018

10. DATE OF REVISION OF THE TEXT

29 May 2026