PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 5

1. NAME OF THE MEDICINE

RISPERDAL® 0,5 mg tablets.

RISPERDAL®1 mg tablets.

RISPERDAL® 2 mg tablets.

RISPERDAL® 3 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains risperidone 0,5 mg.

Each film-coated tablet contains risperidone 1 mg.

Each film-coated tablet contains risperidone 2 mg.

Each film-coated tablet contains risperidone 3 mg.

Excipients with known effect:

Each 0.5 mg film-coated tablet contains 91 mg lactose monohydrate.

Each 1 mg film-coated tablet contains 131 mg lactose monohydrate.

Each 2 mg film-coated tablet contains 130 mg lactose monohydrate and 0.05 mg orange yellow S.

aluminium lake (sunset yellow) E110.

Each 3 mg film-coated tablet contains 195 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated Tablets.

- 0.5 mg RISPERDAL as brownish-red, half-scored, oblong, biconvex tablets of 9 mm x 5 mm
- 1 mg RISPERDAL as white, half-scored, oblong, biconvex tablets of 10.5 mm x 5 mm
- 2 mg RISPERDAL as orange, half-scored, oblong, biconvex tablets of 10.5 mm x 5 mm
- 3 mg RISPERDAL as yellow, half-scored, oblong, biconvex tablets of 13.5 mm x 5 mm

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Film-coated tablets are etched on one side with RIS 0.5, RIS 1, RIS 2 and RIS 3 respectively. Additionally, JANSSEN may be etched on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

RISPERDAL is indicated for the treatment of:

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. RISPERDAL also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia. In patients who have shown an initial treatment response, RISPERDAL is also effective in maintaining the clinical improvement.

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 (e.g. aggression, impulsivity and self-injurious behaviours) are prominent.

4.2 Posology and method of administration

Posology

Schizophrenia

Adults:

RISPERDAL may be given once or twice daily**.**

Patients should start with 2 mg/day RISPERDAL. The dosage may be increased on the second day to 4 mg/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 and 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 RISPERDAL if additional sedation is required.

Elderly patients and patients with renal and hepatic impairment

A starting dose of 0,5 mg twice daily is recommended.

This dosage can be individually adjusted with 0,5 mg twice daily increments to 1 - 2 mg twice daily.

Paediatric population

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

Mania in bipolar disorders

RISPERDAL 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 RISPERDAL 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.

Conduct and other Disruptive Behaviour Disorders (DBD) in children 5 - 12 years of age

Patients < 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 RISPERDAL must be evaluated and justified on an ongoing basis.

Experience is lacking in children aged less than 5 years.

Renal and liver impairment:

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.

Irrespective of the indication, starting and consecutive dosing should be halved, and dose titration should be slower for patients with renal or hepatic impairment.

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

Method of administration:

RISPERDAL is for oral administration, food does not affect the absorption.

Switching from other antipsychotics to RISPERDAL:

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

4.3 Contraindications:

RISPERDAL is contraindicated in:

- Patients with known hypersensitivity to risperidone or to any of the components of the medicine.
- Conduct and other disruptive behaviour disorders in children: RISPERDAL is contraindicated in children under 5 years of age as efficacy and safety in these children have not been demonstrated.
- Parkinson's disease and Lewy Body Dementia (see section 4.4).

4.4 Special warnings and precautions for use

Elderly Patients with Dementia

Overall Mortality:

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 RISPERDAL. In placebo-controlled trials with oral RISPERDAL in this population, the incidence of mortality was 4,0 % for RISPERDAL-treated patients compared to 3,1 % for placebo-treated patients. The mean age (range) of patients who died was 86 years (range 67-100 years).

Concomitant use with furosemide:

In RISPERDAL placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide and RISPERDAL (7,3 %; mean age 89 years, range 75-97) when compared to patients treated with RISPERDAL alone (3,1 %; mean age 84 years, range 70-96) or furosemide alone (4,1 %; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus RISPERDAL was observed in two of the four clinical trials.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant medication with RISPERDAL. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular Adverse Events (CVAE):

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

ischaemic attacks), including fatalities, in patients treated with RISPERDAL compared to patients receiving placebo (mean age 85 years; range 73-97 years).

The risk of CVAEs was significantly higher in patients with mixed or vascular type of dementia when compared to Alzheimer's dementia. Therefore, patients with other types of dementias than Alzheimer's should not be treated with RISPERDAL.

Physicians are advised to assess the risks and benefits of the use of RISPERDAL in elderly patients with dementia, taking into account risk predictors for stroke in the individual patient. Patients/caregivers should be cautioned to immediately report signs and symptoms of potential CVAEs such as sudden weakness or numbness in the face, arms or legs, and speech or vision problems. All treatment options should be considered without delay, including discontinuation of RISPERDAL.

RISPERDAL should only be used short term for persistent aggression in patients with moderate to severe Alzheimer's dementia to supplement non-pharmacological approaches which have had limited or no efficacy and when there is potential risk of harm to self or others.

Patients should be reassessed regularly, and the need for continuing treatment reassessed.

Orthostatic Hypotension:

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, and the dosage should be gradually titrated as recommended. A dose reduction should be considered if hypotension occurs.

Leucopaenia, Neutropaenia, and Agranulocytosis:

Events of leucopaenia, neutropaenia and agranulocytosis have been reported with RISPERDAL. 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 leucopaenia/neutropaenia should be monitored during therapy and discontinuation of RISPERDAL 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 neutropaenia 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 neutropaenia (absolute neutrophil count < 1 X 10^9/L) should discontinue RISPERDAL and have their WBC followed until recovery.

Venous thromboembolism:

Cases of venous thromboembolism (VTE) have been reported with RISPERDAL. 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 RISPERDAL and preventive measures undertaken.

Tardive Dyskinesia/Extrapyramidal Symptoms (TD/EPS):

RISPERDAL has been associated with the induction of tardive dyskinesia (TD) characterised by potentially irreversible rhythmical involuntary movements, predominantly of the tongue and/or face. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of tardive dyskinesia. TD appears to be most prominent in the

elderly especially elderly females. If signs and symptoms of tardive dyskinesia appear, the discontinuation of RISPERDAL should be considered.

Extrapyramidal symptoms and psychostimulants - Caution is warranted in patients receiving both psychostimulants (e.g. methylphenidate) and risperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medications (see section 4.5).

Neuroleptic Malignant Syndrome (NMS):

Neuroleptic Malignant Syndrome, a potentially fatal symptom complex, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels has been reported to occur in association with RISPERDAL. Additional signs may include elevated creatine phosphokinase levels, myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, RISPERDAL, should be discontinued.

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 have a higher mortality than placebo treated elderly patients. (see section 4.3).

Hyperglycaemia and diabetes mellitus:

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

Patients with an established diagnosis of diabetes mellitus who are starting on RISPERDAL 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 RISPERDAL should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with RISPERDAL should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when RISPERDAL were discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of RISPERDAL.

Weight gain:

Significant weight gain has been reported. Monitoring weight gain is advisable when RISPERDAL is being used. Patients may be advised to refrain from excessive eating in view of the possibility of weight gain.

Hyperprolactinemia:

Hyperprolactinemia is a common side effect of treatment with RISPERDAL TABLETS. 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, 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.

RISPERDAL TABLETS 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 RISPERDAL is prescribed in patients with a history of cardiac dysrhythmias, in patients with congenital long QT syndrome, or electrolyte disturbances (hypokalaemia, hypomagnesaemia), as it may increase the risk of arrhythmogenic effects, and in concomitant use with medicines known to prolong the QT interval.

Priapism:

Medicines with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with RISPERDAL during postmarketing 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 RISPERDAL 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.

Antiemetic Effect:

An antiemetic effect was observed in preclinical studies with risperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain medicines or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumour.

Renal and hepatic impairment:

Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than adults with normal renal function. Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone (see section 4.2).

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 RISPERDAL.

IFIS may increase the risk of eye complications during and after the operation. Current or past use of RISPERDAL should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping RISPERDAL prior to cataract surgery has not been established and must be weighed against the risk of stopping RISPERDAL therapy.

Seizures:

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

Paediatric population:

Before RISPERDAL 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 RISPERDAL should be closely monitored in this population because of possible consequences on learning ability. A change in the time of administration of risperidone could improve the impact of the sedation on attention faculties of children and adolescents.

RISPERDAL 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 RISPERDAL treatment on sexual maturation and height has not been adequately studied.

Because of the potential effects of prolonged hyperprolactinaemia 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 8-16 years were on average approximately 3.0 to 4.8 cm taller than those who received other atypical antipsychotic medications. This study was not adequate to determine whether exposure to RISPERDAL had any impact on final adult height, or whether the result was due to a direct effect of RISPERDAL 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 RISPERDAL regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.

For specific posology recommendations in children and adolescents see section 4.2.

Galactose intolerance:

RISPERDAL contains lactose. Patients with rare hereditary problems of galactose intolerance, e.g. galactosaemia the Lapp lactase deficiency or glucose-galactose malabsorption should not take RISPERDAL.

Excipients:

Contains sunset yellow (Orange yellow S) (E110). May cause allergic reactions. (Pertains only to the 2 mg film coated tablets).

4.5 Interaction with other medicines and other forms of interaction:

Pharmacodynamic-related interactions:

Drugs known to prolong the QT interval:

As with other antipsychotics, caution is advised when prescribing RISPERDAL with medicines known to prolong the QT interval, such as antiarrhythmics (e.g., quinidine, dysopiramide, procainamide, propafenone, amiodarone, sotalol), tricyclic antidepressants (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 (See section 4.4).

Centrally-acting drugs and alcohol:

The risk of using RISPERDAL in combination with other medicines has not been systematically evaluated. Given the primary CNS depressive effects of RISPERDAL, it should be used with caution in combination with other centrally acting medicines notably

including alcohol, opiates, antihistamines and benzodiazepines due to the increased risk of sedation.

Levodopa and dopamine agonists:

RISPERDAL 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.

Drugs with hypotensive effect:

Clinically significant hypotension has been observed postmarketing with concomitant use of RISPERDAL and antihypertensive treatment (see section 4.4).

Psychostimulants:

The combined use of psychostimulants (e.g. methylphenidate) with RISPERDAL can lead to extrapyramidal symptoms upon change of either or both treatments (see section 4.4).

Paliperidone:

Concomitant use of oral RISPERDAL 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 RISPERDAL.

RISPERDAL is mainly metabolised through CYP2D6, and to a lesser extent through CYP3A4. Both risperidone and its active metabolite 9-hydroxy-risperidone 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 RISPERDAL active antipsychotic fraction.

Strong CYP2D6 inhibitors:

Co-administration of RISPERDAL with a strong CYP2D6 inhibitor may increase the plasma concentrations of RISPERDAL, 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 RISPERDAL 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 RISPERDAL.

CYP3A4 and/or P-gp inhibitors:

Co-administration of RISPERDAL with a strong CYP3A4 and/or P-gp inhibitor may substantially elevate plasma concentrations of the RISPERDAL 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 RISPERDAL.

CYP3A4 and/or P-gp inducers:

Co-administration of RISPERDAL with a strong CYP3A4 and/or P-gp inducer may decrease the plasma concentrations of the RISPERDAL 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 RISPERDAL.

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 drugs:

When RISPERDAL is taken together with highly protein-bound drugs, (e.g. diazepam, warfarin, digoxin, imipramine and propranolol), there is no clinically relevant displacement of either drug from the plasma proteins.

When using concomitant medication, 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 RISPERDAL in children and adolescents did not alter the pharmacokinetics and efficacy of RISPERDAL.

Examples:

Examples of drugs that may potentially interact or that were shown not to interact with RISPERDAL are listed below:

<u>Effect of other medicinal products on the pharmacokinetics of RISPERDAL</u>

Antibacterials:

- Erythromycin, a CYP 3A4 inhibitor and P-gp inhibitor, does not change the pharmacokinetics of RISPERDAL 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:

- The cholinesterase inhibitors, Donepezil and galantamine, both CYP2D6 and CYP3A4 substrates, do not show a clinically relevant effect on the pharmacokinetics of RISPERDAL 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 RISPERDAL. Similar effects may be observed with e.g., phenytoin and phenobarbitone which also induce CYP3A4 hepatic enzyme, as well as P-glycoprotein. On discontinuation of carbamazepine or other hepatic enzyme inducers, the dosage of RISPERDAL should be re-evaluated and, if necessary, decreased.

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

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

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 RISPERDAL 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 RISPERDAL and decreased the plasma concentrations of 9-hydroxy-risperidone.

Antipsychotics:

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

Antivirals:

- Protease inhibitors: No formal study data are available; however, since ritonavir is a strongCYP3A4 inhibitor and a weak CYP2D6 inhibitor, ritonavir and ritonavir-boosted protease inhibitors potentially raise concentrations of the RISPERDAL active antipsychotic fraction.

Beta-blockers:

- Some beta-blockers may increase the plasma concentrations of RISPERDAL 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 RISPERDAL and the active antipsychotic fraction.

Gastrointestinal drugs:

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

SSRIs and tricyclic antidepressants:

- Fluoxetine, a strong CYP2D6 inhibitor, increases the plasma concentration of RISPERDAL, but less so of the active antipsychotic fraction. When concomitant fluoxetine is initiated or discontinued, the dosing of RISPERDAL should be re-evaluated.

- Paroxetine, a strong CYP2D6 inhibitor, increases the plasma concentrations of RISPERDAL, 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 RISPERDAL active antipsychotic fraction. When concomitant paroxetine is initiated or discontinued, the dosing of RISPERDAL should be re-evaluated.

- Tricyclic antidepressants may increase the plasma concentrations of RISPERDAL but not those of the active antipsychotic fraction. Amitriptyline does not affect the pharmacokinetics of RISPERDAL 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 RISPERDAL active antipsychotic fraction. However, doses higher than 100 mg/day of sertraline or fluvoxamine may elevate concentrations of the RISPERDAL active antipsychotic fraction.

<u>Effect of RISPERDAL on the pharmacokinetics of other medicinal products:</u>

Digitalis glycosides:

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

Antipsychotics:

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

Lithium:

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

Concomitant use of RISPERDAL with furosemide:

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

Venlafaxine administered under steady-state conditions at 150 mg/day inhibited the CYP2D6-mediated metabolism of RISPERDAL (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32 % increase in RISPERDAL AUC. However, venlafaxine coadministration did not significantly alter the pharmacokinetic profile of the total active antipsychotic fraction.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

The safety of RISPERDAL in pregnancy and lactating women has not been established.

A retrospective observational cohort study based on a US claims database compared the risk of congenital malformations for live births among women with and without antipsychotic use during the first trimester of pregnancy. The risk of congenital malformations with risperidone, after adjusting for confounder variables available in the database, was elevated compared to no antipsychotic exposure (relative risk=1.26, 95% CI: 1.02-1.56). No biological mechanism has been identified to explain these findings and teratogenic effects have not been observed in non clinical studies. Based on the findings of this single observational study, a causal relationship between in utero exposure to risperidone and congenital malformations has not been established. Caution is however recommended.

Although, in experimental animals, risperidone did not show direct reproductive toxicity, some indirect, prolactin- and CNS-mediated effects were observed.

Neonates exposed to antipsychotic medicines (including RISPERDAL) 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.
Therefore, RISPERDAL should only be used during pregnancy if the benefits outweigh the risks.

Lactation:

In animal studies risperidone and 9-hydroxy- risperidone are excreted in the milk. It has been demonstrated that risperidone and 9-hydroxy-risperidone are also excreted in human breast milk. Therefore, women receiving RISPERDAL should not breastfeed.

Fertility:

RISPERDAL TABLETS elevates prolactin level. 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.

There were no relevant effects observed in the non-clinical studies.

4.7 Effects on ability to drive and use machines

RISPERDAL may impair mental alertness. Patients should therefore be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 Undesirable effects

Clinical trial data

Summary of the safety profile

Adverse drug reactions (ADRs) reported during clinical trials:

ADRs are listed below by frequency are defined as Very common (≥1/10):

Parkinsonism, headache and Insomnia.

Tabulated summary of clinical adverse reactions

ADRs are listed below by system organ class and frequency. Frequencies are defined as:

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

Table 1: Adverse reactions identified in clinical studies with RISPERDAL

Investigations	*Common:* Increased blood prolactin , increased weight. *Uncommon:* Abnormal electrocardiogram, increased blood glucose, increased transaminases, decreased white blood cell count, increased body temperature, increased eosinophil count, decreased haemoglobin, increased blood creatine phosphokinase. *Rare:* Decreased body temperature.
Cardiac disorders	*Common*: Tachycardia *Uncommon:* Atrioventricular block, bundle branch block, sinus bradycardia, palpitations, conduction disorder. Rare: Sinus dysrhythmia.
Blood and lymphatic system disorders:	*Uncommon:* Anaemia, neutropaenia, haematocrit decreased. *Rare:* Granulocytopaenia.

Nervous system disorders	*Very common:* Parkinsonism , headache. *Common:* Akathisia , dizziness, tremor , dystonia , somnolence, sedation, lethargy, dyskinesia. *Uncommon:* Unresponsive to stimuli, loss of consciousness, syncope, depressed level of consciousness, cerebrovascular accident, transient ischaemic attack, dysarthria, disturbance in attention, hypersomnia, postural dizziness, balance disorder, tardive dyskinesia, speech disorder, coordination abnormal, hypoaesthesia, head titubation, psychomotor hyperactivity, paraesthesia. *Rare:* Neuroleptic malignant syndrome, diabetic coma, cerebrovascular disorder, cerebral ischaemia, movement disorder, diabetic coma.
Eye disorder	*Common:* Blurred vision Uncommon: Conjunctivitis, ocular hyperaemia, eye discharge, eye swelling, dry eye, increased lacrimation, photophobia. *Rare:* Reduced visual acuity, eye rolling, glaucoma, eye movement disorder, eyelid margin crusting.
Ear and labyrinth disorders	*Uncommon:* Ear pain, tinnitus, vertigo.

Respiratory, thoracic and mediastinal disorders	*Common:* Dyspnoea, epistaxis, cough, nasal congestion, pharyngolaryngeal pain. *Uncommon:* Wheezing, pneumonia aspiration, pulmonary congestion, respiratory disorder, rales, respiratory tract congestion, dysphonia. *Rare:* Hyperventilation.
Gastrointestinal disorders.	*Common:* Vomiting, diarrhoea, constipation, nausea, abdominal pain, dyspepsia, dry mouth, stomach discomfort, toothache. *Uncommon:* Dysphagia, gastritis, faecal incontinence, faecaloma, gastroenteritis, flatulence. *Rare:* Lip swelling, cheilitis, swollen tongue.
Renal and urinary disorders	*Common:* Enuresis. *Uncommon:* Dysuria, urinary incontinence, pollakiuria.
Musculoskeletal and connective tissue disorders:	*Common:* Arthralgia, back pain, pain in extremity, muscle spasms. *Uncommon:* Muscular weakness, myalgia, neck pain, joint swelling, posture abnormal, joint stiffness, musculoskeletal chest pain. *Rare:* Rhabdomyolysis.

Skin and subcutaneous tissue disorders	*Common:* Rash, erythema. *Uncommon:* Skin lesion, skin disorder, pruritus, acne, skin discolouration, seborrhoeic dermatitis, dry skin, hyperkeratosis, urticaria, eczema. *Rare:* Dandruff, drug eruption. *Very rare:* Angioedema.
Metabolism and nutrition disorders	*Common*: Increased appetite, decreased appetite. *Uncommon*: Anorexia, polydipsia.
Infections and infestations	*Common:* Pneumonia, influenza, bronchitis, upper respiratory tract infection, urinary tract infection. *Uncommon:* Sinusitis, viral infection, ear infection, tonsillitis, cellulitis, otitis media, eye infection, localised infection, acarodermatitis, respiratory tract infection, cystitis, onychomycosis. *Rare:* Otitis media chronic.
Vascular disorders	*Uncommon:* Hypotension, orthostatic hypotension, flushing, hypertension. *Rare*: Pulmonary embolism, venous thrombosis.
General disorders and administration site conditions	*Common:* Pyrexia, fatigue, peripheral oedema, asthenia, chest pain, pain. *Uncommon:* Face oedema, gait disturbance, feeling abnormal, sluggishness, influenza like illness, thirst, chest discomfort, chills *Rare:* Generalised oedema, drug withdrawal syndrome, peripheral coldness.
Immune system disorders	Uncommon: Hypersensitivity. Rare: Drug hypersensitivity.

Reproductive system and breast disorders	*Uncommon:* Amenorrhoea, sexual dysfunction, erectile dysfunction, ejaculation disorder, galactorrhoea, gynaecomastia, menstrual disorder, vaginal discharge, breast pain,breast discomfort. Rare: Mensturation delayed, breast engorgement, breast enlargement, breast discharge.
Psychiatric disorders	*Very Common:* Insomnia. *Common:* Anxiety, agitation, sleep disorder, depression. *Uncommon:* Confusional state, decreased libido, listless, nervousness, nightmares. *Rare:* Anorgasmia, blunted affect.
Endocrine disorders	*Rare:* Glucose urine present.
Hepatobiliary disorders	*Uncommon:* gamma-glutamyltransferase increased, hepatic enzymes increased.
Injury, poisoning and procedural complications:	*Common:* Fall. *Uncommon:* Procedural pain.

Table 2: Adverse reactions reported post-marketing with RISPERDAL	
Investigations	Electrocardiogram QT prolongation.

Cardiac disorders	Atrial fibrillation.
Blood and lymphatic system disorders	Thrombocytopaenia, agranulocytosis.
Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome.
Gastro-intestinal disorders	Intestinal obstruction, pancreatitis, paralytic ileus.
Renal and urinary disorders	Urinary retention.
Skin and subcutaneous tissue disorder	Alopecia.
Endocrine disorder	Inappropriate antidiuretic hormone secretion.
Metabolism and nutrition disorder	Diabetic ketoacidosis, water intoxication, diabetes mellitus, hypoglycaemia, increased blood cholesterol, increased blood triglycerides.
Immune system disorder	Anaphylactic reaction, angioedema.
Psychiatric disorder	Mania.
Nervous System Disorder	Dysgeusia, catatonia, somnambulism, sleep-related eating disorder.
Eye Disorders	Floppy iris syndrome (intraoperative)
Hepatobiliary disorders	Jaundice.
Reproductive system and breast disorders	Priapism.
Pregnancy, Puerperium and Perinatal Conditions	Neonatal drug withdrawal syndrome.

General disorders	Hypothermia

Paediatric population:

The safety and efficacy of RISPERDAL in children under 5 years of age has not been demonstrated.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine product is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via "6.04 Adverse Drug Reaction Reporting Form" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8

Alternatively, suspected adverse reactions may be reported directly to Janssen Pharmaceutica (see section 7 for contact details or visit www.janssen.com).

4.9 Overdose:

Reported signs and symptoms have been those resulting from an exaggeration of the medicine's known pharmacological effects. Symptoms of acute overdosage include drowsiness, sedation, hypotension, tachycardia and extrapyramidal symptoms. In overdose, QT-prolongation and convulsions have been reported. Torsade de pointes has been reported in association with combined overdose of oral RISPERDAL 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. 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 dysrhythmias.

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 medicines. 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

Pharmacological classification:

A.2.6.5 Central nervous system depressants. Miscellaneous structures.

Mechanism of action:

RISPERDAL is a selective monoaminergic antagonist with affinity for serotonin-$5HT_2$, dopamine-D_2, H_1-histamine, α_1- and α_2-adrenergic receptors. It has no affinity for cholinergic receptors and is a D_2-antagonist.

5.2 Pharmacokinetic properties

Absorption:

Risperidone is completely absorbed after oral administration. Food does not affect the

absorption of risperidone.

Distribution:

Peak plasma concentrations are attained within 1 to 2 hours. Following 6 mg or 8 mg once daily, peak levels of the active moiety were about 30 % higher and trough levels about 30 % lower than the peaks and troughs following 3 and 4 mg twice daily.

Steady state is reached within 1 day for risperidone in most patients and 4-5 days for 9-hydroxy-risperidone. Risperidone plasma concentration is dose-proportional within the therapeutic dose-range. Risperidone is bound to albumin and alpha1-acid glycoprotein. Plasma protein binding of risperidone is 88 % and 77 % for 9-hydroxy-risperidone.

Biotransformation:

Risperidone is metabolised by cytochrome CYP 2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity to risperidone. Risperidone and 9-hydroxy-risperidone form the active antipsychotic fraction.

Elimination:

After oral administration to psychotic patients, risperidone's half-life is about 3 hours. The elimination half-life of 9-hydroxy-risperidone and the active antipsychotic fraction is 24 hours. One week after administration, 70 % of the dose is excreted in the urine and 14 % in the faeces. In urine, risperidone and 9-hydroxy-risperidone represent 35 - 45 % of the dose.

A single dose study showed higher active plasma concentrations and a reduced clearance of the active antipsychotic fraction by 30 % in the elderly and 50 % in patients with moderate 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 liver insufficiency, but the mean free fraction of risperidone in plasma was increased by about 35 %.

Paediatric population:

The Pharmacokinetics of risperidone, 9-hydroxy-risperidone and active moety in children are similar to those in adults.

Patients with hepatic impairment:

Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone. Irrespective of the indication, starting and consecutive dosing should be halved, and dose titration should be slower for patients with hepatic impairment.
RISPERDAL should be used with caution in these groups of patients.

Patients with renal impairment:

Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than normal adults. Irrespective of the indication, starting and consecutive dosing should be halved, and dose titration should be slower for patients with renal impairment.
RISPERDAL should be used with caution in these groups of patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Lactose, maize starch, cellulose, hypromellose, magnesium stearate, silicon dioxide, sodium laurylsulfate and propylene glycol.

The 0,5 milligram tablet also contains talc, titanium dioxide and red ferric oxide.

The 2 milligram tablet also contains talc, titanium dioxide and orange yellow S.

The 3 milligram tablet also contains talc, titanium dioxide and quinoline yellow.

6.2 Incompatibilities:

Not Applicable.

6.3 Shelf life:

36 Months

6.4 Special precautions for storage:

Store at or below 25 ºC.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container:

Cartons containing one or more clear PVC-PE-PVDC/aluminium blisters of 10 tablets each.

6.6 Special precautions for disposal and other handling:

No Special Requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

JANSSEN PHARMACEUTICA (Pty.) Ltd.

(Reg No.: 1980/011122/07)

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8. REGISTRATION NUMBER

RISPERDAL TABLETS 0,5 mg – 33/2.6.5/0111

RISPERDAL TABLETS 1 mg; 2 mg; 3 mg; - 27/2.6.5/0235/6/7

9. DATE OF FIRST AUTHORISATION

Date of registration:

RISPERDAL TABLETS 0,5 mg: 18 July 2001

RISPERDAL TABLETS 1 mg; and 2 mg and 3 mg: 23 September 1993

10. DATE OF REVISION OF THE TEXT

Date of the most recently revised Professional Information as approved by SAHPRA:

TBA