PROFESSIONAL INFORMATION

SCHEDULING STATUS: **S5**

1. NAME OF THE MEDICINE

RISPIDE® 0,5, film-coated tablets

RISPIDE® 1, film-coated tablets

RISPIDE® 2, film-coated tablets

RISPIDE® 3, film-coated tablets

RISPIDE® 4, film-coated tablets

RISPIDE® 6, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

RISPIDE 1: Each film-coated tablet contains 1 mg risperidone.

RISPIDE 2: Each film-coated tablet contains 2 mg risperidone.

RISPIDE 3: Each film-coated tablet contains 3 mg risperidone.

RISPIDE 4: Each film-coated tablet contains 4 mg risperidone.

RISPIDE 6: Each film-coated tablet contains 6 mg risperidone.

RISPIDE 1 contains sugar (1,6 mg lactose monohydrate per tablet).

RISPIDE 0,5, 2, 3, 4 & **6** are sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

RISPIDE 0,5: Cream, round, biconvex tablets with a diameter of approximately 8,1 mm.

RISPIDE 1: White, round, biconvex tablets with a diameter of approximately 8,1 mm.

RISPIDE 2: Yellow, round, biconvex tablets with a diameter of approximately 8,1 mm.

RISPIDE 3: Peach, round, biconvex tablets with a diameter of approximately 8,1 mm.

RISPIDE 4: Green, round, biconvex tablets with a diameter of approximately 8,1 mm.

RISPIDE 6: Light green, round, biconvex tablets with a diameter of approximately 8,1 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RISPIDE is indicated for the treatment of:

- Acute and chronic schizophrenic psychoses and related psychosis in which positive symptoms (hallucinations, delusions, thought disturbances, hostility and suspiciousness) and/or the negative symptoms (blunted affect, emotional and social withdrawal, poor speech) are prominent. RISPIDE also alleviates affective symptoms associated with schizophrenia. In patients who have shown an initial treatment response, RISPIDE is also effective in maintaining the clinical improvement.

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

4.2 Posology and method of administration

Posology

Schizophrenia

Switching from other antipsychotics to RISPIDE:

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

Adults

RISPIDE may be given once or twice daily.

Patients should start with RISPIDE 2 mg/day. 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) are associated with more extrapyramidal symptoms and other adverse effects and are not 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 RISPIDE if additional sedation is required.

Special populations

Renal and liver impairment

Caution should be exercised with these groups of patients, as clinical experience is lacking in these patient populations. It is recommended to halve both the starting dose and the subsequent dose increments.

Elderly patients

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

Paediatric population

RISPIDE should not be used in children under 15 years, as efficacy and safety in children under the age of 15 years have not been demonstrated in schizophrenia.

Behavioural disturbances in adult patients with dementia

A starting dose of 0,25 mg twice daily is recommended. This dosage can be individually adjusted 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. Some patients, however, 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 RISPIDE 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 to 0,04 mg/kg once daily. The mean dose is 0,03 mg/kg once daily.

The continued use of RISPIDE must be evaluated and justified on an ongoing basis.

Experience is lacking in children aged less than 5 years (see section 4.5).

Method of administration

Oral use. Can be taken with or without food.

4.3 Contraindications

RISPIDE is contraindicated in patients with known sensitivity to risperidone or any of the components of RISPIDE.

Conduct and other disruptive behaviour disorders in children: RISPIDE 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).

Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Intraoperative floppy iris syndrome

Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with α1-adrenergic antagonist effect, including RISPIDE (see section 4.8). IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with α1-adrenergic antagonist effect, (including RISPIDE), should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping RISPIDE therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

Tardive dyskinesia

Tardive dyskinesia (TD), a syndrome consisting of potentially irreversible, involuntary dyskinetic movements, predominantly of the face and tongue, may develop in patients treated with RISPIDE. 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.

It has been suggested that the occurrence of Parkinsonian side effects is 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.

RISPIDE 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, RISPIDE should be prescribed in a manner that is most likely to minimise the risk of TD. RISPIDE 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, RISPIDE 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 RISPIDE.

Clinical manifestations of NMS are hyperthermia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, cardiac dysrhythmias and diaphoresis). Additional signs may include elevated creatine phosphokinase (CPK) levels, myoglobinuria (rhabdomyolysis), and acute renal failure.

In arriving at a diagnosis, it is important to identify 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). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, medicine fever and primary central nervous system pathology.

The management of NMS should include:

1. Immediate discontinuation of all antipsychotic medicines and other medicines not essential to concurrent therapy;
2. Intensive symptomatic treatment and medical monitoring; and
3. Treatment of any concomitant serious medical problems for which specific 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 from NMS, the potential reintroduction of medicine therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Concomitant use with furosemide

In placebo-controlled trials in the elderly patients with dementia, there was a higher mortality in patients treated with furosemide and risperidone, as in RISPIDE**,** when compared to patients treated with risperidone alone. Caution is advised when prescribing RISPIDE and furosemide concomitantly in these patients. Dehydration is an overall risk for mortality and should be carefully avoided in these patients.

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

Cerebrovascular adverse events

Cerebrovascular adverse events (CAE), including cerebrovascular accidents and transient ischaemic attacks, have been reported during treatment with RISPIDE**.** 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 RISPIDE compared to patients receiving placebo (mean age 85 years; range 73-97 years). Caution is advised in all patients with risk factors for stroke and regular assessment for the need for RISPIDE treatment is recommended.

Dementia associated with Parkinson's disease and senile dementia

Prescribing RISPIDE to patients with Parkinson's disease or dementia with Lewy bodies (DLB) is contraindicated, since both groups may be at risk of neuroleptic malignant syndrome (NMS) as well as having an increased sensitivity to antipsychotic medicines such as RISPIDE (see section 4.3). Manifestations of this increased sensitivity can include confusion, obtundation, and postural instability with frequent falls, in addition to extrapyramidal symptoms.

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

Leukopenia, neutropenia, and agranulocytosis

Events of leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics, including RISPIDE.

Patients with a history of a clinically significant low white blood cell count (WBC) or a medicine-induced leukopenia/neutropenia should be monitored during the first few months of therapy. Discontinuation of RISPIDE 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 RISPIDE and have their WBC followed until recovery.

QT prolongation

QT prolongation has been reported during post-marketing experience. Caution should be exercised when RISPIDE is prescribed in patients with known cardiovascular disease, family history of QT prolongation, bradycardia, or electrolyte disturbances (hypokalaemia, hypomagnesaemia), as it may increase the risk of dysrhythmogenic effects, and in concomitant use with medicines known to prolong the QT interval.

Orthostatic hypotension

Due to the alpha-blocking activity of RISPIDE (orthostatic) hypotension can occur, especially during the initial dose-titration period. RISPIDE 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 RISPIDE. 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 may occur. Monitoring weight gain is advisable when RISPIDE is used.

Patients may be advised to refrain from excessive eating in view of the possibility of weight gain.

Benign pituitary adenomas

Benign pituitary adenomas have been reported during post-marketing surveillance. No causal association could be detected.

Hyperprolactinemia

A dose-dependant increase in plasma prolactin concentration may occur.

Hyperprolactinaemia is a common side-effect of treatment with risperidone (as in RISPIDE). 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**.** Premenopausal women who develop secondary amenorrhoea of greater than six months duration should receive appropriate preventative therapy to avoid hypo-oestrogenic bone loss.

RISPIDE should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours.

Body temperature regulation

Disruption of the body's ability to reduce core body temperature may occur.

Appropriate care is advised when prescribing RISPIDE 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 treatment with anticholinergic activity, or being subject to dehydration.

Priapism

Medicines with alpha-adrenergic blocking effects such as RISPIDE, may induce priapism (see section 4.8).

Excipients

RISPIDE 1 contains 1,6 mg lactose per tablet. Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take **RISPIDE 1**.

4.5 Interactions with other medicines and other forms of interaction

Pharmacodynamic-related Interactions

Medicines known to prolong the QT interval

There may be an increased risk of QT prolongation when RISPIDE is given with other medicines known to cause this effect, such as antidysrhythmics (e.g., quinidine, dysopiramide, 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.

Central-acting medicines and alcohol

RISPIDE should be used with caution in combination with alcohol and other centrally acting medicines, including opiates, antihistamines and benzodiazepines due to the increased risk of sedation.

Levodopa and dopamine agonists

RISPIDE may antagonise the effect of levodopa and other dopamine-agonists (bromocriptine and pergolide). If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.

Medicines with hypotensive effect

RISPIDE may enhance the effects of antihypertensive treatment (see section 4.4).

Psychostimulants

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

Paliperidone

Concomitant use of oral RISPIDE 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 metabolized 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 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 CYP 2D6 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 physician should re-evaluate the dosing of RISPIDE.

CYP3A4 and/or P-gp inhibitors

Co-administration of RISPIDE 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 RISPIDE.

CYP3A4 and/or P-gp Inducers

Co-administration of risperidone with a strong CYP3A4 and/or P-gp inducer can decrease the plasma levels of the risperidone active antipsychotic fraction. Similar effects may be observed with other hepatic enzyme inducers. 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 RISPIDE.

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 RISPIDE 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 professional leaflets should be consulted for information on the route of metabolism and the possible need to adjust dosage.

Effect of other medicines on the pharmacokinetics of risperidone

Antibacterials:

- Rifampicin, a strong CYP3A4 inducer and a P-gp inducer, decreased the plasma concentrations of the active antipsychotic fraction.
- Erythromycin, a moderate CYP3A4 inhibitor and P-gp inhibitor, does not change the pharmacokinetics of risperidone and 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 which also induce CYP 3A4 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:

  Co-administration of RISPIDE 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 RISPIDE.
- 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-hydroxy-risperidone.

Antipsychotics:

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

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:

- H_2-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 concomitant treatment with fluoxetine is initiated or discontinued, the dosing of RISPIDE should be re-evaluated.
- 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 concomitant treatment with paroxetine is initiated or discontinued, the dosing of RISPIDE should be re-evaluated.

- 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 than 100 mg/day of sertraline or fluvoxamine may elevate concentrations of the risperidone active antipsychotic fraction.
- Venlafaxine: Risperidone AUC increased and risperidone clearance decreased, but no effect was observed on 9-hydroxy–risperidone and the active moiety.
- Galantamine and donepezil do not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction.

Effect of RISPIDE on the pharmacokinetics of other medicines

Antiepileptics:

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

Digitalis glycosides:

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

Antipsychotics:

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

Lithium:

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

Concomitant use of risperidone with furosemide

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

  In placebo-controlled studies in elderly patients with dementia there was a higher mortality in patients treated with furosemide and risperidone, as in RISPIDE, when compared to patients treated with risperidone alone. Caution is advised in these patients. Dehydration was an overall risk for mortality and should be carefully avoided in these patients.

4.6 Fertility, pregnancy and lactation

Pregnancy

RISPIDE is contraindicated during pregnancy and lactation (see section 4.3).

Reversible extrapyramidal symptoms, including hypertonia, hypotonia, jitteriness, tremor, muscle rigidity, twitching and convulsions, feeding disorder and withdrawal symptoms have been observed in neonates following use of risperidone, as in RISPIDE, during the last trimester of pregnancy.

Breastfeeding

Risperidone and 9-hydroxy-risperidone are excreted in human breast milk. Therefore, women receiving RISPIDE should not breastfeed their infants (see section 4.3).

Fertility

Risperidone as in RISPIDE elevates prolactin level, which may suppress hypothalamic GnRH resulting in reduced pituitary gonadotropin secretion. This may inhibit reproductive function by impairing gonadal steroidogenesis in both male and female patients.

4.7 Effects on ability to drive or operate machinery

RISPIDE has an influence on driving or handling machines.

RISPIDE may cause dizziness, blurred vision and impairment of mental alertness. Patients should therefore be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 Undesirable effects

The following side effects may occur:

Infections and infestations

Frequent:	Pneumonia, influenza, bronchitis, upper respiratory tract infection, sinusitis, urinary tract infection.
Less frequent:	Viral infection, ear infection, tonsilitis, cellulitis, otitis media, eye infection, localised infections,

acrodermatitis, respiratory tract infection, cystitis, onychomycosis.

Blood and lymphatic system disorders

Less frequent: Anaemia, granulocytopenia, white blood cell count decreased, thrombocytopenia, haematocrit decreased, eosinophil count increased, agranulocytosis.

Immune system disorders

Less frequent: Hypersensitivity, anaphylactic reaction, medicine hypersensitivity, angioedema.

Endocrine disorders

Frequent: Hyperprolactinaemia

Less frequent: Inappropriate antidiuretic hormone secretion, glucose urine present.

Metabolism and nutrition disorders

Frequent: Weight increase, increased appetite, decreased appetite.

Less frequent: Anorexia, polydipsia, diabetes mellitus, hyperglycaemia, weight decreased, increased blood cholesterol, water intoxication, hypoglycaemia, hyperinsulinaemia, increased blood triglycerides, diabetic ketoacidosis.

Psychiatric disorders

Frequent: Insomnia, agitation, anxiety, sleep disorder, depression.

Less frequent: Confused state, decreased libido, listless, nervousness, anorgasmia, blunted affect, mania, nightmares, catatonia, somnambulism, sleep-related eating disorder.

Nervous system disorders

Frequent: Parkinsonism, headache, akathisia, dizziness, tremor, dystonia, somnolence, sedation, lethargy, dyskinesia.

Less frequent: 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, abnormal coordination, hypoaesthesia, neuroleptic malignant syndrome, diabetic coma, cerebrovascular disorders, cerebral ischaemia, movement disorder (see section 4.4).

Eye disorders

Frequent: Blurred vision, conjunctivitis.

Less frequent: Photophobia, dry eyes, increased lacrimation, ocular hyperaemia, eye discharge, eye swelling, reduced visual acuity, glaucoma, eye movement disorder, eye rolling, eyelid margin crusting, floppy iris syndrome (intraoperative).

Ear and labyrinth disorders

Less frequent: Ear pain, tinnitus, vertigo.

Cardiac disorders

Frequent: Tachycardia

Less frequent: Atrioventricular block, bundle branch block, sinus bradycardia, palpitations, atrial fibrillation, QT-prolongation, abnormal electrocardiogram, bradycardia, conduction disorders, sinus dysrhythmia.

Vascular disorders

Less frequent: Hypotension, orthostatic hypotension, hypertension, flushing, pulmonary embolism, venous thrombosis**.**

Respiratory system disorders

Frequent: Dyspnoea, epistaxis, cough, nasal congestion, pharyngolaryngeal pain.

Less frequent: Wheezing, pneumonia aspiration, pulmonary congestion, respiratory disorders, rales, respiratory tract congestion, dysphonia, hyperventilation, sleep apnoea syndrome.

Frequency unknown: Apnoea, pulmonary embolism.

Gastrointestinal disorders

Frequent: Vomiting, diarrhoea, constipation, nausea, abdominal pain, dyspepsia, dry mouth, abdominal discomfort, toothache.

Less frequent: Dysphagia, gastritis, faecal incontinence, faecaloma, lip swelling, cheilitis, gastroenteritis, flatulence, pancreatitis, intestinal obstruction, swollen tongue, ileus.

Hepatobiliary disorders

Less frequent: Increased transaminases, increased gamma-glutamyl transferase, increased hepatic enzymes, jaundice.

Skin and subcutaneous tissue disorders

Frequent: Skin rash, erythema.

Less frequent: Skin lesions, skin disorders, dry skin, skin discolouration, seborrheic dermatitis, seborrhoea, medicine eruption, urticaria, pruritus, eczema, hyperkeratosis, dandruff.

Frequency unknown: Alopecia, Stevens-Johnson syndrome/toxic epidermal necrolysis.

Musculoskeletal, connective tissue and bone disorders

Frequent: Back pain, arthralgia, pain in extremities, muscle spasms, musculoskeletal pain.

Less frequent: Muscular weakness, myalgia, neck pain, joint swelling, abnormal posture, joint stiffness, musculoskeletal chest pain, rhabdomyolysis, increased blood creatinine phosphokinase.

Renal and urinary disorders

Frequent: Urinary incontinence, enuresis.

Less frequent: Dysuria, pollakiuria, urinary retention.

Pregnancy, puerperium and perinatal conditions

Less frequent: Neonatal medicine withdrawal syndrome.

Reproductive system and breast disorders

Less frequent: Gynaecomastia, galactorrhoea, amenorrhoea**,** erectile dysfunction, ejaculation disorder, menstrual disorder, vaginal discharge, sexual dysfunction, breast pain, breast discomfort, priapism, menstruation delayed, breast engorgement, breast enlargement, breast discharge.

General disorders and administration site conditions

Frequent: Pyrexia, fatigue, oedema, asthenia, chest pain.

Less frequent: Face oedema, abnormal gait, feeling abnormal, sluggishness, influenza-like illness, thirst, chest discomfort, chills, medicine withdrawal syndrome, peripheral coldness, hypothermia, malaise.

Investigations

Frequent: Increased blood prolactin, increased weight.

Less frequent: Abnormal electrocardiogram, increased blood glucose, increased transaminases, decreased white blood cell count, increased body temperature, increased eosinophil count, decreased haemoglobin, increased blood

creatinine phosphokinase, decreased body temperature.

Injury, poisoning and procedural complications

Frequent: Fall

Less frequent: Procedural pain.

Reporting of 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

Reported signs and symptoms have been those resulting from an exaggeration of RISPIDE's known pharmacological effects. Symptoms of acute overdosage include drowsiness, sedation, hypotension, tachycardia and extrapyramidal symptoms. In overdose, cases of QT prolongation have been reported.

In the case of acute overdosage, the possibility of multiple medicine ingestion 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 agents. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

A 2.6.5 Central nervous system depressants. Miscellaneous structures

Pharmacotherapeutic group: Other antipsychotics, ATC code: N05A X08

Risperidone is an antipsychotic of the benzisoxazole derivatives. It is a selective monoaminergic antagonist. Risperidone has affinity for serotonin-5-HT_2, dopamine-D_2, H_1-histamine, alpha$_1$- and alpha$_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. It is a dopamine D_2-antagonist.

5.2 Pharmacokinetic properties:

Absorption

Risperidone is completely absorbed after oral administration. Peak plasma concentrations are attained within 1 to 2 hours. Food does not affect the absorption of risperidone.

Distribution

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 $alpha_1$-acid glycoprotein. Plasma protein binding of risperidone is 88 % and 77 % for 9-hydroxy-risperidone. One week after administration, 70 % of the dose is excreted in the urine and 14 % in the faeces. In the urine, risperidone and 9-hydroxy-risperidone represent 35 - 45 % of the dose.

Biotransformation

Risperidone is metabolised by cytochrome CYP2D6 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.

Special populations

Risperidone showed significantly higher active plasma concentrations and slower elimination in the elderly and in patients with moderately severe renal

insufficiency. The plasma concentrations of risperidone were normal in patients with mild to moderate liver insufficiency.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose PH102

Pregelatinised starch

Hypromellose (Methocel E50 LV)

Magnesium stearate (vegetable grade)

Film coating:

RISPIDE 0,5: Hypromellose, propylene glycol, quinoline yellow, sunset yellow, talc and titanium dioxide

RISPIDE 1: Hypromellose, lactose monohydrate, macrogol and titanium dioxide

RISPIDE 2: Hypromellose, propylene glycol, quinoline yellow, talc and titanium dioxide

RISPIDE 3: Hypromellose, propylene glycol, sunset yellow, talc and titanium dioxide

RISPIDE 4: Hypromellose, indigotine, macrogol, quinoline yellow, talc and titanium dioxide

RISPIDE 6: Hypromellose, indigotine, macrogol, propylene glycol, quinoline yellow, talc and titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

36 Months

6.4 Special precautions for storage

Store in the original packaging (in the carton) at or below 25 °C.

6.5 Nature and contents of container

Packs of 30 tablets packed in opaque white PVC/PE/PVDC/Aluminium blisters in a cardboard carton.

Not all strengths are necessarily marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATES OF REGISTRATION

Abex Pharmaceutica (Pty) Ltd

Suite C, Rubenstein Ridge

617 Rubenstein Drive

Moreleta Park

0181

8. REGISTRATION NUMBERS

RISPIDE 0,5: 44/2.6.5/0673

RISPIDE 1: 44/2.6.5/0674

RISPIDE 2: 44/2.6.5/0675

RISPIDE 3: 44/2.6.5/0676

RISPIDE 4: 44/2.6.5/0677

RISPIDE 6: 44/2.6.5/0678

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 21 April 2016

10. DATE OF REVISION OF THE TEXT

01 April 2025