PROFESSIONAL INFORMATION

SCHEDULING STATUS **S5**

1 NAME OF THE MEDICINE

RISPIDE ® 1 mg/ml oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml oral solution contains 1 mg of risperidone.

Excipient(s) with known effect

1 ml oral solution contains 1,5 mg benzoic acid (E210) as preservative

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

The solution is clear and colourless.

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

patients who have shown an initial treatment response, RISPIDE 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 to 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

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 2 mg/day RISPIDE. 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 RISPIDE 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 to 2 mg twice daily.

Children

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

RISPIDE 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 RISPIDE 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 to 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.

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.

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

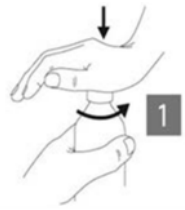
Method of administration

RISPIDE is for oral use.

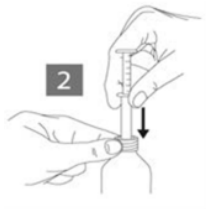
Directions for opening the bottle and using the pipette:

The solution comes with a pipette (syringe). This should be used to help you to measure the exact amount of medicine you need. To open the bottle and use the pipette:

1. The bottle comes with a child resistant cap and should be opened as follows: push the plastic screw cap down while turning it counterclockwise (Figure 1). Remove the unscrewed cap.

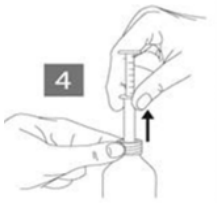


2. Insert the pipette into the bottle (Figure 2).



3. While holding the bottom ring, pull the top ring up to the mark that corresponds to the number of millilitres or milligram you need to give / take (Figure 3).

4. Holding the bottom ring, remove the entire pipette from the bottle (Figure 4).



5. Empty the pipette into any non-alcoholic drink, except for tea, by sliding the upper ring down.
6. Close the bottle.
7. Rinse the pipette with some water.

4.3 Contraindications

- Hypersensitivity to risperidone or to any of the excipients of RISPIDE listed in section 6.1.
- Conduct and other disruptive behaviour disorders in children: RISPIDE is contra-indicated 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 (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 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).

Concomitant use with furosemide (see section 4.5)

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

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 risperidone compared to patients receiving placebo (mean age 85 years; range 73 to 97 years).

Orthostatic hypotension

Due to the alpha-blocking activity of risperidone, (orthostatic) hypotension can occur, especially during the initial dose titration period. Risperidone as in 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.

Leukopenia, neutropenia, and agranulocytosis

Events of leukopenia, neutropenia and agranulocytosis have been reported with risperidone as in RISPIDE. 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 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.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with risperidone. 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 risperidone as in RISPIDE and preventive measures undertaken.

Tardive dyskinesia/ extrapyramidal symptoms (TD/EPS)

Risperidone as in RISPIDE 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 RISPIDE should be considered.

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 risperidone as in RISPIDE. Additional signs may include elevated creatine phosphokinase levels, myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, RISPIDE 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 medicines (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 risperidone as in RISPIDE.

Patients with an established diagnosis of diabetes mellitus who are starting on risperidone as in 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 risperidone was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of risperidone.

Weight gain

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

Hyperprolactinaemia

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).

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. RISPIDE 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 RISPIDE 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 risperidone as in RISPIDE 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 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 medicines with anticholinergic activity, or being subject to dehydration.

Antiemetic effect

An antiemetic effect was observed in preclinical studies with risperidone as in RISPIDE. 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 risperidone as in RISPIDE.

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

Seizures

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

Paediatric population

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

Risperidone as in RISPIDE 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 RISPIDE regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.

RISPIDE contains 1,5 mg benzoic acid per 1 ml solution.

An increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

4.5 Interaction with other medicines and other forms of interaction

The risk of using risperidone as in RISPIDE 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, 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.

Centrally acting medicines and alcohol

Risperidone as in RISPIDE 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 RISPIDE 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 RISPIDE 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 RISPIDE and antihypertensive treatment.

Paliperidone

Concomitant use of oral risperidone as in 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 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 RISPIDE 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 RISPIDE.

CYP3A4 and/or P-gp inhibitors

Co-administration of risperidone as in 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 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 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 risperidone as in 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 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 RISPIDE 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 RISPIDE 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.

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.
- 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.

- Venlafaxine administered under steady state conditions at 150 mg/day inhibited the CYP2D6-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 than 100 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 RISPIDE with furosemide

There is increased mortality in elderly patients with dementia concomitantly receiving furosemide and risperidone as in RISPIDE. (see section 4.4)

4.6 Fertility, pregnancy, and lactation

The safety of risperidone as in RISPIDE in pregnancy and breastfeeding women has not been established.

Pregnancy

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.

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.

Therefore, RISPIDE should only be used during pregnancy if the benefits outweigh the risks.

Breastfeeding

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 RISPIDE should not breastfeed.

Fertility

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

RISPIDE 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

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 summary of adverse reactions

System Organ Class	**Frequent**	**Less frequent**
Infections and infestations	pneumonia, influenza, bronchitis, upper respiratory tract infection, urinary tract infection, sinusitis, ear infection	viral infection, tonsillitis, cellulitis, otitis media, eye infection, localised infection, acarodermatitis, respiratory tract infection, cystitis, onychomycosis, chronic otitis media

System Organ Class	Frequent	Less frequent
Blood and lymphatic system disorders		anaemia, neutropenia, granulocytopenia, white blood cell count decreased, thrombocytopenia, haematocrit decreased, eosinophil count increased, agranulocytosis
Immune system disorders		hypersensitivity, anaphylactic reaction, angioedema
Endocrine disorders	Hyperprolactinaemia (which can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhoea, anovulation, galactorrhoea, fertility disorder, decreased libido, erectile dysfunction)	inappropriate antidiuretic hormone secretion, glucose urine present
Metabolism and nutrition disorders	weight increased, increased appetite, decreased appetite	diabetes mellitus, hyperglycaemia, polydipsia, weight decreased, anorexia, blood cholesterol increased, water intoxication, hypoglycaemia, hyperinsulinemia, blood triglycerides increased, diabetic ketoacidosis
Psychiatric disorders	insomnia (1), sleep disorder, agitation, depression, anxiety	mania, confusional state, libido decreased, nervousness, nightmare, catatonia,

System Organ Class	Frequent	Less frequent
		somnambulism, sleep related eating disorder, blunted affect, anorgasmia
Nervous system disorders	Sedation / somnolence, parkinsonism (1), headache, akathisia[1], dystonia[1], dizziness, dyskinesia[1], tremor	tardive dyskinesia, cerebral ischaemia, unresponsive to stimuli, loss of consciousness, depressed level of consciousness, cerebrovascular accident, transient ischaemic attack, convulsion (1), syncope, psychomotor hyperactivity, balance disorder, coordination abnormal, dizziness postural, disturbance in attention, dysarthria, dysgeusia, hypoaesthesia, paraesthesia, neuroleptic malignant syndrome, cerebrovascular disorder, diabetic coma, head titubation
Eye disorders	vision blurred, conjunctivitis	photophobia, dry eye, lacrimation increased, ocular hyperaemia, glaucoma, eye movement disorder, eye rolling, eyelid margin crusting, floppy iris syndrome (intraoperative)

System Organ Class	Frequent	Less frequent
Ear and labyrinth disorders		vertigo, tinnitus, ear pain
Cardiac disorders	tachycardia	atrial fibrillation, atrioventricular block, conduction disorder, electrocardiogram QT prolonged, bradycardia, electrocardiogram abnormal, palpitations, sinus dysrhythmia
Vascular disorders	hypertension	hypotension, orthostatic hypotension, flushing, pulmonary embolism, venous thrombosis
Respiratory, thoracic and mediastinal disorders	dyspnoea, pharyngolaryngeal pain, cough, epistaxis, nasal congestion	pneumonia aspiration, pulmonary congestion, respiratory tract congestion, rales, wheezing, dysphonia, respiratory disorder, sleep apnoea syndrome, hyperventilation
Gastrointestinal disorders	abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhoea, dyspepsia, dry mouth, toothache	faecal incontinence, faecaloma, gastroenteritis, dysphagia, flatulence, pancreatitis, intestinal obstruction, swollen tongue, ileus, cheilitis

System Organ Class	Frequent	Less frequent
Skin and subcutaneous tissue disorders	rash, erythema	urticaria, pruritus, alopecia, hyperkeratosis, eczema, dry skin, skin discolouration, acne, seborrheic dermatitis, skin disorder, skin lesion, drug eruption, dandruff
Musculoskeletal and connective tissue disorders	muscle spasms, musculoskeletal pain, back pain, arthralgia	blood creatine phosphokinase increased, posture abnormal, joint stiffness, joint swelling, muscular weakness, neck pain, rhabdomyolysis
Renal and urinary disorders	urinary incontinence	pollakiuria, urinary retention, dysuria
Pregnancy, puerperium, and neonatal conditions		neonatal medicine withdrawal syndrome
Reproductive system and breast disorders		erectile dysfunction, ejaculation disorder, amenorrhoea, menstrual disorder(1), gynaecomastia, galactorrhoea, sexual dysfunction, breast pain, breast discomfort, vaginal discharge, priapism, menstruation delayed, breast engorgement, breast enlargement,

System Organ Class	Frequent	Less frequent
		breast discharge
General disorders and administration site conditions	oedema(1), pyrexia, chest pain, asthenia, fatigue, pain	face oedema, chills, body temperature increased, gait abnormal, thirst, chest discomfort, malaise, feeling abnormal, discomfort, hypothermia, body temperature decreased, peripheral coldness, drug withdrawal syndrome, induration
Hepatobiliary disorders		transaminases increased, gamma-glutamyltransferase increased, hepatic enzyme increased, jaundice
Injury, poisoning and procedural complications	fall	procedural pain

(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 RISPIDE.

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 medicinal product. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

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, 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 risperidone as in RISPIDE 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 medicine should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class:

A.2.6.5 Central nervous system depressants. Miscellaneous structures.

Pharmacotherapeutic group: Other antipsychotics, ATC code: N05AX08.

Risperidone is an antipsychotic of the benzoxazole derivatives. It is a selective monoaminergic antagonist. Risperidone has affinity for serotonin-5-HT_2, dopamine-D_2, H_1-histamine, α_1- and α_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.

Steady state is reached within 1 day for risperidone in most patients and 4 to 5 days for 9-hydroxy-risperidone.

Distribution

Risperidone is bound to albumin and alpha$_1$-acid glycoprotein. Plasma protein binding of risperidone is 88 % and 77 % for 9-hydroxy-risperidone.

Biotransformation and elimination

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.

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 to 45 % of the dose.

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.

Linearity/non-linearity

Risperidone plasma concentration is dose-proportional within the therapeutic dose-range.

Special populations

Elderly, hepatic, and renal impairment

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 the active moiety in children are similar to those in adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tartaric acid (E334)

Benzoic acid (E210) (as preservative)

Hydrochloric acid, concentrated (for pH adjustment)

Purified water

6.2 Incompatibilities

Incompatible with most types of tea, including black tea.

6.3 Shelf life

RISPIDE oral solution: 3 years

Shelf life after first opening: 4 months

6.4 Special precautions for storage

Store at or below 25 °C. Store in the original package until required for use. Do not freeze.

6.5 Nature and contents of container

Type III amber glass bottle with a plastic (polypropylene/LDPE) child resistant and tamper-evident cap. RISPIDE oral solution is presented in bottle sizes of 30 ml, 60 ml, 100 ml and 120 ml.

Additionally, a dosing pipette (syringe) is supplied in each pack consisting of a polystyrene plunger and a LDPE-barrel and piston.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Abex Pharmaceutica (Pty) Ltd

Suite C, Rubenstein Ridge

617 Rubenstein Drive

Moreleta Park, 0181

8. REGISTRATION NUMBER(S)

56/2.6.5/0424

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration date: 08 August 2023

10. DATE OF REVISION OF THE TEXT

Not applicable