PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

RESKIT 0,5 film-coated tablets

RESKIT 1 film-coated tablets

RESKIT 2 film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar: lactose monohydrate 18,25 mg per tablet.

RESKIT 1: Each tablet contains risperidone 1 mg.

Contains sugar: lactose monohydrate 36,5 mg per tablet.

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

Contains sugar: lactose monohydrate 73,0 mg per tablet

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets.

RESKIT 0,5

Brown coloured, film-coated, oval shaped tablets with a scoreline on both sides and **'RSN'** and **'0,5'** debossed on either side of the scoreline on one side.

RESKIT 1

White, film-coated, capsule shaped tablets with a scoreline on both sides and **'RSN'** and **'1'** debossed on either side of the scoreline on one side.

RESKIT 2

Peach coloured, film-coated, capsule shaped tablets with a scoreline on both sides and **'RSN'** and **'2'** debossed on either side of the scoreline on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

RESKIT 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. RESKIT also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia. In patients who have shown an initial treatment response, RESKIT 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 sub-average 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 RESKIT*:*

When medically appropriate, gradual discontinuation of the previous treatment, while RESKIT therapy is initiated, is recommended. Also if medically appropriate, when switching patients from

depot antipsychotics, initiate RESKIT therapy in place of the next scheduled injection. The need for continuing existing anti-Parkinson medications should be re-evaluated periodically.

Adults

RESKIT may be given once or twice daily.

Patients should start with RESKIT 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) 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 RESKIT 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.

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***

RESKIT 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 RESKIT 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 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 RESKIT tablets 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.

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

Method of administration

For oral use.

4.3 Contraindications

- RESKIT tablets are contraindicated in patients with known sensitivity to risperidone or to any of the components of RESKIT (see section 6.1).
- Conduct and other disruptive behaviour disorders in children: **RESKIT** 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

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

Concomitant use with furosemide

In elderly patients with dementia there may be a higher mortality in patients treated with furosemide and RESKIT if compared to patients treated with RESKIT alone. Caution is advised in these patients.

Dehydration is an overall risk for mortality and should be carefully avoided in these patients. Caution is advised in these patients when prescribing RESKIT.

Cerebrovascular Adverse Events

Cerebrovascular adverse events (CAE), including cerebrovascular accidents and transient ischaemic attacks, have been reported during treatment with RESKIT. In placebo-controlled clinical trials in elderly patients with dementia, there was a higher incidence of cerebrovascular

adverse events, including cerebrovascular accidents and transient ischaemic attacks, in patients treated with risperidone compared to patients receiving placebo (mean age 85 years; range 73-97 years).

Orthostatic Hypotension

Due to the alpha-blocking activity of RESKIT, (orthostatic) hypotension can occur, especially during the initial dose-titration period. RESKIT 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 RESKIT. 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 RESKIT 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 RESKIT and have their WBC followed until recovery.

Venous thromboembolism

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

Tardive dyskinesia/Extrapyramidal Symptoms (TD/EPS)

Tardive dyskinesia (TD), a syndrome consisting of potentially irreversible, involuntary dyskinetic movements may develop in patients treated with RESKIT. Although this syndrome of TD appears to be most prevalent in the elderly, especially elderly females, it is possible to predict at the onset of treatment which patients are likely to develop TD. If signs and symptoms of tardive dyskinesia appear, discontinuation of RESKIT should be considered.

Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS) is a potentially fatal symptom complex that has been reported in association with the use of RESKIT. Clinical manifestations of NMS are hyperthermia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, cardiac arrhythmias and diaphoresis). Additional signs may include elevated creatine phosphokinase (CPK) levels, myoglobinuria (rhabdomyolysis), and acute renal failure. In this event, all antipsychotic medicines 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 NMS as well as having an increased risk of having an increased sensitivity to antipsychotic medications. Manifestations of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

In clinical trials, patients had a higher mortality than placebo treated patients (see section 4.3).

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis and hyperosmolar coma and death, has been reported. Patients with an established diagnosis of diabetes mellitus who are started on RESKIT 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 RESKIT should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with RESKIT should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when RESKIT was discontinued. However, some patients required continuation of anti-diabetic treatment despite discontinuation of RESKIT.

Weight gain

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

QT Interval

Caution should be exercised when RESKIT 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 RESKIT 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 RESKIT 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.

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 RESKIT.

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

Seizures

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

Hyperprolactinaemia

Hyperprolactinaemia is a frequent side effect of treatment with RESKIT. 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. RESKIT should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours.

Renal or 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).

Galactose intolerance

RESKIT tablets contain lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemic, Lapp lactase deficiency, ~~or~~ glucose-galactose malabsorption or fructose intolerance should not take RESKIT.

4.5 Interaction with other medicines and other forms of interaction

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 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.

Centrally-acting medicines and alcohol

RESKIT 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

RESKIT 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.

Medicines with hypotensive effect

Clinically significant hypotension has been observed post-marketing with concomitant use of risperidone and antihypertensive treatment.

Psychostimulants

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

Paliperidone

Concomitant use of oral RESKIT 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 RESKIT.

Risperidone 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 risperidone active antipsychotic fraction.

Strong CYP2D6 inhibitors

Co-administration of RESKIT 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 RESKIT.

CYP3A4 and/or P-gp inhibitors

Co-administration of RESKIT 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 RESKIT.

CYP3A4 and/or P-gp inducers

Co-administration of RESKIT 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 RESKIT.

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 RESKIT is taken together with highly protein-bound medicines, there is no clinically relevant displacement of either medicine from the plasma proteins. [(2)]

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 RESKIT in children and adolescents did not alter the pharmacokinetics and efficacy of RESKIT.

Examples

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

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 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 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-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.
- 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.
- 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.

Digitalis glycosides:

- 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 risperidone with furosemide

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of RESKIT in pregnancy or lactating women has not been established.

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

Breastfeeding

Risperidone and 9-hydroxy-risperidone are excreted in human breast milk. Therefore, women receiving RESKIT should not breast feed.

Fertility

As with other medicines that antagonise dopamine D2 receptors, RESKIT 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

RESKIT 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

a. Summary of the safety profile

The most frequently reported adverse drug reactions (ADRs) (incidence ≥ 10 %) are: Parkinsonism, sedation/somnolence, headache, and insomnia.

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

b. Tabulated summary of adverse reactions

The following are all the ADRs that were reported in clinical trials and post-marketing experience with risperidone. The following terms and frequencies are applied: frequent, less frequent and frequency unknown.

MedDRA system organ class	Frequency	Adverse reactions
Infections and infestations	Frequent	Pneumonia, bronchitis, upper respiratory tract infection, sinusitis, urinary tract

MedDRA system organ class	**Frequency**	**Adverse reactions**
		infection, ear infection, influenza
	Less frequent	Respiratory tract infection, cystitis, eye infection, tonsillitis, onychomycosis, cellulitis localised infection, viral infection, acarodermatitis, infection
Blood and lymphatic system disorders	Less frequent	Granulocytopaenia, white blood cell count decreased, haematocrit decreased, eosinophil count increased, neutropenia, thrombocytopenia, anaemia, agranulocytosis[c]
Immune system disorders	Frequency unknown	Hypersensitivity, anaphylactic reaction[c]
Endocrine disorders	Frequent	Hyperprolactinaemia[a]
	Less frequent	Inappropriate antidiuretic hormone secretion, glucose urine present
Metabolism and nutrition disorders	Frequent	Increased weight, increased appetite, decreased appetite
	Less frequent	Diabetes mellitus[b], hyperglycaemia, polydipsia, weight decreased, anorexia, increased blood cholesterol, water intoxication[c], hypoglycaemia, hyperinsulinaemiac, increased blood triglycerides, diabetic ketoacidosis
Psychiatric disorders	Frequent	Insomnia[d], sleep disorder, agitation,

MedDRA system organ class	**Frequency**	**Adverse reactions**
		depression, anxiety
	Less frequent	Catatonia, somnambulism, sleep-related eating disorder, nightmares, mania, confusional state, libido decreased, nervousness, blunted affect, anorgasmia
Nervous system disorders	Frequent	Sedation/somnolence, parkinsonism[d], headache, akathisia[d], dystonia[d], dizziness, dyskinesia[d], tremor
	Less frequent	Tardive dyskinesia, cerebral ischaemia, unresponsive to stimuli, loss of consciousness, depressed level of consciousness, convulsion[d], 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	Frequent	Blurred vision, conjunctivitis
	Less frequent	Photophobia, dry eye, lacrimation increased, ocular hyperaemia, glaucoma, eye movement disorder, eye rolling, eyelid margin crusting,

MedDRA system organ class	**Frequency**	**Adverse reactions**
		floppy iris syndrome (intraoperative)[c]
Ear and labyrinth disorders	Less frequent	Vertigo, tinnitus, ear pain
Cardiac disorders	Frequent	Tachycardia
	Less frequent	Atrial fibrillation, atrioventricular block, electrocardiogram QT prolonged, conduction disorder, bradycardia, electrocardiogram abnormal, palpitations, sinus dysrhythmia
Vascular disorders	Frequent	Hypertension
	Less frequent	Hypotension, orthostatic hypotension, flushing, pulmonary embolism, venous thrombosis
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea, pharyngolaryngeal pain, cough, epistaxis, nasal congestion
	Less frequent	Pneumonia aspiration, pulmonary congestion, respiratory tract congestion, rales, wheezing, dysphonia, respiratory disorder, sleep apnoea syndrome, hyperventilation
Gastrointestinal disorders	Frequent	Abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhoea, dyspepsia, dry mouth, toothache
	Less frequent	Faecal incontinence, faecaloma, gastroenteritis, dysphagia, flatulence, pancreatitis, intestinal obstruction, swollen tongue, cheilitis, ileus

MedDRA system organ class	**Frequency**	**Adverse reactions**
Hepatobiliary disorders	Less frequent	Transaminases increased, gamma-glutamyltransferase increased, hepatic enzyme increased, jaundice
Skin and subcutaneous tissue disorders	Frequent	Rash, erythema
	Less frequent	Urticaria, pruritus, alopecia, hyperkeratosis, eczema, dry skin, skin discolouration, acne, seborrhoeic dermatitis, skin disorder, skin lesion, drug eruption, dandruff, angioedema
Musculoskeletal and connective tissue disorder	Frequent	Muscle spasms, musculoskeletal pain, back pain, arthralgia
	Less frequent	Blood creatine phosphokinase increased, posture abnormal, joint stiffness, joint swelling, muscular weakness, neck pain, rhabdomyolysis
Renal and urinary disorders	Frequent	Enuresis, urinary incontinence
	Less frequent	Pollakiuria, urinary retention, dysuria
Pregnancy, puerperium, and neonatal conditions	Less frequent	Neonatal drug withdrawal syndrome[c]

MedDRA system organ class	**Frequency**	**Adverse reactions**
Reproductive system and breast disorders	Less frequent	Erectile dysfunction, ejaculation disorder, amenorrhoea, menstrual disorder[d], gynaecomastia, galactorrhoea, sexual dysfunction, vaginal discharge, breast pain, breast discomfort, priapism[c], menstruation delayed, breast engorgement, breast enlargement, breast discharge
General disorders and administration site conditions	Frequent	Oedema[d], pyrexia, chest pain, asthenia, fatigue, pain
	Less frequent	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[c]
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 creatine phosphokinase, decreased body temperature

MedDRA system organ class	Frequency	Adverse reactions
Injury, poisoning and procedural complications	Frequent	Fall
	Less frequent	Procedural pain

[a] Hyperprolactinaemia can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhoea, anovulation, galactorrhoea, fertility disorder, decreased libido, erectile dysfunction.

[b] In placebo-controlled trials diabetes mellitus was reported in 0,18 % in risperidone-treated subjects compared to a rate of 0,11 % in placebo group. Overall incidence from all clinical trials was 0,43 % in all risperidone-treated

subjects.

[c] Not observed in risperidone clinical studies but observed in post-marketing environment with risperidone.

[d] 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 are included, that do not necessarily have an extrapyramidal

origin. **Insomnia** includes initial insomnia, middle insomnia. **Convulsion** includes grand mal

MedDRA system organ class	Frequency	Adverse reactions
convulsion. **Menstrual disorder** includes menstruation irregular, oligomenorrhoea. **Oedema** includes generalised oedema, oedema peripheral, pitting oedema.		

c. Description of selected adverse reactions

Undesirable effects noted with paliperidone formulations

Paliperidone is the active metabolite of risperidone, therefore, the adverse reaction profiles of these medicines (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 medicines and can be expected to occur with RESKIT.

Cardiac disorders

Postural orthostatic tachycardia syndrome

Class effects

Less frequent 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 arrhythmia, 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 R (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 5-12 years of age is 3 to 5 kg per year. From 12-16 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

Adverse drug reactions 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.

d. Paediatric population

In general, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are 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

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, cases of QT-prolongation and convulsions have been reported. Torsade de pointes has been reported in association with combined overdose of oral RESKIT 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. Gastric lavage (after intubation, if the patient is unconscious) and 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

A.2.6.5 Central nervous system depressants. Miscellaneous structures.

Pharmacotherapeutic group: Other antipsychotics, ATC code: N05AX08.

Risperidone is an antipsychotic of the benzisoxazol 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

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

Biotransformation

Risperidone is metabolised by cytochrome P-450 2D6 to 9-hydroxy-risperidone which has a similar pharmacological activity to risperidone. Risperidone and 9-hydroxy-risperidone form the active antipsychotic fraction.

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.

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.

Elimination

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.

Special populations

Elderly, hepatic and renal impairment

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, but the mean free fraction of risperidone was increased by about 35 %.

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:

Colloidal anhydrous silica

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose (E460)

Pregelatinized starch

Sodium lauryl sulphate

Coating:

HPMC 2910/Hypromellose 15 CP (E464)

Iron oxide red CI No. 77491 (E170) – 0,5 mg

Lactose monohydrate

Macrogol/PEG 4000

Sunset Yellow FCF LAKE (CI No. 15985) – 2 mg

Talc (E553b)

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C in the original package, protected from light and moisture.

6.5 Nature and contents of container

Cartons containing 10, 30 or 60 tablets packed in clear PVdC coated PVC blister strips with a backing of aluminium foil coated with a heat seal lacquer on the inner side.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

LHC Pharmaceuticals (Pty) Ltd

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33 Ghaap Street

Pretoria 0184

8 REGISTRATION NUMBERS

RESKIT 0,5: A40/2.6.5/0527

RESKIT 1: A40/2.6.5/0528

RESKIT 2: A40/2.6.5/0529

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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Namibia Only: NS3

Reg. No. RESKIT 0,5: 10/2.6.5/0635

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