PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

RISPEVON 1: 1 mg film-coated tablet

RISPEVON 2: 2 mg film-coated tablet

RISPEVON 3: 3 mg film-coated tablet

RISPEVON 4: 4 mg film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

RISPEVON 1: each film-coated tablet contains 1 mg of risperidone

RISPEVON 2: each film-coated tablet contains 2 mg of risperidone

RISPEVON 3: each film-coated tablet contains 3 mg of risperidone

RISPEVON 4: each film-coated tablet contains 4 mg of risperidone

Each 1 mg film-coated tablet contains 156,00 mg lactose monohydrate.

Each 2 mg film-coated tablet contains 156,00 mg lactose monohydrate.

Each 3 mg film-coated tablet contains 232,50 mg lactose monohydrate.

Each 4 mg film-coated tablet contains 310,00 mg lactose monohydrate.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

RISPEVON 1: White, capsule shaped, biconvex film coated tablets debossed with 'R1' on one side and '1037'.

RISPEVON 2: Orange, capsule shaped, biconvex film coated tablets debossed with 'R2' on one side and '1038'.

RISPEVON 3: Yellow, capsule shaped, biconvex film coated tablets debossed with 'R3' on one side and '1039'.

RISPEVON 4: Green, capsule shaped, biconvex film coated tablets debossed with 'R4' on one side and '1040'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

RISPEVON tablets are indicated for the treatment of:

Acute and chronic schizophrenic psychoses and related psychosis in which positive symptoms and / or the negative symptoms are prominent. **RISPEVON** also alleviates affective symptoms associated with schizophrenia. In patients who have shown an initial treatment response, **RISPEVON** tablets are 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 antipsychotic medicines to **RISPEVON**:*

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

periodically.

Adults:

RISPEVON may be given once or twice daily.

Patients should start **RISPEVON** tablets with a dose of 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 therefore 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 risks. The maximum total daily dose is 16 mg/day. If additional sedation is required, a benzodiazepine may be added to **RISPEVON** tablets treatment.

Special populations

Renal- and liver diseased patients:

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

Elderly patients:

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

Paediatric population

The use of **RISPEVON** is not recommended for children under 15 years of age as efficacy and safety in children under the age of 15 years have not been demonstrated in schizophrenia.

Behavioural disturbances in patients with dementia:

A recommended starting dose is 0,25 mg twice daily. This dosage can be adjusted by increments of 0,25 mg twice daily as needed per individual but not more frequently than every other day, if needed. For most patients the optimum dose is 0,5 mg twice daily. Some patients, however, may benefit from doses up to 1 mg twice daily.

A once-daily dosing regimen can be considered once patients have reached their target dose.

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

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 but 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 **RISPEVON** must be evaluated and justified on an ongoing basis. Experience is lacking in children less than 5 years (see section 4.5).

Method of administration

Oral use. Can be taken with or without food

4.3 Contraindications

- Hypersensitivity to risperidone or to any of the excipients (see section 6.1)
- Risperidone is contraindicated in pregnancy and for lactating mothers (see section 4.6)
- Parkinson's disease and Lewy Body Dementia (see section 4.4)
- Conduct and other disruptive behaviour disorders in children: Risperidone tablets are not indicated for children under 5 years as efficacy and safety in children under the age of 5 years have not been demonstrated.

4.4 Special warnings and precautions for use

Intraoperative Floppy Iris Syndrome (IFIS)

Intraoperative floppy iris syndrome may occur during cataract surgery in patients treated with medicines with α_1-adrenergic antagonist effect, including **RISPEVON** (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 **RISPEVON**), should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping **RISPEVON** 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 may develop in patients treated with **RISPEVON**. 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.

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

Reproductive system and breast disorders

A dose-dependent increase in plasma prolactin concentration may occur. Possible associated manifestations are galactorrhoea, gynaecomastia, disturbances of the menstrual cycle and amenorrhoea. Premenopausal women who develop secondary amenorrhoea of greater than six months duration should receive appropriate preventative therapy to avoid hypo-oestrogenic bone loss.

Concomitant use with furosemide

Caution is advised in patients treated with furosemide due to possible dehydration (see section 4.5).

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

Caution should be exercised, and the risks and benefits of this combination should be considered prior to the decision to use.

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 **RISPEVON**.

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

Hyperglycaemia and exacerbation of pre-existing diabetes mellitus have been reported during **RISPEVON** treatment.

Cerebrovascular adverse events

Cerebrovascular adverse events (CAE), including cerebrovascular accidents and transient ischaemic attacks, have been reported during treatment with **RISPEVON**. 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 **RISPEVON** compared to patients receiving placebo (mean age 85 years; range 73 – 97 years).

Parkinson's disease and senile dementia

Prescribing **RISPEVON** to patients with Parkinson's disease or Dementia with Lewy Bodies (DLB) is not recommended, since both groups may be at risk of Neuroleptic Malignant Syndrome (NMS) as well as having an increased sensitivity to antipsychotic medicines such as **RISPEVON** (see **CONTRAINDICATIONS**). 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 patients treated with risperidone, as in **RISPEVON**, had a higher mortality than placebo treated elderly patients.

Caution should be used when prescribing **RISPEVON** to patients with Parkinson's disease since, theoretically, it might cause a deterioration of the disease.

Concomitant medicine usage

The risk of using **RISPEVON** in combination with other medicines has not been systematically evaluated.

Given the primary CNS depressive effects of **RISPEVON**, it should be used with caution in combination with alcohol and other centrally acting medicines. **RISPEVON** may antagonise the effect of levodopa and other dopamine agonists

(see section 4.5).

Orthostatic hypotension

Due to the alpha-blocking activity of **RISPEVON**, (orthostatic) hypotension can occur, especially during the initial dose-titration period. **RISPEVON** 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 **RISPEVON**. Caution is recommended when treating patients with epilepsy, a history of seizures or other conditions that potentially lower the seizure threshold.

Renal or liver insufficiency

It is recommended to have both the starting dose and the subsequent dose increments in geriatric patients and patients with renal or liver insufficiency.

Benign pituitary adenomas

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

Weight gain

Significant weight gain may occur. Monitoring weight gain is advisable when **RISPEVON** is being used.

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

Antiemetic effect

An antiemetic effect may be observed during treatment with **RISPEVON**. This effect may mask the signs and symptoms of overdosage with certain medicines or of conditions such as intestinal obstruction, Reye's syndrome and brain tumour.

Body temperature regulation

Disruption of the body's ability to reduce core body temperature may occur. Appropriate care is advised when prescribing **RISPEVON** 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.

Priapism

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

QT interval

Caution should be exercised when **RISPEVON** is prescribed in patients with a history of cardiac dysrhythmias, congenital long QT syndrome and in concomitant use with medicines known to prolong the QT interval.

Excipients

The film coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic-related interactions

The risk of using **RISPEVON** in combination with other medicines has not been systematically evaluated.

Central-acting medicines and alcohol

RISPEVON should be used with caution in combination with alcohol and other centrally acting medicines, due to possible additive central nervous system depression.

Levodopa and dopamine agonists

Risperidone may antagonise the effect of levodopa and other dopamine agonists (bromocriptine and pergolide).

Medicines with hypotensive effects

RISPEVON may enhance the effects of anti-hypertensives.

Medicines known to prolong the QT interval

There may be an increased risk of QT prolongation when **RISPEVON** is given with other medicines that are known to cause this effect (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.

Psychostimulants

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

Paliperidone

Concomitant use of oral **RISPEVON** 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 **RISPEVON.**

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

Clozapine: Chronic administration of clozapine may decrease the clearance of **RISPEVON** resulting in increased plasma levels.

Phenothiazines, tricyclic antidepressants and some beta-blockers may increase the plasma concentration of risperidone but not that of the antipsychotic fraction.

Fluoxetine and paroxetine may increase the plasma concentration of risperidone but less so of the anti-psychotic fraction, and therefore dose adjustments may be necessary.

When **RISPEVON** is taken together with other highly protein-bound medicines (e.g. diazepam, warfarin, digitoxin, imipramine and, propranolol), there is no clinically relevant displacement of either medicine from the plasma proteins.

Lithium: C_{max} and AUC of lithium were not significantly increased but T_{max} of lithium was increased from 2,4 hours – 3,0 hours.

Cimetidine and ranitidine increased the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction.

Venlafaxine: Risperidone AUC increased and risperidone clearance decreased, but no effect on 9-hydroxy–risperidone and the active moiety.

Valproate: T_{max} of valproate increased from 1,3 hours to 2,0 hours.

Furosemide: In placebo-controlled trials in elderly patients with dementia, there was a higher mortality in patients treated with furosemide and risperidone, as in **RISPEVON**, 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.

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.

Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increased the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction.

Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction.

The cholinesterase inhibitors, galantamine and donepezil, do not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction.

Strong CYP2D6 inhibitors

Co-administration of **RISPEVON** 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 physician should re-evaluate the dosing of **RISPEVON**.

CYP3A4 and/or P-gp inhibitors

Co-administration of **RISPEVON** 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 physician should re-evaluate the dosing of **RISPEVON**.

CYP3A4 and/or P-gp inducers

Carbamazepine has been shown to decrease the plasma levels of the active antipsychotic fraction of **RISPEVON**. Similar effects may be observed with other hepatic enzyme inducers. On discontinuation of carbamazepine or other hepatic enzyme inducers the dosage of RISPEVON should be re-evaluated and, if necessary, decreased.

When concomitant carbamazepine or another strong CYP3A4 and/or P-gp inducer is initiated or discontinued, the prescribing health care professional should re-evaluate the dosing of **RISPEVON**. 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 **RISPEVON** is taken together with highly protein-bound drugs, there is no clinically relevant displacement of either drug from the plasma proteins.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

Breastfeeding

RISPEVON and 9-hydroxy-risperidone are excreted in human breast milk. Therefore, women receiving **RISPEVON** should not breastfeed.

4.7 Effects on ability to drive and use machines

RISPEVON 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

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent:	Pneumonia, influenza, bronchitis, upper respiratory tract infection, sinusitis, urinary tract infection.
	Less frequent:	Viral infection, ear infection, tonsillitis, cellulitis, otitis media, eye infection, localised infections, acarodermatitis, respiratory tract

MedDRA system organ class	**Frequency**	**Adverse reactions**
		infection, cystitis, onychomycosis.
Blood and lymphatic system disorders	Less frequent:	Anaemia, neutropenia, granulocytopenia, white blood cell count decreased, thrombocytopenia, haematocrit decreased, eosinophil count increased, agranulocytosis.
Cardiac disorders	Frequent:	Tachycardia.
	Less frequent:	Atrioventricular block, bundle branch block, sinus bradycardia, palpitations, atrial fibrillation, conduction disorder, electrocardiogram QT prolonged, bradycardia, abnormal electrocardiogram, sinus dysrhythmia.
Immune system disorders	Less frequent:	Hypersensitivity, anaphylactic reaction, medicine hypersensitivity.
Endocrine disorders	Frequent	Hyperprolactinaemia
	Less frequent	Inappropriate antidiuretic hormone secretion, glucose urine present

MedDRA system organ class	**Frequency**	**Adverse reactions**
Metabolism and nutrition disorders	Frequent:	Weight increase, increased appetite, decreased appetite.
	Less frequent:	Anorexia, polydipsia, diabetes mellitus, hyperglycaemia, weight decreased, blood cholesterol increase, water intoxication, hypoglycaemia, hyperinsulinaemia, blood triglycerides increase, diabetic ketoacidosis.
Psychiatric disorders	Frequent:	Insomnia, anxiety, agitation, sleep disorder, depression.
	Less frequent:	Confused state, decreased libido, listless, nervousness, anorgasmia, blunted effect, 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

MedDRA system organ class	Frequency	Adverse reactions
		consciousness, cerebrovascular accident, transient ischaemic attack, dysarthria, disturbance in attention, hypersomnia, postural dizziness, balance disorder, tardive dyskinesia, speech disorder, abnormal coordination, hypoaesthesia, head intubation, neuroleptic malignant syndrome, diabetic coma, cerebrovascular disorders, cerebral ischaemia, movement disorder.
Eye disorders	Frequent:	Blurred vision, conjunctivitis.
	Less frequent:	Ocular hyperaemia, eye discharge, eye swelling, dry eye, increased lacrimation, photophobia, reduced visual acuity, eye movement disorder, eye rolling, eyelid margin crusting, floppy iris syndrome (intraoperative), glaucoma.
Ear and labyrinth disorders	Less frequent:	Ear pain, tinnitus, vertigo.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Vascular disorders	Less frequent:	Hypertension, hypotension, orthostatic hypotension, flushing, pulmonary embolism, venous thrombosis.
	Frequency unknown:	Angioedema.
Respiratory, thoracic and mediastinal 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, respiratory disorder.
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, cheilitis, ileus.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Hepato-biliary disorders	Less frequent	Increase transaminases, increased gamma-glutamyltransferase, increased hepatic enzymes
Skin and subcutaneous tissue disorders	Frequent	Rash, erythema
	Less frequent	Skin lessions, skin disorders, pruritus, acne, skin discoloration, seborrheic dermatisis, dry skin, hyperkeratosis, dandruff
Musculoskeletal and connective tissue disorders	Frequent:	Arthralgia, back pain, 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 creatine 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	Less	Amenorrhoea, sexual dysfunction,

MedDRA system organ class	**Frequency**	**Adverse reactions**
breast disorders	frequent:	erectile dysfunction, ejaculation disorder, galactorrhoea, gynaecomastia, menstrual disorder, vaginal discharge, breast pain, breast discomfort, priapism, delayed menstruation, 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,

MedDRA system organ class	Frequency	Adverse reactions
		increased blood creatine phosphokinase, decreased body temperature.
Injury, poisoning and procedural complications	Frequent:	Fall.
	Less frequent:	Procedural pain.

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 **RISPEVON** known pharmacological effects. Symptoms of acute overdosage include drowsiness, sedation, hypotension, tachycardia and extrapyramidal symptoms. In overdose, QT-prolongation have been reported.

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 medicines 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, ATC code: N05A X08

Risperidone is a benzisoxazole atypical antipsychotic substance. It is a selective mono-aminergic antagonist. Risperidone has affinity as an antagonist for serotonin-5-HT_2, H_1-histamine, α_1- and α_2-adrenergic receptors and affinity for dopamine-D_2. Risperidone has no affinity for cholinergic receptors.

5.2 Pharmacokinetic properties

Absorption

Risperidone is readily absorbed after oral administration and within 1 – 2 hours peak plasma concentrations are attained. Food does not affect the absorption of risperidone.

Distribution

After a dose of 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 a dose of 3 mg and 4 mg twice daily. In most patients, steady state is reached within 1 day for risperidone 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 α_1-acid glycoprotein. Plasma protein binding of risperidone is 88 % and 77 % for 9-hydroxy-risperidone. In the elderly and in patients with renal insufficiency risperidone showed higher active plasma concentrations and slower elimination rates. In patients with liver insufficiency plasma concentrations of risperidone were normal. The pharmacokinetics of risperidone and 9-hydroxy-risperidone, which forms the active antipsychotic fraction, are similar in children to those in adults.

Biotransformation

Risperidone is extensively metabolised in the liver by hydroxylation to the main active metabolite, 9-hydroxy-risperidone. Hydroxylation is mediated by the cytochrome P-450 CYP2D6. Risperidone and 9-hydroxy-risperidone from the active antipsychotic fraction.

Elimination

The half-life, after oral administration to psychotic patients, of risperidone is about 3 hours. The elimination half-life of 9-hydroxy-risperidone and the active antipsychotic fraction is 24 hours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:

Lactose anhydrous

Microcrystalline cellulose (avicel PH 101)

Colloidal silicon dioxide (aerosil 200)

Sodium starch glycolate (primogel) type A

Pregelatinized starch (starch 1500)

Purified water

Microcrystalline cellulose (avicel PH 102)

Talc (purified)

Magnesium stearate

Film coating:

Hypromellose 2910

Polyethylene glycol 400

Titanium dioxide (CI No:77891)

2mg: Orange yellow S (E110) and Aluminium lake (CI No:15985)

3 mg: Ferric oxide yellow (CI No: 77492)

4 mg: Ferric oxide yellow (CI No: 77492) and Lake of indigo carmine (C.I. No. 73015).

6.2 Incompatibilities

There are no known incompatibilities

6.3 Shelf life

24 months.

6.4 Special precautions for storage

This medicine does not require any special storage conditions. Store at or below 25 °C. Protect from light and moisture. Keep in original blister packs until a dose

should be taken. KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

RISPEVON 1: Aluminium/ PVC/LDPE/PVdC Blistered tablets pack sizes of 30 or 60 tablets.

RISPEVON 2: Aluminium/ PVC/LDPE/PVdC Blistered tablets pack sizes of 30 or 60 tablets.

RISPEVON 3: Aluminium/ PVC/LDPE/PVdC Blistered tablets pack sizes of 30 or 60 tablets.

RISPEVON 4: Aluminium/ PVC/LDPE/PVdC Blistered tablets pack sizes of 30 or 60 tablets.

3 or 6 blister packs of 10 tablets each in a printed carton.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd.

106 16th Road

Midrand

1686

8 REGISTRATION NUMBER(S)

RISPEVON 1: 43/2.6.5/0039

RISPEVON 2: 43/2.6.5/0040

RISPEVON 3: 43/2.6.5/0041

RISPEVON 4: 43/2.6.5/0042

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registered: 20 April 2012

10 DATE OF REVISION OF THE TEXT

8 February 2023