PROPOSED AMENDED PACKAGE INSERT FOR

RISNIA TABLETS

SCHEDULING STATUS:

S5

PROPRIETARY NAME (AND DOSAGE FORM):

RISNIA 0,5 mg (Tablets)

RISNIA 1 mg (Tablets)

RISNIA 2 mg (Tablets)

RISNIA 3 mg (Tablets)

RISNIA 4 mg (Tablets)

RISNIA 6 mg (Tablets)

COMPOSITION:

RISNIA 0,5 mg:	Each tablet contains risperidone 0,5 mg. Inactive ingredients include lactose monohydrate, corn starch, microcrystalline cellulose, sodium starch glycollate, red oxide of iron, magnesium stearate, opadry brown, and opacode black.
RISNIA 1 mg:	Each tablet contains risperidone 1 mg. Inactive ingredients include lactose monohydrate, corn starch, microcrystalline cellulose, sodium starch glycollate, magnesium stearate, opadry white, and opacode black.

RISNIA 2 mg: Each tablet contains risperidone 2 mg. Inactive ingredients include lactose monohydrate, corn starch, microcrystalline cellulose, sodium starch glycollate, magnesium stearate, opadry orange, and opacode black.

RISNIA 3 mg: Each tablet contains risperidone 3 mg. Inactive ingredients include lactose monohydrate, corn starch, microcrystalline cellulose, sodium starch glycollate, magnesium stearate, opadry yellow, and opacode black.

RISNIA 4 mg: Each tablet contains risperidone 4 mg. Inactive ingredients include lactose monohydrate, corn starch, microcrystalline cellulose, sodium starch glycollate, magnesium stearate, opadry green, and opacode black.

RISNIA 6 mg: Each tablet contains risperidone 6 mg. Inactive ingredients include lactose monohydrate, corn starch, microcrystalline cellulose, sodium starch glycollate, magnesium stearate, opadry yellow, and opacode black.

PHARMACOLOGICAL CLASSIFICATION:

A.2.6.5 Central nervous system depressants. Miscellaneous structures.

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

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.

Pharmacokinetics:

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. 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.
After oral administration, risperidone's half-life is about 3 hours. The elimination half-life of 9-hydroxy-risperidone and the active antipsychotic fraction is 24 hours.

Interchangeability between strengths: since **RISNIA** tablets are not scored, individual tablets should not be halved, but lower dosage strength formulations are recommended. For patients who require less than 0,5 mg per dose the use of an appropriate oral solution is advisable.

Steady state is reached within 1 day for risperidone in most patients and 4 – 5 days for 9-hydroxy-risperidone. Risperidone plasma concentration is dose-proportional within the therapeutic dose-range.

Risperidone is bound to albumin and alpha$_1$-acid glycoprotein. Plasma protein binding of risperidone is 88 % and 77 % for 9-hydroxy-risperidone. One week after administration, 70 % of the dose is excreted in the urine and 14 % in the faeces. In the urine, risperidone and 9-hydroxy-risperidone represent 35 – 45 % of the dose.

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.

INDICATIONS:

RISNIA is indicated for the treatment of:

- Acute and chronic schizophrenic psychoses and related psychosis in which positive symptoms and/or negative symptoms are prominent. **RISNIA** also alleviates affective symptoms associated with schizophrenia. In patients who have shown an initial treatment response, **RISNIA** is also effective in maintaining clinical improvement.
- 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.

CONTRA-INDICATIONS:

RISNIA is contra-indicated in:

- Patients with known hypersensitivity to any of the components of the medicine.
- Children under 5 years of age with conduct and other disruptive behaviour disorders as efficacy and safety in these children have not been demonstrated.
- Patients with Lewy body dementia (see **"WARNINGS"**).
- Lactation (see **"PREGNANCY AND LACTATION"**).

WARNINGS:

Tardive dyskinesia:

Tardive dyskinesia (TD), a syndrome consisting of potentially irreversible, involuntary dyskinetic movements, may develop in patients treated with **RISNIA**. 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 (see **"Special Precautions"**).

Neuroleptic malignant syndrome:

Neuroleptic malignant syndrome (NMS) is a potentially fatal symptom complex that has been reported in association with the use of **RISNIA**. 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 (see **"Special Precautions"**).

Concomitant use with furosemide:

In elderly patients with dementia, there is a higher mortality in patients treated with furosemide and **RISNIA** when compared to patients treated with **RISNIA** alone. Caution is advised in these patients.

Dehydration was an overall risk for mortality and should be carefully avoided in these patients.

Hyperglycaemia and diabetes mellitus:

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

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

Cerebrovascular adverse events:

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

Dementia associated with Parkinson's disease and senile dementia:

Doctors should weigh the risks versus the benefits when prescribing **RISNIA** to patients with Parkinson's disease, since these patients may be at risk of development of neuroleptic malignant syndrome (NMS) as well as having an increased sensitivity to antipsychotic medications such as **RISNIA**. 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 **RISNIA**-treated patients had a higher mortality than placebo-treated elderly patients.

The risk of using **RISNIA** in combination with other medicines has not been systematically evaluated. Given the primary central nervous system (CNS) depressive effects of **RISNIA**, it should be used with caution in combination with alcohol and other centrally acting medicines. **RISNIA** may antagonise the effect of levodopa and other dopamine agonists.

Alpha-blocking activity:

Due to the alpha-blocking activity of **RISNIA**, (orthostatic) hypotension can occur, especially during the initial dose-titration period. **RISNIA** 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.

Prolongation of QT interval:

Caution is advised when prescribing **RISNIA** with medicines known to prolong the QT interval as concomitant use have been associated with occurrence of a life-threatening dysrhythmia (see **"INTERACTIONS"**).

Other:

Seizures have been reported after treatment with **RISNIA**. Caution is recommended when treating patients with epilepsy.

Intraoperative Floppy Iris Syndrome:

Cases of intraoperative floppy iris syndrome (IFIS) during cataract surgery have been reported in patients taking risperidone, as in **RISNIA** (see **"Side-Effects"**). IFIS may increase the risk of eye complications during and after cataract surgery.

Complications of IFIS during cataract surgery include: iris trauma, posterior capsule rupture, and vitreous loss. Postoperative complications include increased intraocular pressure and cystoid macular oedema.

It is therefore recommended to verify pre-surgery data gathering on patient history and the previous or current use of risperidone, as in **RISNIA**.

The potential benefit of stopping alpha1 blocking therapy, including **RISNIA**, prior to

cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

INTERACTIONS:

Carbamazepine has been shown to decrease the plasma levels of the active antipsychotic fraction of risperidone by about 50 %. Similar effects may be observed with other hepatic enzyme inducers. On discontinuation of carbamazepine or other hepatic enzyme inducers the dosage of **RISNIA** should be re-evaluated and, if necessary, decreased.

Furosemide: In placebo controlled trials in elderly patients with dementia, there was a higher mortality in patients treated with furosemide and **RISNIA** when compared to patients treated with **RISNIA** alone. Caution is advised in these patients. Dehydration was an overall risk for mortality and should be carefully avoided in these patients (see **"Special Precautions"**).

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

Topiramate: modest decrease in **RISNIA** bioavailability, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance.

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

so of the antipsychotic fraction. Fluoxetine kinetics are not changed in combination with **RISNIA**. When concomitant fluoxetine or paroxetine is initiated or discontinued, the dosing of **RISNIA** should be re-evaluated.

Amytriptyline: non-significant interactions.

Venlafaxine: risperidone AUC increases and risperidone clearance decreases, but there is no effect on 9-OH-risperidone and the active moiety.

Quetiapine: no significant interaction.

Clozapine: no significant interaction.

Lithium: C_{max} and AUC of lithium are non-significantly increased, but T_{max} of lithium is increased from 2,4 hours to 3,0 hours.

Erythromycin: non-significant increase in risperidone exposure.

There are non-significant effects on risperidone kinetics and that of the active fraction in combination with donepezil or galantamine.

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

When **RISNIA** is taken together with other highly protein-bound medicines (e.g.,

diazepam, warfarin, digoxin, imipramine and propranolol), there is no clinically relevant displacement of either agent from plasma proteins.

See **"WARNINGS"** and **"Special Precautions"** regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

Medicines that prolong the QT interval: Concomitant use of other medicines that prolong the QT interval has been associated with the occurrence of torsades de pointes, a life-threatening dysrhythmia.

PREGNANCY AND LACTATION:

The safety of **RISNIA** in pregnancy and 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 use of **RISNIA** during the last trimester of pregnancy.

Risperidone and 9-hydroxy-risperidone are excreted in human breast milk. Therefore, women receiving **RISNIA** should not breastfeed (see **"CONTRA-INDICATIONS"**).

DOSAGE AND DIRECTIONS FOR USE:

Schizophrenia:

Switching from other antipsychotics to **RISNIA**:

When medically appropriate, gradual discontinuation of the previous treatment, while **RISNIA** therapy is initiated, is recommended. Also if medically appropriate, when

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

Adults:

RISNIA may be given once or twice daily.

Patients should start with **RISNIA** 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 **RISNIA** if additional sedation is required.

Elderly patients:

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

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 **RISNIA** must be evaluated and justified on an ongoing basis. Experience is lacking in children aged less than 5 years (see **"CONTRA-INDICATIONS"**).

For children who require less than 0,5 mg per dose or who cannot swallow tablets, the use of an appropriate oral solution is advisable.

Renal and liver impairment:

Caution should be exercised with these groups of patients, as clinical experience is lacking in these patient populations. It is recommended to halve both the starting dose and the subsequent dose increments. Since **RISNIA** tablets are not scored, individual tablets should not be halved, but lower dosage strength formulations are recommended. For patients who require less than 0,5 mg per dose the use of an appropriate oral solution is advisable.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects:

The adverse events considered at least possibly related to the treatment are listed below by body system organ class and frequency (wherever applicable).

Infections and infestations:

Frequent:	Upper and lower respiratory tract infection, pneumonia, bronchitis, rhinitis, pharyngitis, tonsillitis, sinusitis, otitis media, eye infection, influenza, viral infection, urinary tract infection, cellulitis, acarodermatitis, onychomycosis.
Less frequent:	Cystitis, gastroenteritis, infection.

Blood and lymphatic system disorders:

Frequent:	Anaemia.
Less frequent:	Thrombocytopenic purpura, a decrease in neutrophil and/or thrombocyte count.
Frequency not known:	Agranulocytosis.

Immune system disorders:

Frequency not known:	Anaphylactic reactions, angioedema, and other allergic reactions, hypersensitivity.

Endocrine disorders:

Less frequent:	Increased plasma prolactin levels and associated manifestations (see **"Reproductive system and breast disorders"** and **"Special Precautions"**).
	Body temperature dysregulation, including hyperthermia and hypothermia, and polydipsia.
Frequency not known:	Water intoxication, either due to polydipsia or the syndrome of inappropriate secretion of the antidiuretic hormone (SIADH), aggravation of diabetes mellitus or diabetic ketoacidosis and hyperglycaemia have been reported. Also weight gain, diabetic coma.

Metabolism and nutrition disorders:

Less frequent:	Increased appetite, decreased appetite.
Frequency not known:	Polydipsia.

Psychiatric disorders:

Frequent:	Anxiety or nervousness, somnolence, insomnia, agitation, impaired concentration, memory problems, mood or mental changes, including aggressive behaviour, depression.

Less frequent:	Mania or hypomania.
Frequency not known:	Blunted affect, confusion states.

In some instances it has been difficult to differentiate adverse events from symptoms of the underlying psychosis.

Nervous system disorders:

Frequent:	Parkinsonism, headache, dizziness, and extrapyramidal disorder (dystonic or Parkinsonian), sedation, dose-dependent extrapyramidal symptoms including tremor, rigidity, hypersalivation, bradykinesia, dyskinesia, oculogyric crisis, akathisia (hyperkinesia), acute dystonia, hypokinesia, and tardive dyskinesia (see **"Special Precautions"**). These may be reversible upon dose reduction and/or administration of anti-Parkinson medication, if necessary.
Less frequent:	Cerebrovascular accidents have been observed during treatment with **RISNIA**. These included stroke and transient ischaemic attacks. Other side-effects include neuroleptic malignant syndrome (see **"Special Precautions"**), convulsions, syncope, postural hypoesthesia,

	paraesthesia, nervousness, lethargy, hypersomnia, and tardive dystonia.
Frequency not known:	Aggravation of Parkinson's disease, hypertonia, balance disorder, unresponsive to stimuli, loss or depressed level of consciousness, movement disorder, involuntary muscle contraction, masked facies, speech disorder, cerebral ischaemia, cerebral vascular disorder.
Eye disorders:	
Frequent:	Blurred vision, conjunctivitis.
Frequency not known:	Ocular hyperaemia, eye discharge, eye rolling, eyelid oedema, eyelid margin crusting, dry eyes, increased lacrimation, photophobia, glaucoma, retinal artery occlusion, eye movement disorder, intraoperative floppy iris syndrome (not observed in risperidone clinical studies, but observed post-marketing with risperidone, as in **RISNIA**) (see **"WARNINGS"**).
Ear and labyrinth disorders:	
Frequent:	Vertigo.
Less frequent:	Ear pain.

Frequency not known:	Tinnitus.

Cardiac disorders:

Frequent:	Atrioventricular block, tachycardia.
Less frequent:	Bundle branch block, bradycardia, palpitations, chest pain.
Frequency not known:	Atrial fibrillation, QT prolongation, increased heart rate.

Vascular disorders:

Frequent:	Hypotension, hypertension.
Less frequent:	Orthostatic hypotension, flushing, orthostatic dizziness.

Respiratory, thoracic and mediastinal disorders:

Frequent:	Cough.
Less frequent:	Dyspnoea, nasal congestion.
Frequency not known:	Apnoea, pulmonary embolism, epistaxis, wheezing, dysphonia, respiratory and pulmonary congestion, rales, hyperventilation, nasal oedema.

Gastrointestinal disorders:

Frequent:	Constipation, dyspepsia, nausea, diarrhoea, abdominal pain, gastritis, vomiting,

	toothache, and decreased salivation or dryness of the mouth.
Less frequent:	Anorexia.
Frequency not known:	Intestinal obstruction, pancreatitis, dysphagia, faecaloma, abdominal discomfort, faecal incontinence, cheilitis, aptyalism.

Hepato-biliary disorders:

Frequency not known:	Jaundice.

Skin and subcutaneous tissue disorders:

Frequent:	Skin rash or itching, eczema.
Less frequent:	Dry skin, increased pigmentation, increased sweating, photosensitivity, seborrhoea, pruritus, acne.
Frequency not known:	Erythema, skin discolouration, skin lesion, erythematous rash, hyperkeratosis, dandruff, macula-papular rash, seborrhoeic dermatitis, alopecia.

Musculoskeletal, connective tissue and bone disorders:

Less frequent:	Arthralgia, back pain.
	Muscular weakness, neck pain, musculoskeletal chest pain, buttock pain.

Frequency not known:	Joint swelling, joint stiffness, rhabdomyolysis, torticollis.

Renal and urinary disorders:

Frequent:	Urinary incontinence, micturition disturbances or polyuria.
Frequency not known:	Urinary retention, enuresis, dysuria, pollakiuria.

Reproductive system and breast disorders:

Frequent:	Amenorrhoea, galactorrhoea, oligomenorrhoea, breast discomfort, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, priapism, dysmenorrhoea or menorrhagia, and sexual dysfunction or decreased libido.
Less frequent:	Gynaecomastia, disturbances in the menstrual cycle (see **"Special Precautions"**).

General disorders:

Frequent:	Pyrexia, peripheral oedema, asthenia, fatigue, lassitude, malaise.
Less frequent:	Induration, sluggishness, chest discomfort, feeling abnormal.

Frequency not known:	Thirst, chills, peripheral coldness, generalised oedema, withdrawal syndrome, hyperthermia, hypothermia.

Investigations:

Frequent:	Abnormal electrocardiogram, increased blood prolactin, increased blood glucose, increased hepatic enzymes, increased transaminases, increased gamma-glutamyl transferase, increased weight, decreased weight.
Less frequent:	Prolonged QT electrocardiogram.
Frequency not known:	Increased eosinophil count, decreased haemoglobin, and white blood cell count, decreased haematocrit.

Injury and poisoning:

Frequent:	Fall.

<u>Special Precautions:</u>

Tardive dyskinesia:

Tardive dyskinesia (TD), a syndrome consisting of potentially irreversible, involuntary dyskinetic movements, may develop in patients treated with **RISNIA**. 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 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 **RISNIA** treatment is withdrawn.

RISNIA 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, **RISNIA** should be prescribed in a manner that is most likely to minimise the risk of TD. **RISNIA** 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, **RISNIA** 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 **RISNIA**. Clinical manifestations of NMS are hyperthermia, muscle rigidity, altered mental status (including catatonic

signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, cardiac dysrhythmias and diaphoresis). Additional signs may include elevated creatine phosphokinase (CPK) levels, myoglobinuria (rhabdomyolysis), and acute renal failure.

In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illnesses (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, medicine fever and primary central nervous system pathology.

The management of NMS should include:

1. Immediate discontinuation of all antipsychotic medicines and other medicines not essential to concurrent therapy;
2. Intensive symptomatic treatment and medical monitoring; and
3. Treatment of any concomitant serious medical problems for which specific treatments are available.

There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic medicine treatment after recovery from NMS, the potential reintroduction of medicine therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Epilepsy:

Seizures have been reported after treatment with **RISNIA**. Caution is recommended when treating patients with epilepsy.

Hyperprolactinaemia:

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:

In elderly patients with dementia, there is a higher mortality in patients treated with furosemide and **RISNIA** when compared to patients treated with **RISNIA** alone. Caution is advised in these patients. Dehydration was an overall risk for mortality and should be carefully avoided in these patients.

Alpha-blocking activity:

Due to the alpha-blocking activity of **RISNIA**, (orthostatic) hypotension can occur, especially during the initial dose-titration period. **RISNIA** 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.

Galactose intolerance:

RISNIA contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take **RISNIA**.

Renal or hepatic insufficiency:

It is recommended to halve both the starting dose and the subsequent dose increments in elderly patients and patients with renal or liver insufficiency. Since **RISNIA** tablets are not scored, individual tablets should not be halved, but lower dosage strength formulations are recommended. For patients who require less than 0,5 mg per dose the use of an appropriate oral solution is advisable.

Parkinson's disease:

Caution should be used when prescribing **RISNIA** to patients with Parkinson's disease since it may cause a deterioration of the disease.

Weight gain:

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

Hyperglycaemia:

Hyperglycaemia and exacerbation of pre-existing diabetes mellitus have been reported on **RISNIA** treatment (see **"WARNINGS"**).

Other:

Benign pituitary adenomas have been reported during postmarketing surveillance. No causal association could be detected.

Effects on ability to drive or operate machinery:

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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 have been reported.

In the case of acute overdosage, the possibility of multiple medicine ingestion should be considered.

Treatment:

Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. 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 agents. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

IDENTIFICATION:

RISNIA 0,5 mg:	Brown coloured, circular, biconvex, film-coated tablets debossed “0.5” on one side and plain on the other side.
RISNIA 1 mg:	White, round, film-coated tablets debossed “1” on one side and plain on the other side.
RISNIA 2 mg:	Orange, round, film-coated tablets debossed “2” on one side and plain on the other side.
RISNIA 3 mg:	Yellow, round, film-coated tablets debossed “3” on one side and plain on the other side.
RISNIA 4 mg:	Green, round, film-coated tablets debossed “4” on one side and plain on the other side.
RISNIA 6 mg:	Yellow, capsule-shaped, biconvex, film-coated tablets debossed “6” on one side and plain on the other side.

PRESENTATION:

RISNIA 0,5 mg:	Blister strips of 10 tablets, packed in 30’s.
RISNIA 1 mg:	Blister strips of 10 tablets, packed in 30’s.
RISNIA 2 mg:	Blister strips of 10 tablets, packed in 30’s.

RISNIA 3 mg: Blister strips of 10 tablets, packed in 30's.

RISNIA 4 mg: Blister strips of 10 tablets, packed in 30's.

RISNIA 6 mg: Blister strips of 10 tablets, packed in 30's.

STORAGE INSTRUCTIONS:

Store at or below 25 ºC.

Keep the blisters in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

RISNIA 0,5 mg: 42/2.6.5/0792

RISNIA 1 mg: 42/2.6.5/0793

RISNIA 2 mg: 42/2.6.5/0794

RISNIA 3 mg: 42/2.6.5/0795

RISNIA 4 mg: 42/2.6.5/0796

RISNIA 6 mg: 42/2.6.5/0797

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:

CIPLA MEDPRO (PTY) LTD

Building 9

Parc du Cap

Mispel Street

Bellville

7530

RSA

DATE OF PUBLICATION OF THE PACKAGE INSERT:

07 June 2012

Revised: To be allocated.