PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ASPEN RISPERIDONE 0,5 mg (film coated tablets)

ASPEN RISPERIDONE 1 mg (film coated tablets)

ASPEN RISPERIDONE 2 mg (film coated tablets)

ASPEN RISPERIDONE 3 mg (film coated tablets)

ASPEN RISPERIDONE 4 mg (film coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of ASPEN RISPERIDONE 0,5 mg contains 0,5 mg risperidone.

Contains sugar: Lactose monohydrate 65,126 mg

Each film-coated tablet of ASPEN RISPERIDONE 1 mg contains 1 mg risperidone.

Contains sugar: Lactose monohydrate 88,804 mg

Each film-coated tablet of ASPEN RISPERIDONE 2 mg contains 2 mg risperidone.

Contains sugar: Lactose monohydrate 87,804 mg

Each film-coated tablet of ASPEN RISPERIDONE 3 mg contains 3 mg risperidone.

Contains sugar: Lactose monohydrate 131,706 mg

Each film-coated tablet of ASPEN RISPERIDONE 4 mg contains 4 mg risperidone.

Contains sugar: Lactose monohydrate 175,608 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

ASPEN RISPERIDONE 0,5 mg: Red brown colour, normal round, scored biconvex film-coated tablets. Tablets might be embossed with either “PhI” or “A 27” on one side.

ASPEN RISPERIDONE 1 mg: White colour, normal round, scored biconvex film-coated tablets. Tablets might be embossed with either “PhI” or “A 28” on one side.

ASPEN RISPERIDONE 2 mg: Peach colour, normal round, scored biconvex film-coated tablets. Tablets might be embossed with either “PhI” or “A 29” on one side.

ASPEN RISPERIDONE 3 mg: Yellow colour, normal round, film-coated tablets. Tablets might be embossed with either “PhI” or “A 30” on one side.

ASPEN RISPERIDONE 4 mg: Green colour, normal round, scored biconvex film-coated tablets. Tablets might be embossed with either “PhI” or “A 31” on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ASPEN RISPERIDONE is indicated in adults, children and adolescents for:

- 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. ASPEN RISPERIDONE also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia. In patients who have shown an initial treatment response, ASPEN RISPERIDONE is also effective in maintaining the clinical improvement.
- Behavioural disturbances in patients with dementia in whom symptoms such as aggressiveness, activity disturbances or psychotic symptoms are prominent.
- Mania in bipolar disorder. These episodes are characterized by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, or poor judgement, including disruptive or aggressive behaviours.
- Conduct and other disruptive behaviour disorders in children (aged 5 to 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 ASPEN RISPERIDONE:

When medically appropriate, gradual discontinuation of the previous treatment, while ASPEN

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

Adults

ASPEN RISPERIDONE may be given once or twice daily.

Patients should start with ASPEN RISPERIDONE 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 ASPEN RISPERIDONE if additional sedation is required.

Special populations

Elderly population

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

Paediatric population

Not for children under 15 years as efficacy and safety in children under the age of 15 years have not been demonstrated in schizophrenia.

Behavioural disturbances in adult patients with dementia

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

Once patients have reached their target dose, a once-daily dosing regimen can be considered. The continued use of ASPEN RISPERIDONE must be evaluated and justified on an ongoing basis.

Mania in bipolar disorder

ASPEN RISPERIDONE 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 has been demonstrated in flexible doses over a range of 1 to 6 mg per day.

Paediatric population

Experience is lacking in bipolar mania in children and adolescents less than 18 years of age.

Conduct and other disruptive behaviour disorders (DBD) in children 5 to 12 years of age

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 to 0,04 mg/kg once daily. The mean dose is 0,03 mg/kg once daily.

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

Experience is lacking in children aged less than 5 years (see section 4.3).

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 risperidone.

Caution should be exercised with these groups of patients, as clinical experience is lacking in these patient populations. Irrespective of the indication, it is recommended that starting and consecutive dosing should be halved, and dose titration should be slower for patients with renal or hepatic impairment.

Method of administration

For oral administration.

4.3. Contraindications

ASPEN RISPERIDONE is contraindicated in:

- Patients with hypersensitivity to risperidone or to any of the excipients in ASPEN RISPERIDONE (see section 6.1).
- Conduct and other disruptive behaviour disorder in children: ASPEN RISPERIDONE is contraindicated in children under 5 years of age as efficacy and safety in these children

have not been demonstrated.

- Parkinson's disease and Lewy Body Dementia (see section 4.4).

4.4. Special warnings and precautions for use

Elderly Patients with Dementia

Overall Mortality

Elderly patients with dementia treated with atypical antipsychotic medicines, such as ASPEN RISPERIDONE, have an increased risk of mortality.

Concomitant use with furosemide

In risperidone, as contained in ASPEN RISPERIDONE, placebo- controlled trials conducted in elderly patients with dementia, there was a higher incidence of mortality in patients treated with furosemide and risperidone when compared to patients treated with risperidone alone or furosemide alone.

Therefore, caution should be exercised in these patients. There has been no reported increase in the incidence of mortality among patients taking other diuretics as concomitant medication with risperidone, as contained in ASPEN RISPERIDONE irrespective of treatment. Dehydration is an overall risk for mortality and should be carefully avoided in elderly patients with dementia.

Cerebrovascular adverse events

Cerebrovascular adverse events (CAE), including cerebrovascular accidents and transient ischaemic attacks, have been reported during treatment with risperidone, as contained in ASPEN RISPERIDONE.

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, as contained in ASPEN RISPERIDONE compared to patients receiving placebo (mean age 85 years; range 73 to 97 years).

Tardive dyskinesia/ Extrapyramidal Symptoms (TD/EPS)

Tardive dyskinesia (TD), a syndrome consisting of potentially irreversible, rhythmical involuntary dyskinetic movements, predominantly of the tongue and/or face, may develop in patients treated with ASPEN RISPERIDONE. It has been reported that the occurrence of extrapyramidal symptoms is a risk factor for the development of TD. 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 the treatment which patients are likely to develop TD.

If signs and symptoms of TD appear, discontinuation of ASPEN RISPERIDONE should be considered.

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.

Risperidone, as contained in ASPEN RISPERIDONE, 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, ASPEN RISPERIDONE should be prescribed in a manner that is most likely to minimise the risk of TD. ASPEN RISPERIDONE should be reserved for patients who appear to be obtaining substantial benefit from ASPEN RISPERIDONE. 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,

ASPEN RISPERIDONE 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 complex that has been reported in association with the use of risperidone, as contained in ASPEN RISPERIDONE. Clinical manifestations of NMS are hyperthermia, muscle rigidity, altered mental status (including catatonic signs), altered consciousness and evidence of autonomic instability (irregular pulse orblood pressure, tachycardia, cardiac arrhythmias and diaphoresis). Additional signs may include elevated creatine phosphokinase (CPK) levels, myoglobinuria (rhabdomyolysis), and acute renal failure. In this event, ASPEN RISPERIDONE should be discontinued.

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, including ASPEN RISPERIDONE, 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.

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.

Parkinson's disease or senile dementia /Lewy Body dementia and NMS

Prescribing ASPEN RISPERIDONE to patients with Parkinson's disease or Dementia with Lewy Bodies (DLB) is not recommended (see section 4.3) since both groups may be at risk of NMS as well as having and increased sensitivity to antipsychotic medicines such as ASPEN RISPERIDONE. Manifestations of this increased sensitivity can include confusion, obtundation and postural instability with frequent falls, in addition to extrapyramidal symptoms. In addition, in previous studies, elderly risperidone treated patients had a higher mortality.

Caution should be used when prescribing ASPEN RISPERIDONE to patients with Parkinson disease since, theoretically, it might cause a deterioration of the disease.

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 atypical antipsychotic medicines including risperidone, as contained in ASPEN RISPERIDONE.

Patients with an established diagnosis of diabetes mellitus who are started on ASPEN RISPERIDONE 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 ASPEN RISPERIDONE should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with ASPEN RISPERIDONE should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when ASPEN RISPERIDONE

was discontinued. However, some patients required continuation of anti-diabetic treatment despite discontinuation of ASPEN RISPERIDONE.

Hyperglycaemia and exacerbation of pre-existing diabetes mellitus have been reported on ASPEN RISPERIDONE treatment.

Weight gain

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

QT interval

QT prolongation has been reported with risperidone, as contained in ASPEN RISPERIDONE. Caution should be exercised when ASPEN RISPERIDONE 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.

Intraoperative Floppy Iris Syndrome

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1$_a$-adrenergic antagonist effect, including ASPEN RISPERIDONE (see section 4.8). IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect (including ASPEN RISPERIDONE) should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping ASPEN RISPERIDONE therapy.

Leukopenia, neutropenia, and agranulocytosis

Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotic medicines, including risperidone, as contained in ASPEN RISPERIDONE.

Patients with a history of a clinically significant low white blood cell count (WBC) or a medicine-induced leukopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of ASPEN RISPERIDONE should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 X 10^9/L) should discontinue ASPEN RISPERIDONE and have their WBC followed until recovery.

Hyperprolactinaemia

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

Priapism

Priapism may occur with risperidone, as contained in ASPEN RISPERIDONE treatment due to its alpha-adrenergic blocking effects.

Body temperature regulation

Disruption of the body's ability to reduce core body temperature has been attributed to ASPEN RISPERIDONE. Appropriate care is advised when prescribing ASPEN RISPERIDONE to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant treatment with anticholinergic activity, or being subject to dehydration.

Antiemetic effect

An antiemetic effect has been observed with risperidone, as contained in ASPEN RISPERIDONE. 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.

Renal and hepatic impairment

Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than adults with normal renal function. Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone, as contained in ASPEN RISPERIDONE.

Venous thromboembolism

Venous thromboembolism (VTE) has been reported with antipsychotic medicines, including ASPEN RISPERIDONE. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with ASPEN RISPERIDONE and preventative measures undertaken.

Hypotension

Due to the alpha-blocking activity of risperidone, as contained in ASPEN RISPERIDONE, (orthostatic) hypotension can occur, especially during the initial dose-titration period. ASPEN RISPERIDONE 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 risperidone, as contained in ASPEN RISPERIDONE. Caution is recommended when treating patients with epilepsy.

Benign pituitary adenomas

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

Paediatric population

Before ASPEN RISPERIDONE is prescribed to a child or adolescent with conduct disorder they should be fully assessed for physical and social causes of the aggressive behaviour such as pain or inappropriate environmental demands.

The sedative effect of ASPEN RISPERIDONE should be closely monitored in this population because of possible consequences on learning ability. A change in the time of administration of ASPEN RISPERIDONE could improve the impact of the sedation on attention faculties of children and adolescents.

Risperidone, as in ASPEN RISPERIDONE was associated with mean increases in body weight and body mass index (BMI). Baseline weight measurement prior to treatment and regular weight monitoring are recommended. Changes in height in the long-term open-label extension studies were within expected age-appropriate norms. The effect of long-term risperidone treatment on sexual maturation and height has not been adequately studied.

Because of the potential effects of prolonged hyperprolactinemia on growth and sexual maturation in children and adolescents, regular clinical evaluation of endocrinological status should be considered, including measurements of height, weight, sexual maturation, monitoring of menstrual functioning, and other potential prolactin-related effects.

During treatment with ASPEN RISPERIDONE regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.

Excipients

ASPEN RISPERIDONE contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp 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

Medicines known to prolong the QT interval

Caution is advised when prescribing ASPEN RISPERIDONE with medicines known to prolong the QT interval, such as antidysrhythmics (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 ASPEN RISPERIDONE. This list is indicative and not exhaustive.

Centrally-acting medicines and alcohol

ASPEN RISPERIDONE 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

ASPEN RISPERIDONE 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, as contained in ASPEN RISPERIDONE and antihypertensive treatment.

Psychostimulants

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

Paliperidone

Concomitant use of oral ASPEN RISPERIDONE with paliperidone is not recommended as paliperidone is the active metabolite of risperidone, as contained in ASPEN 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 ASPEN RISPERIDONE.

ASPEN RISPERIDONE is mainly metabolised through CYP2D6, and to a lesser extent through CYP3A4. Both risperidone, as contained in ASPEN 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 ASPEN RISPERIDONE with a strong CYP2D6 inhibitor may increase the plasma concentrations of risperidone, as contained in ASPEN 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 Effect of other medicinal products on the pharmacokinetics of ASPEN RISPERIDONE

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 ASPEN RISPERIDONE.

CYP3A4 and/or P-gp inhibitors

Co-administration of ASPEN RISPERIDONE 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 ASPEN RISPERIDONE.

CYP3A4 and/or P-gp inducers

Co-administration of ASPEN RISPERIDONE with a strong CYP3A4 and/or P-gp inducer may decrease the plasma concentrations of the risperidone active antipsychotic fraction. When concomitant carbamazepine or another strong CYP3A4 and/or P-gp inducer is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL. CYP3A4 inducers exert their effect in a time-dependent manner, and may take at least 2 weeks to reach maximaleffect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least 2weeks to decline.

Highly protein-bound medicines

When ASPEN RISPERIDONE is taken together with highly protein-bound medicines, there is no clinically relevant displacement of either medicine from the plasma proteins.

When using concomitant medicine, 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 ASPEN RISPERIDONE in children and adolescents did not alter the pharmacokinetics and efficacy of ASPEN RISPERIDONE.

Examples

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

Effect of other medicinal products on the pharmacokinetics of ASPEN RISPERIDONE

Antibacterials:

- Erythromycin, a moderate CYP3A4 inhibitor and P-gp inhibitor, does not change the pharmacokinetics of ASPEN 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 ASPEN 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 ASPEN 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- ASPEN 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.
- *Venlafaxine:* Venlafaxine administered under steady-state conditions at 150 mg/day slightly inhibited the CYP2D6-mediated metabolism of risperidone (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxy-risperidone, resulting in an approximate 32 % increase in risperidone AUC. However, venlafaxine coadministration did not significantly alter the pharmacokinetic profile of the total active antipsychotic fraction.

Effect of risperidone on the pharmacokinetics of other medicinal products

Antiepileptics:

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

valproate or topiramate.

Antipsychotics:

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

Digoxin:

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

Lithium:

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

- Concomitant use of ASPEN RISPERIDONE with furosemide.
- See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

4.6. Fertility, pregnancy and lactation

The safety of ASPEN RISPERIDONE in pregnancy and lactating women has not been established.

Pregnancy

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

Breastfeeding

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

Fertility

No data available.

4.7. Effects on ability to drive and use machines

ASPEN RISPERIDONE 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) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent
Infections and infestations	Pneumonia, influenza, bronchitis, upper respiratory tract infection, urinary tract infection	Sinusitis, viral infection, ear infection, tonsillitis, cellulitis, otitis media, eye infection, localised infection, acrodermatitis, respiratory tract infection, cystitis, onychomycosis, chronic otitis media, lower respiratory tract infection, viral infection, gastroenteritis, subcutaneous abscess
Blood and the lymphatic system disorders		Anaemia, neutropenia, granulocytopenia, decrease in thrombocyte count, agranulocytosis, decreased haematocrit , increased eosinophil count, agranulocytosis
Immune system disorders		Hypersensitivity, anaphylactic reaction
Endocrine disorders	Increased blood prolactin	Water intoxication, either due to polydipsia or the syndrome of inappropriate secretion of the antidiuretic hormone (SIADH), and body temperature dysregulation, glucose urine

Metabolism and nutrition disorders	Increased appetite, decreased appetite	Anorexia, polydipsia, hyperglycaemia and exacerbation of pre-existing diabetes mellitus, diabetic ketoacidosis, water intoxication, diabetes mellitus, hypoglycaemia, increased blood cholesterol, increased blood triglycerides, hyperinsulinaemia, diabetic ketoacidosis
Psychiatric disorders	Insomnia, anxiety, agitation, sleep disorder, depression	Confusional state, decreased libido, listless, nervousness, anorgasmia, blunted effect, impaired concentration, mania, nightmare
Nervous system disorders	Parkinsonism, headache, akathisia, dizziness, tremor, dystonia, somnolence, sedation, lethargy, dyskinesia.	Unresponsive to stimuli, loss of consciousness, syncope, depressed level of consciousness, cerebrovascular accident, transient ischaemic attack, dysarthria, disturbance in attention, hypersomnia, dizziness postural,
		balance disorder, tardive dyskinesia, speech disorder, coordination abnormal, hypoaesthesia, head intubation, neuroleptic malignant syndrome, diabetic coma, cerebrovascular disorder, cerebral ischaemia, movement disorder, sedation, dysgeusia, paraesthesia, convulsion, psychomotor hyperactivity
Eye disorders	Vision blurred	Conjunctivitis, ocular hyperaemia, eye discharge, eye swelling, dry eye, increased lacrimation, photophobia, visual acuity reduced, eye rolling glaucoma, floppy iris syndrome (intraoperative), blepharospasm, eye movement disorder, eyelid margin crusting
Ear and labyrinth disorders		Ear pain, tinnitus, vertigo
Cardiac disorders	Tachycardia	Atrioventricular block, bundle branch block, sinus bradycardia, palpitations, atrial fibrillation, bradycardia, electrocardiogram QT prolongation, abnormal electrocardiogram
Vascular disorders		Hypotension, orthostatic hypotension and (reflex) tachycardia or hypertension, flushing, hypertension, pulmonary embolism, venous thrombosis
Respiratory, thoracic and mediastinal disorders	Dyspnoea, epistaxis, cough, nasal congestion, pharyngolaryngeal pain	Wheezing, pneumonia aspiration, pulmonary congestion, respiratory disorder, rales, respiratory tract congestion, dysphonia, hyperventilation, rhinitis, sleep apnoea syndrome, hyperventilation
Gastrointestinal disorders	Vomiting, diarrhoea, constipation, nausea, abdominal pain, dyspepsia, dry mouth, stomach discomfort.	Dysphagia, gastritis, faecal incontinence, faecaloma, lip swelling cheilitis, intestinal obstruction, pancreatitis, toothache, tongue spasm, ileus
Hepato-biliary disorders		Jaundice, increased transaminases, increased gamma-glutamyl transferase, increased hepatic enzyme increased

Skin and subcutaneous tissue disorders	Skin rash, erythema	Skin lesion, skin disorder, pruritus, acne, skin discoloration, seborrheic dermatitis, dry skin, hyperkeratosis, dandruff, angioedema, alopecia, eczema, drug eruption
Musculoskeletal and connective tissue disorders	Arthralgia, back pain, pain in extremity, muscle spasms, musculoskeletal pain	Muscular weakness, myalgia, neck pain, joint swelling, posture abnormal, joint stiffness, musculoskeletal chest pain, rhabdomyolysis, buttock pain
Renal and urinary disorders	Enuresis	Dysuria, urinary incontinence, pollakiuria, urinary retention
Pregnancy, puerperium and perinatal conditions		Neonatal drug withdrawal syndrome
Reproductive system and breast disorders		Amenorrhoea, sexual dysfunction, erectile dysfunction, ejaculation disorder, galactorrhoea, gynaecomastia, disturbances in the menstrual cycle (frequently), vaginal discharge, orgasmic dysfunction, priapism, menstruation delayed, ejaculation delayed, oligomenorrhoea, breast discomfort, breast engorgement, breast enlargement, breast discharge
General disorders and administrative site conditions	Pyrexia, fatigue, peripheral oedema, asthenia, chest pain	Face oedema, gait disturbance, feeling abnormal, sluggishness, influenza like illness, thirst, chest discomfort, chills, generalised oedema, drug withdrawal syndrome, peripheral coldness, fatigue, angioedema and other allergic reactions, hypothermia, pain
Investigations	Weight gain	Increased blood glucose, decreased white blood cell count, increased or decreased body temperature, increased eosinophil count, decreased haemoglobin, increased blood creatine phosphokinase, decreased weight
Injury, poisoning and procedural complications		Fall

b) Description of selected adverse reactions

Dose dependent extrapyramidal symptoms including tremor, rigidity, hypersalivation, bradykinesia, oculogyric crisis, akathisia (hyperkinesia) and acute dystonia, hypokinesia. These may be reversible upon dose reduction and/or administration of anti-Parkinson medication, if necessary.

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. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

Reported signs and symptoms have been those resulting from an exaggeration of risperidone'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. Torsade de pointes has been reported in association with combined overdose of risperidone, as contained in ASPEN RISPERIDONE, and paroxetine.

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

Treatment

Establish and maintain a clear airway, and ensure adequate oxygenation and ventilation.

Administration of activated charcoal together with a laxative should be considered.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible dysrhythmias.

Since there is no known antidote if accidental poisoning or overdosage is suspected,

appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic 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

Category and Class: A.2.6.5 Central nervous system depressants. Miscellaneous structures.

Pharmacotherapeutic group: Nervous system. Psycholeptics. Other antipsychotics.

ATC code: N05AX Risperidone

Mechanism of action

Risperidone is an antipsychotic of the benzisoxazol derivatives. It is a selective monoaminergic antagonist. Risperidone has affinity for serotonin-5-HT2, dopamine-D2, H1-histamine, alpha1- and alpha2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. It is a dopamine D2–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

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 mg and 4 mg twice daily.

Steady state is reached within 1 day for risperidone in most patients and 4 to 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 % to 45 % of the dose.

Risperidone showed significantly higher active plasma concentrations and slower elimination of the active antipsychotic fraction by 30 % in the elderly and 50 % in patients with moderate renal insufficiency. In patients with severe renal insufficiency the clearance was one third that of normal. The plasma concentrations of risperidone were normal in patient's liver insufficiency, but the mean free fraction of risperidone in plasma was increased by about 35 %.

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

Biotransformation

Risperidone is metabolised by cytochrome CYP2D6 to 9-hydroxy-risperidone which has a similar pharmacological activity to risperidone. Risperidone and 9-hydroxy-risperidone form the active antipsychotic fraction.

After oral administration to psychotic patients, risperidone's half-life is about 3 hours.

Elimination

The elimination half-life of 9-hydroxy-risperidone and the active antipsychotic fraction is 24 hours.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

ASPEN RISPERIDONE 0,5 mg

FD&C blue/indigo carmine aluminium lake (C.I. 73015), FD&C yellow/sunset yellow FCF aluminium lake (C.I. 15985), hypromellose, iron oxide yellow (C.I. 77492), lactose monohydrate, macrogol, magnesium stearate, microcrystalline cellulose, pregelatinised starch, silica colloidal anhydrous, sodium lauryl sulphate, sodium starch glycollate, titanium dioxide (C.I. 77891)

ASPEN RISPERIDONE 1 mg

Hypromellose, lactose monohydrate, macrogol, magnesium stearate, microcrystalline cellulose, pregelatinised starch, silica colloidal anhydrous, sodium lauryl sulphate, sodium starch glycollate, titanium dioxide (C.I. 77891)

ASPEN RISPERIDONE 2 mg

FD&C yellow/sunset yellow FCF (C.I. 15985), hypromellose, iron oxide yellow (C.I. 77492), lactose monohydrate, macrogol, magnesium stearate, microcrystalline cellulose, pregelatinised starch, silica colloidal anhydrous, sodium lauryl sulphate, sodium starch glycollate, titanium dioxide (C.I. 77891)

ASPEN RISPERIDONE 3 mg

FD&C blue/indigo carmine aluminium lake (C.I. 73015), FD&C yellow/sunset yellow FCF aluminium lake (C.I. 15985), hypromellose, lactose monohydrate, macrogol, magnesium stearate, microcrystalline cellulose, pregelatinised starch, quinoline yellow aluminium lake (C.I. 47005), silica colloidal anhydrous, sodium lauryl sulphate, sodium starch glycollate, titanium dioxide (C.I. 77891)

ASPEN RISPERIDONE 4 mg

FD&C blue/indigo carmine aluminium lake (C.I. 73015), hypromellose, lactose monohydrate, macrogol, magnesium stearate, microcrystalline cellulose, pregelatinised starch, quinoline yellow aluminium lake (C.I. 47005), silica colloidal anhydrous, sodium lauryl sulphate, sodium starch glycollate, titanium dioxide (C.I. 77891)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C, protected from light.

Keep the blister strip in the unit carton until required for use.

6.5. Nature and contents of container

28 or 30 film-coated tablets are packed in a clear polyvinyl chloride/polyvinylidene chloride blister strip sealed with an aluminium foil backing. The blister strips are packed into a cardboard unit carton together with a leaflet.

Not all pack sizes are necessarily marketed.

6.6. Special precautions for disposal <and other handling>

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead,

2191

8. REGISTRATION NUMBER

ASPEN RISPERIDONE 0,5 mg: 41/2.6.5/0339

ASPEN RISPERIDONE 1 mg: 41/2.6.5/0340

ASPEN RISPERIDONE 2 mg: 41/2.6.5/0341

ASPEN RISPERIDONE 3 mg: 41/2.6.5/0346

ASPEN RISPERIDONE 4 mg: 41/2.6.5/0347

9. DATE OF FIRST AUTHORISATION

09 December 2008

10. DATE OF REVISION OF TEXT

14 February 2022

Namibia:	NS3
0,5 mg	10/2.6.5/0535
1 mg	10/2.6.5/0536
2 mg	10/2.6.5/0537
3 mg	10/2.6.5/0538
4 mg	10/2.6.5/0539

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