1. Name of the Medicinal Product
Product name: ZEPIDONE-3
Generic name: Risperidone Tablets USP 3mg
Strength: 3mg per Tablet

2. Qualitaive and Quantitative Composition
Each film coated tablet contains:
Risperidone USP 3mg
Colour: Brilliant Blue

Excipients with known effect:
Each Tablet Contains: 59mg of lactose monohydrate
For a full list of excipients, see section 6.1

3. Pharmaceutical form
Solid dosage form (film coated Tablet)
Blue coloured, elongated, biconvex, scored on one side & plain on other side, film coated tablets.
Note: " *The score line is not intended for the divisions of the tablet into two equal doses. The Tablets should be swallowed whole"*

4. Clinical Particulars
4.1 Therapeutic Indications
Risperidone is indicated for the treatment of schizophrenia.

Risperidone is indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders.

Risperidone is indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.

Risperidone is indicated for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with sub average intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours require pharmacologic treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment programme, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of conduct disorder of children and adolescents.

4.2 Posology and Method of Administration

Schizophrenia

Adults

Risperidone Tablets may be given once daily or twice daily.

Patients should start with 2 mg/day Risperidone Tablets. The dosage may be increased on the second day to 4 mg. Subsequently, the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6 mg. In some patients, a slower titration phase and a lower starting and maintenance dose may be appropriate.

Doses above 10 mg/day have not demonstrated superior efficacy to lower doses and may cause increased incidence of extrapyramidal symptoms. Safety of doses above 16 mg/day has not been evaluated, and are therefore not recommended.

Elderly

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

Risperidone is not recommended for use in children below age 18 with schizophrenia due to a lack of data on efficacy.

Manic episodes in bipolar disorder

Adults

Risperidone should be administered on a once daily schedule, starting with 2 mg risperidone. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. Risperidone can be administered in flexible doses over a range of 1 to 6 mg per day to optimize each patient's level of efficacy and tolerability. Daily doses over 6 mg risperidone have not been investigated in patients with manic episodes.

As with all symptomatic treatments, the continued use of Risperidone Tablets must be evaluated and justified on an ongoing basis.

Elderly

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. Since clinical experience in elderly is limited, caution should be exercised.

Paediatric population

Risperidone is not recommended for use in children below age 18 with bipolar mania due to a lack of data on efficacy.

Persistent aggression in patients with moderate to severe Alzheimer's 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. Risperidone should not be used more than 6 weeks in patients with persistent aggression in Alzheimer's dementia. During treatment, patients must be evaluated frequently and regularly, and the need for continuing treatment

reassessed.

Conduct disorder

Children and adolescents from 5 to 18 years of age

For subjects ≥ 50 kg, a starting dose of 0.5 mg once daily is recommended. This dosage can be individually adjusted by increments of 0.5 mg once daily not more frequently than every other day, if needed. The optimum dose is 1 mg once daily for most patients. Some patients, however, may benefit from 0.5 mg once daily while others may require 1.5 mg once daily. For subjects <50 kg, a starting dose of 0.25 mg once daily is recommended. This dosage can be individually adjusted by increments of 0.25 mg once daily not more frequently than every other day, if needed. The optimum dose is 0.5 mg once daily for most patients. Some patients, however, may benefit from 0.25 mg once daily while others may require 0.75 mg once daily.

As with all symptomatic treatments, the continued use of Risperidone Tablets must be evaluated and justified on an ongoing basis.

Risperidone is not recommended in children less than 5 years of age, as there is no experience in children less than 5 years of age with this disorder.

Renal and hepatic impairment

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

Irrespective of the indication, starting and consecutive dosing should be halved, and dose titration should be slower for patients with renal or hepatic impairment.

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

Method of administration

Risperidone Tablets are for oral use. Food does not affect the absorption of risperidone.

Upon discontinuation, gradual withdrawal is advised. Acute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotic medicines. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported.

Switching from other antipsychotics

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warning and precautions for use

Elderly patients with dementia:

Increased mortality in elderly people with dementia

In a meta-analysis of 17 controlled trials of atypical antipsychotics, including Risperidone, elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo. In placebo-controlled trials with oral Risperidone in this population, the incidence of mortality was 4.0% for Risperidone -treated patients compared to 3.1% for placebo-treated patients. The odds ratio (95% exact confidence interval) was 1.21 (0.7; 2.1). The mean age (range) of patients who died was 86 years (range 67-100). Data from two large observational studies showed that elderly people with dementia who are treated with conventional antipsychotics are also at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

Concomitant use with furosemide

In the Risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination or co-treatment with other potent diuretics should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular adverse events (CVAE):

An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics. The pooled data from six placebo-controlled studies with Risperidone in mainly elderly patients (> 65 years of age) with dementia showed that CVAEs (serious and non-serious, combined) occurred in 3.3% (33/1,009) of patients treated with risperidone and 1.2% (8/712) of patients treated with placebo. The odds ratio (95% exact confidence interval) was 2.96 (1.34; 7.50). The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or

other patient populations. Risperidone should be used with caution in patients with risk factors for stroke.

The risk of CVAEs was significantly higher in patients with mixed or vascular type of dementia when compared to Alzheimer's dementia. Therefore, patients with other types of dementias than Alzheimer's should not be treated with risperidone.

Physicians are advised to assess the risks and benefits of the use of Risperidone in elderly patients with dementia, taking into account risk predictors for stroke in the individual patient. Patients/caregivers should be cautioned to immediately report signs and symptoms of potential CVAEs such as sudden weakness or numbness in the face, arms or legs, and speech or vision problems. All treatment options should be considered without delay, including discontinuation of risperidone.

Risperidone should only be used short term for persistent aggression in patients with moderate to severe Alzheimer's dementia to supplement non-pharmacological approaches which have had limited or no efficacy and when there is potential risk of harm to self or others.

Patients should be reassessed regularly, and the need for continuing treatment reassessed.

Orthostatic hypotension:

Due to the alpha-blocking activity of risperidone, (orthostatic) hypotension can occur, especially during the initial dose-titration period. Clinically significant hypotension has been observed post-marketing with concomitant use of risperidone and antihypertensive treatment. Risperidone should be used with caution in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolaemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended. A dose reduction should be considered if hypotension occurs.

Leucopenia, neutropenia, and agranulocytosis:

Events of leucopenia, neutropenia and agranulocytosis have been reported with antipsychotic agents, including Risperidone. Agranulocytosis has been reported very rarely (<1/10,000 patients) during post-marketing surveillance.

Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leucopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of 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 × 109/L) should discontinue Risperidone and have their WBC followed until recovery.

Tardive dyskinesia/extrapyramidal symptoms (TD/EPS):

Medicines with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. The onset of extrapyramidal symptoms is a risk factor for tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics should be considered.

Caution is warranted in patients receiving both psychostimulants (e.g. methylphenidate) and risperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medications. Gradual withdrawal of stimulant treatment is recommended.

Neuroleptic malignant syndrome (NMS):

Neuroleptic Malignant Syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels has been reported to occur with antipsychotics. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, all antipsychotics, including Risperidone, should be discontinued.

Parkinson's disease and dementia with Lewy bodies:

Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including RISPERIDONE, to patients with Parkinson's disease or Dementia with Lewy Bodies (DLB). Parkinson's disease may worsen with risperidone. Both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medicinal products; these patients were excluded from clinical trials. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Hyperglycaemia and diabetes mellitus:

Hyperglycaemia, diabetes mellitus, and exacerbation of pre-existing diabetes have been reported during treatment with Risperidone. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Association with ketoacidosis has been reported very rarely and rarely with diabetic coma. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any atypical antipsychotic, including Risperidone, should be monitored for symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus should be monitored regularly for worsening of glucose control.

Weight gain:

Significant weight gain has been reported with Risperidone use. Weight should be monitored regularly.

Hyperprolactinaemia:

Hyperprolactinaemia is a common side effect of treatment with Risperidone. Evaluation of the prolactin plasma level is recommended in patients with evidence of possible prolactin-related side

effects (e.g., gynaecomastia, menstrual disorders, anovulation, fertility disorder, decreased libido, erectile dysfunction, and galactorrhoea).

Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. Risperidone should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours.

QT prolongation

QT prolongation has very rarely been reported post-marketing. As with other antipsychotics, caution should be exercised when risperidone is prescribed in patients with known cardiovascular disease, family history of QT prolongation, bradycardia, or electrolyte disturbances (hypokalaemia, hypomagnesaemia), as it may increase the risk of arrhythmogenic effects, and in concomitant use with medicines known to prolong the QT interval.

Seizures:

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

Priapism:

Priapism may occur with 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 antipsychotic medicines. Appropriate care is advised when prescribing 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 was observed in preclinical studies with risperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain medicines or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumour.

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.

Venous thromboembolism:

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors

for VTE should be identified before and during treatment with Risperidone and preventative measures undertaken.

Intraoperative floppy iris syndrome:

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, including Risperidone.

IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect 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 the antipsychotic therapy.

Paediatric population:

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

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

Results from a small post-marketing observational study showed that Risperidone-exposed subjects between the ages of 8-16 years were on average approximately 3.0 to 4.8 cm taller than those who received other atypical antipsychotic medications. This study was not adequate to determine whether exposure to Risperidone had any impact on final adult height, or whether the result was due to a direct effect of Risperidone on bone growth, or the effect of the underlying disease itself on bone growth, or the result of better control of the underlying disease with resulting increase in linear growth.

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

This medicine contain

Lactose monohydrate: 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 medicinal products and other forms of interaction

Pharmacodynamic-related interactions:

Drugs known to prolong the QT interval

As with other antipsychotics, caution is advised when prescribing risperidone with medicinal products known to prolong the QT interval, such as antiarrhythmics (e.g., quinidine, dysopiramide, procainamide, propafenone, amiodarone, sotalol), tricyclic antidepressants (i.e., amitriptyline), tetracyclic antidepressants (i.e., maprotiline), some antihistamines, other antipsychotics, some antimalarials (i.e., quinine and mefloquine), and with medicines causing electrolyte imbalance (hypokalaemia, hypomagnesaemia), bradycardia, or those which inhibit the hepatic metabolism of risperidone. This list is indicative and not exhaustive.

Centrally-acting drugs and alcohol

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

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.

Drugs with hypotensive effect

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

Psychostimulants

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

Paliperidone

Concomitant use of oral Risperidone with paliperidone is not recommended as paliperidone is the active metabolite of risperidone and the combination of the two may lead to additive active antipsychotic fraction exposure.

Pharmacokinetic-related interactions:

Food does not affect the absorption of Risperidone.

Risperidone is mainly metabolised through CYP2D6, and to a lesser extent through CYP3A4. Both risperidone and its active metabolite 9-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 Risperidone 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 RISPERIDONE.

CYP3A4 and/or P-gp inhibitors

Co-administration of 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 RISPERIDONE.

CYP3A4 and/or P-gp inducers

Co-administration of RISPERIDONE with a strong CYP3A4 and/or P-gp inducer may decrease the plasma concentrations of the risperidone active antipsychotic fraction. When concomitant carbamazepine or another strong CYP3A4 and/or P-gp inducer is initiated or discontinued, the physician should re-evaluate the dosing of RISPERIDONE. 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 drugs

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

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

Paediatric population

Interaction studies have only been performed in adults. The relevance of the results from these studies in paediatric patients is unknown.

The combined use of psychostimulants (e.g., methylphenidate) with RISPERIDONE in children and adolescents did not alter the pharmacokinetics and efficacy of RISPERIDONE.

Examples

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

Effect of other medicinal products on the pharmacokinetics of risperidone

Antibacterials:

Erythromycin, a moderate CYP3A4 inhibitor and P-gp inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction.

Rifampicin, a strong CYP3A4 inducer and a P-gp inducer, decreased the plasma concentrations of the active antipsychotic fraction.

Anticholinesterases:

Donepezil and galantamine, both CYP2D6 and CYP3A4 substrates, do not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction.

Antiepileptics:

Carbamazepine, a strong CYP3A4 inducer and a P-gp inducer, has been shown to decrease the plasma concentrations of the active antipsychotic fraction of risperidone. Similar effects may be observed with e.g., phenytoin and phenobarbital which also induce CYP3A4 hepatic enzyme, as well as P-glycoprotein.

Topiramate modestly reduced the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance.

Antifungals:

Itraconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200mg/day increased the plasma concentrations of the active antipsychotic fraction by about 70%, at risperidone doses of 2 to 8 mg/day.

Ketoconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200mg/day increased the plasma concentrations of risperidone and decreased the plasma concentrations of 9-hydroxy-risperidone.

Antipsychotics:

Phenothiazines may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

Antivirals:

Protease inhibitors: No formal study data are available; however, since ritonavir is a strong CYP3A4 inhibitor and a weak CYP2D6 inhibitor, ritonavir and ritonavir-boosted protease inhibitors potentially raise concentrations of the risperidone active antipsychotic fraction.

Beta-blockers:

Some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

Calcium channel blockers:

Verapamil, a moderate inhibitor of CYP3A4 and an inhibitor of P-gp, increases the plasma concentration of risperidone and the active antipsychotic fraction.

Gastrointestinal drugs:

H2-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 20mg/day, less so of the active antipsychotic fraction. However, higher doses of paroxetine may elevate concentrations of the risperidone active antipsychotic fraction.

Tricyclic antidepressants may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction.

Sertraline, a weak inhibitor of CYP2D6, and fluvoxamine, a weak inhibitor of CYP3A4, at dosages up to 100 mg/day are not associated with clinically significant changes in concentrations of the risperidone active antipsychotic fraction. However, doses higher than 100 mg/day of sertraline or fluvoxamine may elevate concentrations of the risperidone active antipsychotic fraction.

Effect of risperidone on the pharmacokinetics of other 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.

Digitalis glycosides:

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

Lithium:

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

4.6 Pregnancy and lactation

Pregnancy:

There are no adequate data from the use of risperidone in pregnant women. Risperidone was not teratogenic in animal studies but other types of reproductive toxicity were seen. The potential risk for humans is unknown.

Neonates exposed to antipsychotics (including RISPERIDONE) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia,

hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

RISPERIDONE should not be used during pregnancy unless clearly necessary. If discontinuation during pregnancy is necessary, it should not be done abruptly.

Breast-feeding:

In animal studies, risperidone and 9-hydroxy-risperidone are excreted in the milk. It has been demonstrated that risperidone and 9-hydroxy-risperidone are also excreted in human breast milk in small quantities. There are no data available on adverse reactions in breast-feeding infants. Therefore, the advantage of breast-feeding should be weighed against the potential risks for the child.

Fertility:

As with other drugs that antagonise dopamine D2 receptors, RISPERIDONE elevates prolactin level. Hyperprolactinaemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients.

There were no relevant effects observed in the non-clinical studies.

4.7 Effects on ability to drive and use machines

Risperidone can have minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 Undesirable effects

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

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

The following are all the ADRs that were reported in clinical trials and post-marketing experience with risperidone by frequency category estimated from Risperidone clinical trials. The following terms and frequencies are applied: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	**Adverse Drug Reaction**				
	Frequency				
	Very Common	**Common**	**Uncommon**	**Rare**	**Very Rare**
Infections and infestations		pneumonia, bronchitis, upper respiratory tract infection, sinusitis, urinary tract infection, ear	respiratory tract infection, cystitis, eye infection, tonsillitis, onychomycosis, cellulitis localised	infection	

		infection, influenza	infection, viral infection, acarodermatitis		
Blood and lymphatic system disorders			neutropenia, white blood cell count decreased, thrombocytopenia, anaemia, haematocrit decreased, eosinophil count increased	Agranulocytosis C	
Immune system disorders			hypersensitivity	anaphylactic reaction C	
Endocrine disorders		hyperprolactinaemia a		inappropriate antidiuretic hormone secretion, glucose urine present	
Metabolism and nutrition disorders		weight increased, increased appetite, decreased appetite	diabetes mellitus b, hyperglycaemia, polydipsia, weight decreased, anorexia, blood cholesterol increased	water intoxication c, hypoglycaemia, hyperinsulinaemia c, blood triglycerides increased	diabetic ketoacidosis
Psychiatric disorders	insomnia d	sleep disorder, agitation, depression, anxiety	mania, confusional state, libido decreased, nervousness, nightmare	catatonia, somnambulism, sleep-related eating disorder, blunted affect, anorgasmia	

Nervous system disorders	sedation/ somnolence, parkinsonism d, headache	akathisiad, dystoniad, dizziness, dyskinesiad, tremor	tardive dyskinesia, cerebral ischaemia, unresponsive to stimuli, loss of consciousness, depressed level of consciousness, convulsiond, syncope, psychomotor hyperactivity, balance disorder, coordination abnormal, dizziness postural, disturbance in attention, dysarthria, dysgeusia, hypoaesthesia, paraesthesia	neuroleptic malignant syndrome, cerebrovascular disorder, diabetic coma, head titubation	
Eye disorders		vision blurred, conjunctivitis	photophobia, dry eye, lacrimation increased, ocular hyperaemia	glaucoma, eye movement disorder, eye rolling, eyelid margin crusting, floppy iris syndrome (intraoperative)c	
Ear and labyrinth disorders			vertigo, tinnitus, ear pain		
Cardiac disorders		tachycardia	atrial fibrillation, atrioventricular block, conduction disorder, electrocardiogram QT prolonged, bradycardia, electrocardiogram abnormal, palpitations	sinus arrhythmia	
Vascular disorders		hypertension	hypotension, orthostatic hypotension,	pulmonary embolism, venous	

			flushing	thrombosis	
Respiratory, thoracic and mediastinal disorders		dyspnoea, pharyngolaryngeal pain, cough, epistaxis, nasal congestion	pneumonia aspiration, pulmonary congestion, respiratory tract congestion, rales, wheezing, dysphonia, respiratory disorder	sleep apnoea syndrome, hyperventilation	
Gastrointestinal disorders		abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhoea, dyspepsia, dry mouth, toothache	faecal incontinence, faecaloma, gastroenteritis, dysphagia, flatulence	pancreatitis, intestinal obstruction, swollen tongue, cheilitis	ileus
Skin and subcutaneous tissue disorders		rash, erythema	urticaria, pruritus, alopecia, hyperkeratosis, eczema, dry skin, skin discolouration, acne, seborrhoeic dermatitis, skin disorder, skin lesion	drug eruption, dandruff	angioedema
Musculoskeletal and connective tissue disorders		muscle spasms, musculoskeletal pain, back pain, arthralgia	blood creatine phosphokinase increased, posture abnormal, joint stiffness, joint swelling muscular weakness, neck pain	rhabdomyolysis	
Renal and urinary disorders		urinary incontinence	pollakiuria, urinary retention, dysuria		
Pregnancy, puerperium, and neonatal conditions				drug withdrawal syndrome neonatalc	
Reproductive system and breast disorders			erectile dysfunction, ejaculation disorder, amenorrhoea, menstrual disorderd, gynaecomastia, galactorrhoea, sexual	priapismc, menstruation delayed, breast engorgement, breast enlargement,	

			dysfunction, breast pain, breast discomfort, vaginal discharge	breast discharge	
General disorders and administration site conditions		oedemad, pyrexia, chest pain, asthenia, fatigue, pain	face oedema, chills, body temperature increased, gait abnormal, thirst, chest discomfort, malaise, feeling abnormal, discomfort	hypothermia, body temperature decreased, peripheral coldness, drug withdrawal syndrome, indurationc	
Hepatobiliary disorders			transaminases increased, gamma-glutamyltransferase increased, hepatic enzyme increased	jaundice	
Injury, poisoning and procedural complications		fall	procedural pain		

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

bIn placebo-controlled trials diabetes mellitus was reported in 0.18% in risperidone-treated subjects compared to a rate of 0.11% in placebo group. Overall incidence from all clinical trials was 0.43% in all risperidone-treated subjects.

cNot observed in RISPERIDONE clinical studies but observed in post-marketing environment with risperidone.

dExtrapyramidal disorder may occur: Parkinsonism (salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies, muscle tightness, akinesia, nuchal rigidity, muscle rigidity, parkinsonian gait, and glabellar reflex abnormal, parkinsonian rest tremor), akathisia (akathisia, restlessness, hyperkinesia, and restless leg syndrome), tremor, dyskinesia (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia. Dystonia includes dystonia, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus. It should be noted that a broader spectrum of symptoms are included, that do not necessarily have an extrapyramidal origin. Insomnia includes initial insomnia, middle insomnia. Convulsion includes grand mal convulsion. Menstrual disorder includes menstruation irregular, oligomenorrhoea. Oedema includes generalised oedema, oedema peripheral, pitting oedema.

Undesirable effects noted with paliperidone formulations:

Paliperidone is the active metabolite of risperidone, therefore, the adverse reaction profiles of these compounds (including both the oral and injectable formulations) are relevant to one another. In addition to the above adverse reactions, the following adverse reaction has been noted with the use of paliperidone products and can be expected to occur with RISPERIDONE.

Cardiac disorders:

Postural orthostatic tachycardia syndrome

Class effects

As with other antipsychotics, very rare cases of QT prolongation have been reported post-marketing with risperidone. Other class-related cardiac effects reported with antipsychotics which prolong QT interval include ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia, sudden death, cardiac arrest and Torsades de Pointes.

Venous thromboembolism

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis, have been reported with antipsychotic drugs (frequency unknown).

Weight gain

The proportions of RISPERIDONE and placebo-treated adult patients with schizophrenia meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6- to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERIDONE (18%) compared to placebo (9%). In a pool of placebo-controlled 3-week studies in adult patients with acute mania, the incidence of weight increase of ≥ 7% at endpoint was comparable in the RISPERIDONE (2.5%) and placebo (2.4%) groups, and was slightly higher in the active-control group (3.5%).

In a population of children and adolescents with conduct and other disruptive behaviour disorders, in long-term studies, weight increased by a mean of 7.3 kg after 12 months of treatment. The expected weight gain for normal children between 5-12 years of age is 3 to 5 kg per year. From 12-16 years of age, this magnitude of gaining 3 to 5 kg per year is maintained for girls, while boys gain approximately 5 kg per year.

Additional information on special populations

Adverse drug reactions that were reported with higher incidence in elderly patients with dementia or paediatric patients than in adult populations are described below:

Elderly patients with dementia

Transient ischaemic attack and cerebrovascular accident were ADRs reported in clinical trials with a frequency of 1.4% and 1.5%, respectively, in elderly patients with dementia. In addition, the following ADRs were reported with a frequency ≥ 5% in elderly patients with dementia and with at least twice

the frequency seen in other adult populations: urinary tract infection, peripheral oedema, lethargy, and cough.

Paediatric population

In general, type of adverse reactions in children is expected to be similar to those observed in adults.

The following ADRs were reported with a frequency ≥ 5% in paediatric patients (5 to 17 years) and with at least twice the frequency seen in clinical trials in adults: somnolence/sedation, fatigue, headache, increased appetite, vomiting, upper respiratory tract infection, nasal congestion, abdominal pain, dizziness, cough, pyrexia, tremor, diarrhoea, and enuresis.

The effect of long-term risperidone treatment on sexual maturation and height has not been adequately studied.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

Symptoms:

In general, reported signs and symptoms have been those resulting from an exaggeration of the known pharmacological effects of risperidone. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, QT prolongation and convulsions have been reported. Torsade de Pointes has been reported in association with combined overdose of RISPERIDONE and paroxetine.

In case of acute overdose, the possibility of multiple drug 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 only when drug intake was less than one hour before. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to RISPERIDONE. Therefore, 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, an anticholinergic medicinal product should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5.0 Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Other antipsychotics, ATC code: N05AX08.

Mechanism of action:

Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT2 and dopaminergic D2 receptors. Risperidone binds also to alpha1-adrenergic receptors, and, with lower affinity, to H1-histaminergic and alpha2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D2 antagonist, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical antipsychotics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

Pharmacodynamic effects:

Clinical efficacy:

Schizophrenia:

The efficacy of risperidone in the short-term treatment of schizophrenia was established in four studies, 4 to 8 weeks in duration, which enrolled over 2,500 patients who met DSM-IV criteria for schizophrenia. In a 6-week, placebo-controlled trial involving titration of risperidone in doses up to 10 mg/day administered twice daily, risperidone was superior to placebo on the Brief Psychiatric Rating Scale (BPRS) total score. In an 8-week, placebo-controlled trial involving four fixed doses of risperidone (2, 6, 10, and 16 mg/day, administered twice daily), all four risperidone groups were superior to placebo on the Positive and Negative Syndrome Scale (PANSS) total score. In an 8-week, dose comparison trial involving five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day administered twice daily), the 4, 8, and 16 mg/day risperidone dose groups were superior to the 1 mg risperidone dose group on PANSS total score. In a 4-week, placebo-controlled dose comparison trial involving two fixed doses of risperidone (4 and 8 mg/day administered once daily), both risperidone dose groups were superior to placebo on several PANSS measures, including total PANSS and a response measure (> 20% reduction in PANSS total score). In a longer-term trial, adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medicinal product were randomised to risperidone 2 to 8 mg/day or to haloperidol for 1 to 2 years of observation for relapse. Patients receiving risperidone experienced a significantly longer time to relapse over this time period compared to those receiving haloperidol.

Manic episodes in bipolar disorder

The efficacy of risperidone monotherapy in the acute treatment of manic episodes associated with bipolar I disorder was demonstrated in three double-blind, placebo-controlled monotherapy studies in approximately 820 patients who had bipolar I disorder, based on DSM-IV criteria. In the three studies, risperidone 1 to 6 mg/day (starting dose 3 mg in two studies and 2 mg in one study) was shown to be significantly superior to placebo on the pre-specified primary endpoint, i.e., the change from baseline in total Young Mania Rating Scale (YMRS) score at week 3. Secondary efficacy outcomes were

generally consistent with the primary outcome. The percentage of patients with a decrease of ≥ 50% in total YMRS score from baseline to the 3-week endpoint was significantly higher for risperidone than for placebo. One of the three studies included a haloperidol arm and a 9-week double-blind maintenance phase. Efficacy was maintained throughout the 9-week maintenance treatment period. Change from baseline in total YMRS showed continued improvement and was comparable between risperidone and haloperidol at week 12.

The efficacy of risperidone in addition to mood stabilisers in the treatment of acute mania was demonstrated in one of two 3-week double-blind studies in approximately 300 patients who met the DSM-IV criteria for bipolar I disorder. In one 3-week study, risperidone 1 to 6 mg/day starting at 2 mg/day in addition to lithium or valproate was superior to lithium or valproate alone on the pre-specified primary endpoint, i.e., the change from baseline in YMRS total score at week 3. In a second 3-week study, risperidone 1 to 6 mg/day starting at 2 mg/day, combined with lithium, valproate, or carbamazepine was not superior to lithium, valproate, or carbamazepine alone in the reduction of YMRS total score. A possible explanation for the failure of this study was induction of risperidone and 9-hydroxy-risperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxy-risperidone. When the carbamazepine group was excluded in a post-hoc analysis, risperidone combined with lithium or valproate was superior to lithium or valproate alone in the reduction of YMRS total score.

Persistent aggression in dementia

The efficacy of risperidone in the treatment of Behavioural and Psychological Symptoms of Dementia (BPSD), which includes behavioural disturbances, such as aggressiveness, agitation, psychosis, activity, and affective disturbances was demonstrated in three double-blind, placebo-controlled studies in 1,150 elderly patients with moderate to severe dementia. One study included fixed Risperidone doses of 0.5, 1, and 2mg/day. Two flexible-dose studies included Risperidone dose groups in the range of 0.5 to 4 mg/day and 0.5 to 2mg/day, respectively. Risperidone showed statistically significant and clinically important effectiveness in treating aggression and less consistently in treating agitation and psychosis in elderly dementia patients (as measured by the Behavioural Pathology in Alzheimer's disease Rating Scale [BEHAVE-AD] and the Cohen-Mansfield Agitation Inventory [CMAI]). The treatment effect of risperidone was independent of Mini-Mental State Examination (MMSE) score (and consequently of the severity of dementia); of sedative properties of risperidone; of the presence or absence of psychosis; and of the type of dementia, Alzheimer's, vascular, or mixed.

Paediatric population

Conduct disorder

The efficacy of risperidone in the short-term treatment of disruptive behaviours was demonstrated in two double-blind placebo-controlled studies in approximately 240 patients 5 to 12 years of age with a DSM-IV diagnosis of disruptive behaviour disorders (DBD) and borderline intellectual functioning or

mild or moderate mental retardation/learning disorder. In the two studies, risperidone 0.02 to 0.06 mg/kg/day was significantly superior to placebo on the pre-specified primary endpoint, i.e., the change from baseline in the Conduct Problem subscale of the Nisonger-Child Behaviour Rating Form (N-CBRF) at week 6.

5.2 Pharmacokinetic Properties

Risperidone is metabolised to 9-hydroxy-risperidone, which has a similar pharmacological activity to risperidone.

Absorption

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) compared with a solution. The absorption is not affected by food and thus risperidone can be given with or without meals. Steady-state of risperidone is reached within 1 day in most patients. Steady-state of 9-hydroxy-risperidone is reached within 4-5 days of dosing.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 l/kg. In plasma, risperidone is bound to albumin and alpha1-acid glycoprotein. The plasma protein binding of risperidone is 90%, that of 9-hydroxy-risperidone is 77%.

Biotransformation and elimination

Risperidone is metabolised by CYP2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxy-risperidone form the active antipsychotic fraction. CYP2D6 is subject to genetic polymorphism. Extensive CYP2D6 metabolisers convert risperidone rapidly into 9-hydroxy-risperidone, whereas poor CYP2D6 metabolisers convert it much more slowly. Although extensive metabolisers have lower risperidone and higher 9-hydroxy-risperidone concentrations than poor metabolisers, the pharmacokinetics of risperidone and 9-hydroxy-risperidone combined (i.e., the active antipsychotic fraction), after single and multiple doses, are similar in extensive and poor metabolisers of CYP2D6.

Another metabolic pathway of risperidone is N-dealkylation. In vitro studies in human liver microsomes showed that risperidone at clinically relevant concentration does not substantially inhibit the metabolism of medicines metabolised by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. One week after administration, 70% of the dose is excreted in the urine and 14% in the faeces. In urine, risperidone plus 9-hydroxy-risperidone represent 35-45% of the dose. The remainder is inactive metabolites. After oral administration to psychotic patients, risperidone is eliminated with a half-life of about 3 hours. The elimination half-life of 9-hydroxy-risperidone and of the active antipsychotic fraction is 24 hours.

Linearity/non-linearity

Risperidone plasma concentrations are dose-proportional within the therapeutic dose-range.

Elderly, hepatic and renal impairment

A single-dose PK-study with oral risperidone showed on average a 43% higher active antipsychotic fraction plasma concentrations, a 38% longer half-life and a reduced clearance of the active antipsychotic fraction by 30% in the elderly.

In adults with moderate renal disease the clearance of the active moiety was ~48% of the clearance in young healthy adults. In adults with severe renal disease the clearance of the active moiety was ~31% of the clearance in young healthy adults. The half-life of the active moiety was 16.7 h in young adults, 24.9 h in adults with moderate renal disease (or ~1.5 times as long as in young adults), and 28.8 h in those with severe renal disease (or ~1.7 times as long as in young adults). Risperidone plasma concentrations were normal in patients with liver insufficiency, but the mean free fraction of Risperidone in plasma was increased by 37.1%.

The oral clearance and the elimination half-life of Risperidone and of the active moiety in adults with moderate and severe liver impairment were not significantly different from those parameters in young healthy adults.

Paediatric population

The pharmacokinetics of Risperidone, 9-hydroxy-risperidone and the active antipsychotic fraction in children are similar to those in adults.

Gender, race and smoking habits

A population pharmacokinetic analysis revealed no apparent effect of gender, race or smoking habits on the pharmacokinetics of Risperidone or the active antipsychotic fraction.

5.3 Preclinical Safety Data

Not Available

6.0 Pharmaceutical Particulars

6.1 List of Excipients

Maize Starch, Lactose Monohydrate, Calcium hydrogen phosphate, Povidone K-30, Purified Talc, Magnesium Stearate, Croscarmellose Sodium, Colour Brilliant Blue Lake, Opadry white

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

Store at a temperature not exceeding 30°C.

6.5 Nature and Contents of Container

Packing: Alu-PVC blister of 10 tablets, further 3 blisters of each 10 tablets packed in a carton along with product leaflet.

6.6 Special precautions for disposal

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

7. Applicant/Manufacturer

7.0 Applicant/Manufacturer

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8. NAFDAC Registration Number: A4-6114