For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

ZISPER FORTE

1.Generic Name

Risperidone & Trihexyphenidyl Hydrochloride Mouth Dissolving Tablets

2. Qualitative and quantitative composition

Each mouth dissolving uncoated tablet contains:

Risperidone B.P.....….4 mg

Trihexyphenidyl Hydrochloride I.P…….2 mg

Excipients ……...…..... q.s.,

Colour: Lake Sunset Yellow FCF

The excipients used are Lactose, Mannitol, Micro Crystalline Cellulose, Colour Lake Sunset Yellow FCF, Acetone, Ethyl Cellulose, Isopropyl Alcohol, Talcum, Flavour Mix Fruit DC 130 PH, Aspartame, Croscarmellose Sodium, Magnesium Stearate.

3. Dosage form and strength

Dosage form: Uncoated Tablet

Strength Risperidone 4 mg and Trihexyphenidyl Hydrochloride 2 mg

4. Clinical particulars

4.1 Therapeutic indication

ZISPER FORTE is indicated for the treatment of schizophrenia.

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

ZISPER FORTE 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.

ZISPER FORTE 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.

Trihexyphenidyl Hydrochloride is used to treat extrapyramidal symptoms of Risperidone

4.2 Posology and method of administration

Posology

Dosage: As directed by the Physician

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients

4.4 Special warnings and precautions for use

Risperidone

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 $< 1 \times 10^9$/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.

For specific posology recommendations in children and adolescents see Posology and method of administration.

Trihexyphenidyl Hydrochloride

Precautions: Since the use of trihexyphenidyl may, in some cases, continue indefinitely, the patient should be under careful observation over the long term. It should be administered with care to avoid allergic or other untoward reactions.

Except in the case of vital complications, abrupt discontinuation of the drug should be avoided.

Incipient glaucoma may be precipitated by para-sympatholytic drugs such as trihexyphenidyl.

Hypertension, cardiac, liver or kidney disorders are not contra-indicated, but such patients should be followed closely. As trihexyphenidyl may provoke or exacerbate tardive dyskinesia, it is not recommended for use in patients with this condition.

Trihexyphenidyl should be used with caution in patients with glaucoma, obstructive disease of the gastro-intestinal or genito-urinary tracts, and in elderly males with possible prostatic hypertrophy.

Since trihexyphenidyl has been associated with the clinical worsening of myasthenia gravis, the drug should be avoided or used with great caution in patients with this condition.

Since certain psychiatric manifestations such as confusion, delusions and hallucinations, all of which may occur with any of the atropine-like drugs, have been reported rarely with trihexyphenidyl, it should be used with extreme caution in elderly patients (see Dosage and Administration).

Warnings: Trihexyphenidyl may be the subject of abuse (on the basis of hallucinogenic or euphoria properties, common to all anti-cholinergic drugs) if given in sufficient amounts.

4.5 Drugs interactions

Risperidone

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 200 mg/day increased the plasma concentrations of the active antipsychotic fraction by about 70%, at risperidone doses of 2 to 8 mg/day.

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

Antipsychotics:

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

Antivirals:

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

Beta-blockers:

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

Calcium channel blockers:

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

Gastrointestinal drugs:

● 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.

<u>Effect of risperidone on the pharmacokinetics of other medicinal products</u>

Antiepileptics:

● Risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate or topiramate.

Antipsychotics:

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

Digitalis glycosides:

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

Lithium:

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

Concomitant use of risperidone with furosemide

● See Special warnings and precautions for use regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

Trihexyphenidyl Hydrochloride

Extra care should be taken when trihexyphenidyl is given concomitantly with phenothiazines, clozapine, antihistamines, disopyramide, nefopam and amantadine because of the possibility of increased antimuscarinic side-effects.

Synergy has been reported between trihexyphenidyl and tricyclic antidepressants, probably because of an additive effect at the receptor site. This can cause dry mouth, constipation and blurred vision. In the elderly, there is a danger of precipitating urinary retention, acute glaucoma or paralytic ileus.

Monoamine oxidase inhibitors can interact with concurrently administered anticholinergic agents including trihexyphenidyl. This can cause dry mouth, blurred vision, urinary hesitancy, urinary retention and constipation.

In general, anticholinergic agents should be used with caution in patients who are receiving tricyclic antidepressants or monoamine oxidase inhibitors. In patients who are already on antidepressant therapy the dose of trihexyphenidyl should be initially reduced and the patient reviewed regularly.

Trihexyphenidyl may be antagonistic with the actions of metoclopramide and domperidone on gastro-intestinal function.

The absorption of levodopa may possibly be reduced when used in conjunction with trihexyphenidyl.

Trihexyphenidyl may be antagonistic with the actions of parasympathomimetics.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Risperidone

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.

Trihexyphenidyl Hydrochloride

Pregnancy: There is inadequate information regarding the use of trihexyphenidyl in pregnancy. Animal studies are insufficient with regard to effects on pregnancy, embryonal/foetal development, parturition and postnatal development. The potential risk for humans is unknown. Trihexyphenidyl should not be used during pregnancy unless clearly necessary.

Lactation: It is unknown whether trihexyphenidyl is excreted in human breast milk. The excretion of trihexyphenidyl in milk has not been studies in animals. Infants may be very sensitive to the effects of antimuscarinic medications. Trihexyphenidyl should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Risperidone

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.

Trihexyphenidyl Hydrochloride

Can cause blurring of vision, dizziness and mild nausea. Also mental confusion in some cases.

4.8 Undesirable effects

Risperidone

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 infection, influenza	respiratory tract infection, cystitis, eye infection, tonsillitis, onychomycosis, cellulitis localised infection, viral infection, acarodermatitis	infection	
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		inappropriate antidiuretic hormone secretion, glucose urine present	
Metabolism and nutrition		weight increased, increased	diabetes mellitus[b],	water intoxication[c],	diabetic ketoacidos

disorders		appetite, decreased appetite	hyperglycaemia, polydipsia, weight decreased, anorexia, blood cholesterol increased	hypoglycaemia, hyperinsulinaemia[c], blood triglycerides increased	is
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	akathisia[d], dystonia[d], dizziness, dyskinesia[d], tremor	tardive dyskinesia, cerebral ischaemia, unresponsive to stimuli, loss of consciousness, depressed level of consciousness, convulsion[d], syncope, psychomotor hyperactivity, balance disorder, coordination abnormal, dizziness postural, disturbance in attention, dysarthria, dysgeusia, hypoaesthesia, paraesthesia	neuroleptic malignant syndrome, cerebrovascular disorder, diabetic coma, head titubation	
Eye disorders		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, flushing	pulmonary embolism, venous 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		rash, erythema	urticaria,	drug eruption,	angioedem

subcutaneous tissue disorders			pruritus, alopecia, hyperkeratosis, eczema, dry skin, skin discolouration, acne, seborrhoeic dermatitis, skin disorder, skin lesion	dandruff	a
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 neonatal[c]	
Reproductive system and breast disorders			erectile dysfunction, ejaculation disorder, amenorrhoea, menstrual disorder[d], gynaecomastia, galactorrhoea, sexual dysfunction, breast pain, breast discomfort,	priapism[c], menstruation delayed, breast engorgement, breast enlargement, breast discharge	

			vaginal discharge		
General disorders and administration site conditions		oedema[d], 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, induration[c]	
Hepatobiliary disorders			transaminases increased, gamma-glutamyltransferase increased, hepatic enzyme increased	jaundice	
Injury, poisoning and procedural complications		fall	procedural pain		

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

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

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

[d] Extrapyramidal disorder may occur: **Parkinsonism** (salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies, muscle tightness, akinesia, nuchal rigidity, muscle rigidity, parkinsonian gait, and glabellar reflex abnormal, parkinsonian rest tremor), **akathisia** (akathisia, restlessness, hyperkinesia, and restless leg syndrome), tremor, **dyskinesia** (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia. **Dystonia** includes dystonia, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus. It should be noted that a broader spectrum of symptoms is 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 (see subsection "Paediatric population").

Trihexyphenidyl Hydrochloride

Modern clinical data required to determine the frequency of undesirable effects are lacking for trihexyphenidyl. Minor side effects such as dryness of mouth, constipation, blurring of vision, dizziness, mild nausea or nervousness will be experienced by 30-50% of all patients. These reactions tend to become less pronounced as treatment continues. Patients should be allowed to develop a tolerance using the smaller initial dose until an effective level is reached.

Immune system disorders: Hypersensitivity.

Psychiatric disorders: Nervousness, restlessness, confusional states, agitation, delusions, hallucinations, insomnia, especially in the elderly and patients with arteriosclerosis. The development of psychiatric disturbances may necessitate discontinuation of treatment.

Euphoria may occur. There have been reports of abuse of trihexyphenidyl due to its euphoric and hallucinogenic properties.

Nervous system disorders: Dizziness.

Impairment of immediate and short-term memory function has been reported.

Worsening of myasthenia gravis may occur.

Eye disorders: Dilatation of the pupils with loss of accommodation and photophobia, raised intraocular pressure.

Cardiac disorders: Tachycardia.

Respiratory, thoracic and mediastinal disorders: Decreased bronchial secretions.

Gastrointestinal disorders: Dry mouth with difficulty swallowing, constipation, nausea, vomiting.

Skin and subcutaneous tissue disorders: Flushing and dryness of skin, skin rashes.

Renal and urinary disorders: Urinary retention, difficulty in micturition.

General disorders: Thirst, pyrexia.

4.9 Overdose

Risperidone

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.

Trihexyphenidyl Hydrochloride

Symptoms: Symptoms of overdose with antimuscarinic agents include flushing and dryness of the skin, dilated pupils, dry mouth and tongue, tachycardia, rapid respiration, hyperpyrexia, hypertension, nausea, vomiting. A rash may appear on the face or upper trunk. Symptoms of CNS stimulation include restlessness, confusion, hallucinations, paranoid and psychotic reactions, incoordination, delirium and occasionally convulsions. In severe overdose, CNS depression may occur with coma, circulatory and respiratory failure and death.

Treatment: Treatment should always be supportive. An adequate airway should be maintained. Diazepam may be administered to control excitement and convulsions but the risk of central nervous system depression should be considered. Hypoxia and acidosis should be corrected. Antiarrhythmic drugs are not recommended if dysrhythmias occur.

CLINICAL PHARMACOLOGY

Risperidone

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-HT_2 and dopaminergic D_2 receptors. Risperidone binds also to alpha$_1$-adrenergic receptors, and, with lower affinity, to H_1-histaminergic and alpha$_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent

D_2 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 sub therapeutic 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 2 mg/day. Two flexible-dose studies included risperidone dose groups in the range of 0.5 to 4 mg/day and 0.5 to 2 mg/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. Pharmacological properties

5.1 Mechanism of Action

Risperidone

Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT_2 and dopaminergic D_2 receptors. Risperidone binds also to alpha$_1$-adrenergic receptors, and, with lower affinity, to H_1-histaminergic and alpha$_2$-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent

D_2 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.

Trihexyphenidyl Hydrochloride

Trihexyphenidyl hydrochloride is an anticholinergic agent.

5.2 Pharmacodynamic properties

RISPERIDONE

Clinical efficacy

Schizophrenia

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<u>Paediatric population</u>

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.

Trihexyphenidyl Hydrochloride

Trihexyphenidyl hydrochloride is an anticholinergic agent. It is an antispasmodic drug which exerts a direct inhibitory effect on the parasympathetic nervous system. It diminishes salivation, increases the heart rate, dilates the pupils and reduces spasm of smooth muscle.

5.3 Pharmacokinetic properties

RISPERIDONE

RISPERIDONE orodispersible tablets and oral solution are bioequivalent to RISPERIDONE film-coated tablets. Risperidone is metabolised to 9-hydroxy-risperidone, which has a similar pharmacological activity to risperidone (see *Biotransformation and Elimination*).

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 $alpha_1$-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.

Pharmacokinetic properties

Trihexyphenidyl hydrochloride is well absorbed from the gastrointestinal tract. It disappears rapidly from the plasma and tissues and does not accumulate in the body during continued administration of conventional doses.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Risperidone

In (sub)chronic toxicity studies, in which dosing was started in sexually immature rats and dogs, dose-dependent effects were present in male and female genital tract and mammary gland. These effects were related to the increased serum prolactin levels, resulting from the dopamine D_2 receptor blocking activity of risperidone. In addition, tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Risperidone was not teratogenic in rat and rabbit. In rat reproduction studies with risperidone, adverse effects were seen on mating behaviour of the parents, and on the birth weight and survival of the offspring. In rats, intrauterine exposure to risperidone was associated with cognitive deficits in adulthood. Other dopamine antagonists, when administered to pregnant animals, have caused negative effects on

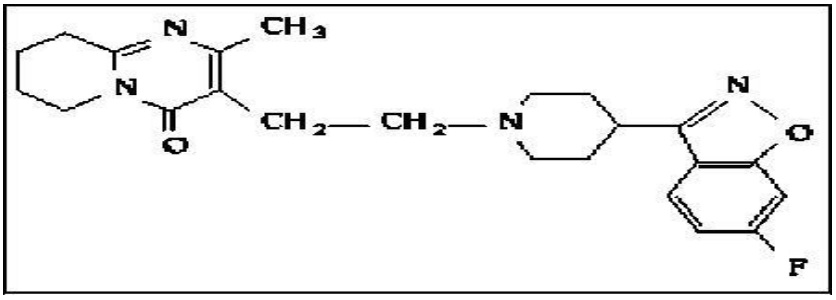
learning and motor development in the offspring. In a toxicity study in juvenile rats, increased pup mortality and a delay in physical development was observed. In a 40-week study with juvenile dogs, sexual maturation was delayed. Based on AUC, long bone growth was not affected in dogs at 3.6-times the maximum human exposure in adolescents (1.5 mg/day); while effects on long bones and sexual maturation were observed at 15 times the maximum human exposure in adolescents.

Risperidone was not genotoxic in a battery of tests. In oral carcinogenicity studies of risperidone in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were seen. These tumours can be related to prolonged dopamine D_2 antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown. *In vitro* and *in vivo*, animal models show that at high doses risperidone may cause QT interval prolongation, which has been associated with a theoretically increased risk of Torsade de Pointes in patients.

7. Description

Risperidone

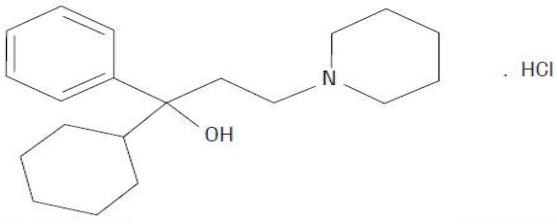
Risperidone is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a] pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

Trihexyphenidyl Hydrochloride

Trihexyphenidyl Hydrochloride is a synthetic antispasmodic drug. It is designated chemically as α-Cyclohexylα-phenyl-1-piperidinepropanol hydrochloride. Its molecular formula is $C_{20}H_{31}NO$, HCl and its molecular weight is 337.9. The structural formula is:



Trihexyphenidyl Hydrochloride occurs as a white or creamy-white, almost odourless, crystalline powder. It is soluble in ethanol (95%), in methanol and in chloroform; slightly soluble in water.

Risperidone & Trihexyphenidyl Hydrochloride Mouth Dissolving Tablets are Orange coloured, oval shaped, slightly biconvex, uncoated mouth dissolving tablets scored on one side in the middle. The excipients used are Lactose, Mannitol, Micro Crystalline Cellulose, Colour Lake Sunset Yellow FCF, Acetone, Ethyl Cellulose, Isopropyl Alcohol, Talcum, Flavour Mix Fruit DC 130 PH, Aspartame, Croscarmellose Sodium, Magnesium Stearate.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

ZISPER FORTE is available in Blister strip of 10 Tablets

8.4 Storage and handing instructions

Store in a cool, dry place. Protect from light. Keep all medicines out of reach of children.

9. Patient Counselling Information

Package leaflet: Information for the user

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist.

This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

.1. What ZISPER FORTE is and what it is used for

1. What ZISPER FORTE is and what it is used for

ZISPER FORTE is combination of Risperidone and Trihexyphenidyl Hydrochloride. Risperidone (belongs to a group of medicines called 'antipsychotics) . Trihexyphenidyl is an antispasmodic (muscle relaxing) drug it improves muscle control and reduces stiffness. Used to treat muscle disorder (muscle spasm).

ZISPER FORTE is used to treat the following:

• Schizophrenia, where you may see, hear or feel things that are not there, believe things that are not true or feel unusually suspicious, or confused

• Mania, where you may feel very excited, elated, agitated, enthusiastic or hyperactive. Mania occurs in an illness called "bipolar disorder"

• Short-term treatment (up to 6 weeks) of long-term aggression in people with Alzheimer's dementia, who harm themselves or others. Alternative (non-drug) treatments should have been used previously

• Short-term treatment (up to 6 weeks) of long-term aggression in intellectually disabled children (at least 5 years of age) and adolescents with conduct disorder.

ZISPER FORTE can help alleviate the symptoms of your disease and stop your symptoms from coming back.

2. What you need to know before you take ZISPER FORTE

Do not take ZISPER FORTE

• If you are allergic (hypersensitive) to risperidone or any of the other ingredients of this medicine.

Take special care if you have

Glaucoma

Heart, liver, kidney disease or suffer from high blood pressures

Prostrate problems,

Trouble passing urine

Suffer condition called myasthenia gravis

Suffer from tardive dyskinesia

Warnings and precautions

Talk to your doctor or pharmacist before taking ZISPER FORTE if:

If you are not sure if the above applies to you, talk to your doctor or pharmacist before using ZISPER FORTE.

• You have a heart problem. Examples include an irregular heart rhythm or if you are prone to low blood pressure or if you are using medicines for your blood pressure. ZISPER FORTE may cause low blood pressure. Your dose may need to be adjusted

• You know of any factors which would favour you having a stroke, such as high blood pressure, cardiovascular disorder or blood vessel problems in the brain

• You have ever experienced involuntary movements of the tongue, mouth and face

• You have ever had a condition whose symptoms include high temperature, muscle stiffness, sweating or a lowered level of consciousness (also known as Neuroleptic Malignant Syndrome)

• You have Parkinson's disease or dementia

• You know that you have had low levels of white blood cells in the past (which may or may not have been caused by other medicines)

• You are diabetic

• You have epilepsy

• You are a man and you have ever had a prolonged or painful erection

• You have problems controlling your body temperature or overheating

• You have kidney problems

• You have liver problems

• You have an abnormally high level of the hormone prolactin in your blood or if you have a possible prolactin-dependent tumour.

• You or someone else in your family has a history of blood clots, as antipsychotics have been associated with formation of blood clots.

If you are not sure if any of the above applies to your doctor or pharmacist before using ZISPER FORTE. As dangerously low numbers of a certain type of white blood cell needed to fight infection in your blood has been seen very rarely with patients taking ZISPER FORTE, your doctor may check your white blood cell counts. ZISPER FORTE may cause you to gain weight. Significant weight gain may adversely affect your health. Your doctor should regularly measure your body weight. As diabetes mellitus or worsening of pre-existing diabetes mellitus have been seen with patients taking ZISPER FORTE, your doctor should check for signs of high blood sugar. In patients with pre-existing diabetes mellitus blood glucose should be monitored regularly. ZISPER FORTE commonly raises levels of a hormone called "prolactin". This may cause side effects such as menstrual disorders or fertility problems in women, breast swelling in men (see Possible side effects). If such side effects occur, evaluation of the prolactin level in the blood is recommended. During an operation on the eye for cloudiness of the lens (cataract), the pupil (the black circle in the middle of your eye) may not increase in size as needed. Also, the iris (the coloured part of the eye) may become floppy during surgery and that may lead to eye damage. If you are planning to have an operation on your eye, make sure you tell your eye doctor that you are taking this medicine.

Elderly people with dementia In elderly patients with dementia, there is an increased risk of stroke. You should not take risperidone if you have dementia caused by stroke. During treatment with risperidone you should frequently see your doctor. Medical treatment should be sought straight away if you or your caregiver notice a sudden change in your mental state or sudden weakness or numbness of your face, arms or legs, especially on one side, or slurred speech, even for a short period of time. These may be signs of a stroke.

Children and adolescents Before treatment is started for conduct disorder, other causes of aggressive behaviour should have been ruled out.

If during treatment with risperidone tiredness occurs, a change in the time of administration might improve attention difficulties. Before treatment is started your, or your child’s body weight may be measured and it may be regularly monitored during treatment. A small and inconclusive study has reported an increase in height in children who took risperidone, but whether this is an effect of the drug or due to some other reason is not known.

Other medicines and ZISPER FORTE

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. It is especially important to talk to your doctor or pharmacist if you are taking any of the following

• Medicines that work on your brain such as to help you calm down (benzodiazepines) or some

medicines for pain (opiates), medicines for allergy (some antihistamines), as risperidone may increase the sedative effect of all of these

• Medicines that may change the electrical activity of your heart, such as medicines for malaria, heart rhythm problems, allergies (antihistamines), some antidepressants or other medicines for mental problems

• Medicines that cause a slow heart beat

• Medicines that cause low blood potassium (such as certain diuretics)

• Medicines to treat raised blood pressure. ZISPER FORTE can lower blood pressure

• Medicines for Parkinson's disease (such as levodopa)

• Medicines that increase the activity of the central nervous system (psychostimulants, such as methylphenidate)

• Water tablets (diuretics) used for heart problems or swelling of parts of your body due to a build-up of too much fluid (such as furosemide or chlorothiazide). ZISPER FORTE taken by itself or with furosemide, may have an increased risk of stroke or death in elderly people with dementia.

The following medicines may reduce the effect of risperidone

• Rifampicin (a medicine for treating some infections)

• Carbamazepine, phenytoin (medicines for epilepsy)

• Phenobarbital.

If you start or stop taking such medicines you may need a different dose of risperidone.

The following medicines may increase the effect of risperidone

• Quinidine (used for certain types of heart disease)

• Antidepressants such as paroxetine, fluoxetine, tricyclic antidepressants

• Medicines known as beta-blockers (used to treat high blood pressure)

• Phenothiazines (such as medicines used to treat psychosis or to calm down)

• Cimetidine, ranitidine (blockers of the acidity of stomach)

• Itraconazole and ketoconazole (medicines for treating fungal infections)

• Certain medicines used in the treatment of HIV/AIDS, such as ritonavir

• Verapamil, a medicine used to treat high blood pressure and/or abnormal heart rhythm

• Sertraline and fluvoxamine, medicines used to treat depression and other psychiatric disorders.

If you start or stop taking such medicines, you may need a different dose of risperidone.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using ZISPER FORTE. Monoamine oxidase inhibitor or tricyclic antidepressant eg. Amitriptyline for treatment of depression.\

Phenothiazine (chlorpromazine, chlorpromazine, thioridazine) or clozapine for the treatment of mental illness. Antihistamine for treatment of allergies

Disopyramide for the treatment of Parkinson's disease

Amantadine for viral infection

Nefopam a pain killer

Metoclopramide or domperidone

Parasympathomimetic (e.g neostigmine, Bethan idol) for the treatment of urinary retention

Pregnancy, breast-feeding and fertility

• If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will decide if you can take it

• The following symptoms may occur in newborn babies, of mothers that have used ZISPER FORTE in the last trimester (last three months of their pregnancy): shaking, muscle stiffness, and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

• ZISPER FORTE can raise your levels of a hormone called "prolactin" that may impact fertility (see Possible side effects).

Driving and using machines

Dizziness, tiredness, and vision problems may occur during treatment with ZISPER FORTE. Do not drive or use any tools or machines without talking to your doctor first.

3. How to take ZISPER FORTE

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dosage: As directed by the Physician
People with kidney or liver problems
Regardless of the disease to be treated, all starting doses and following doses of risperidone should be halved. Dose increases should be slower in these patients.
Risperidone should be used with caution in this patient group.
Method of administration
For oral use
• You should swallow your tablet with a drink of water
If you take more ZISPER FORTE than you should
• See a doctor right away. Take the medicine pack with you
• In case of overdose you may feel sleepy or tired, or have abnormal body movements, problems standing and walking, feel dizzy due to low blood pressure, or have abnormal heartbeats or fits.

If you forget to take **ZISPER FORTE**

• If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose and continue as usual. If you miss two or more doses, contact your doctor
• Do not take a double dose (two doses at the same time) to make up for a forgotten dose

If you stop taking ZISPER FORTE

You should not stop taking this medicine unless told to do so by your doctor. Your symptoms may return. If your doctor decides to stop this medicine, your dose may be decreased gradually over a few days. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you experience any of the following uncommon side effects (may affect up to 1 in 100 people):

• Have dementia and experience a sudden change in your mental state or sudden weakness or numbness of your face, arms or legs, especially on one side, or slurred speech, even for a short period of time. These may be signs of a stroke

• Experience tardive dyskinesia (twitching or jerking movements that you cannot control in your face, tongue, or other parts of your body). Tell your doctor immediately if you experience

involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of ZISPER FORTE may be needed

Tell your doctor immediately if you experience any of the following rare side effects (may affect up to 1 in 1,000 people):

• Experience blood clots in the veins, especially in the legs (symptoms include swelling, pain, and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty breathing. If you notice any of these symptoms seek medical advice immediately

• Experience fever, muscle stiffness, sweating or a lowered level of consciousness (a disorder called “Neuroleptic Malignant Syndrome”). Immediate medical treatment may be needed

• Are a man and experience prolonged or painful erection. This is called priapism. Immediate medical treatment may be needed

• Experience severe allergic reaction characterised by fever, swollen mouth, face, lip or tongue,

shortness of breath, itching, skin rash or drop in blood pressure.

Dryness of mouth

Constipation

Blurred vision

Feeling of sick or nervous

The following other side effects may also happen:

Very common side effects (may affect more than 1 in 10 people):

• Difficulty falling or staying asleep

• Parkinsonism: This condition may include: slow or impaired movement, sensation of stiffness or tightness of the muscles (making your movements jerky), and sometimes even a sensation of

movement "freezing up" and then restarting. Other signs of parkinsonism include a slow shuffling walk, a tremor while at rest, increased saliva and/or drooling, and a loss of expression on the face

• Feeling sleepy, or less alert

• Headache.

Common side effects (may affect up to 1 in 10 people):

• Pneumonia, infection of the chest (bronchitis), common cold symptoms, sinus infection, urinary tract infection, ear infection, feeling like you have the flu

• Raised levels of a hormone called "prolactin" found in a blood test (which may or may not cause symptoms). Symptoms of high prolactin occur uncommonly and may include in men breast swelling, difficulty in getting or maintaining erections, decreased sexual desire or other sexual dysfunction. In women they may include breast discomfort, leakage of milk from the breasts, missed menstrual periods, or other problems with your cycle or fertility problems

• Weight gain, increased appetite, decreased appetite

• Sleep disorder, irritability, depression, anxiety, restlessness

• Dystonia: This is a condition involving slow or sustained involuntary contraction of muscles. While it can involve any part of the body (and may result in abnormal posture), dystonia often involves muscles of the face, including abnormal movements of the eyes, mouth, tongue or jaw

• Dizziness

• Dyskinesia: This is a condition involving involuntary muscle movements, and can include repetitive, spastic or writhing movements, or twitching

Tremor (shaking)

• Blurry vision, eye infection or "pink eye"

• Rapid heart rate, high blood pressure, shortness of breath

• Sore throat, cough, nose bleeds, stuffy nose

• Abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhea, indigestion, dry mouth, toothache

• Rash, skin redness

• Muscle spasms, bone or muscle ache, back pain, joint pain

• Incontinence (lack of control) of urine

• Swelling of the body, arms or legs, fever, chest pain, weakness, fatigue (tiredness), pain

• Fall.

Uncommon side effects (may affect up to 1 in 100 people):

• Infection of the breathing passages, bladder infection, ‘eye infection, tonsillitis, fungal infection of the nails, infection of the skin, an infection confined to a single area of skin or part of the body, viral infection, skin inflammation caused by mites

• Decrease in the type of white blood cells that help to protect you against infection, white blood cell count decreased, decrease in platelets (blood cells that help you stop bleeding), anemia, decrease in red blood cells, increase in eosinophils (a type of white blood cell) in your blood

• Allergic reaction

• Diabetes or worsening of diabetes, high blood sugar, excessive drinking of water

• Weight loss, loss of appetite resulting in malnutrition and low body weight

• Increased cholesterol in your blood

• Elated mood (mania), confusion, decreased sexual drive, nervousness, nightmares

• Unresponsive to stimuli, loss of consciousness, low level of consciousness

• Convulsion (fits), fainting

• A restless urge to move parts of your body, balance disorder, abnormal coordination, dizziness upon standing, disturbance in attention, problems with speech, loss or abnormal sense of taste, reduced sensation of skin to pain and touch, a sensation of tingling, pricking, or numbness skin

• Oversensitivity of the eyes to light, dry eye, increased tears, redness of the eyes

• Sensation of spinning (vertigo), ringing in the ears, ear pain

• Atrial fibrillation (an abnormal heart rhythm), an interruption in conduction between the upper and lower parts of the heart, Abnormal electrical conduction of the heart, prolongation of the QT interval from your heart, slow heart rate, abnormal electrical tracing of the heart (electrocardiogram or ECG), a fluttering or pounding feeling in your chest (palpitations)

• Low blood pressure, low blood pressure upon standing (consequently, some people taking ZISPER FORTE may feel faint, dizzy, or may pass out when they stand up or sit up suddenly, flushing

• Pneumonia caused by inhaling food, lung congestion, congestion of breathing passages, crackly lung sounds, wheezing, voice disorder, breathing passage disorder

• Stomach or intestinal infection, stool incontinence, very hard stool, difficulty swallowing, Excessive passing of gas or wind

• Hives (or "nettle rash"), itching, hair loss, thickening of skin, eczema, dry skin, skin discoloration, acne, flaky, itchy scalp or skin, skin disorder, skin lesion

• An increase of CPK (creatine phosphokinase) in your blood, an enzyme which is sometimes released with muscle breakdown

• Abnormal posture, joint stiffness, joint swelling, muscle weakness, neck pain

• Frequent passing of urine, inability to pass urine, pain when passing urine

• Erectile dysfunction, ejaculation disorder

• Loss of menstrual periods, missed menstrual periods or other problems with your cycle (females)

• Development of breasts in men, leakage of milk from the breasts, sexual dysfunction, breast pain, Breast discomfort, Vaginal discharge

• Swelling of the face, mouth, eyes, or lips

• Chills, an increase in body temperature

• A change in the way you walk

• Feeling thirsty, feeling unwell, chest discomfort, feeling "out of sorts", discomfort

• Increased liver transaminases in your blood, increased GGT (a liver enzyme called gammaglutamyltransferase in your blood, increased liver enzymes in your blood

• Procedural pain.

Rare side effects (may affect up to 1 in 1,000 people):

• Infection

• Inappropriate secretion of a hormone that controls urine volume

• Sleep walking

• Sleep-related eating disorder

• Sugar in the urine, low blood sugar, high blood triglycerides (a fat)

• Lack of emotion, inability to reach orgasm

• Not moving or responding while awake (catatonia)

• Blood vessel problems in the brain

• Coma due to uncontrolled diabetes

• Shaking of the head

• Glaucoma (increased pressure within the eyeball), problems with movement of your eyes, eye rolling, eyelid margin crusting

• Eye problems during cataract surgery. During cataract surgery, a condition called intraoperative floppy iris syndrome (IFIS) can happen if you take or have taken ZISPER FORTE. If you need to have cataract surgery, be sure to tell your eye doctor if you take or have taken this medicine

• Dangerously low numbers of a certain type of white blood cell needed to fight infection in your blood

• Dangerously excessive intake of water

• Irregular heart beat

• Trouble breathing during sleep (sleep apnea), fast, shallow breathing

• Inflammation of the pancreas, a blockage in the bowels

• Swollen tongue, chapped lips, rash on skin related to drug

• Dandruff

• Breakdown of muscle fibers and pain in muscles (rhabdomyolysis)

• A delay in menstrual periods, enlargement of the glands in your breasts, breast enlargement, discharge from the breasts

• Increased insulin (a hormone that controls blood sugar levels) in your blood

• Hardening of the skin

• Decreased body temperature, coldness in arms and legs

• Symptoms of drug withdrawal

• Yellowing of the skin and the eyes (jaundice).

Very rare side effects (may affect up to 1 in 10,000 people):

• Life threatening complications of uncontrolled diabetes

• Serious allergic reaction with swelling that may involve the throat and lead to difficulty breathing

• Lack of bowel muscle movement that causes blockage.

The following side effect has been seen with the use of another medicine called paliperidone that is very similar to risperidone, so these can also be expected with ZISPER FORTE: Rapid heartbeat upon standing. Additional side effects in children and adolescents In general, side effects in children are expected to be similar to those in adults.

The following side effects were reported more often in children and adolescents (5 to 17 years) than in adults: feeling sleepy, or less alert, fatigue (tiredness), headache, increased appetite, vomiting, common cold symptoms, nasal congestion, abdominal pain, dizziness, cough, fever, tremor (shaking), diarrhoea, and incontinence (lack of control) of urine

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

5.How to store ZISPER FORTE

Store in a cool, dry place. Protect from light. Keep all medicines out of reach of children

6. Contents of the pack and other information
The active ingredients are Risperidone & Trihexyphenidyl Hydrochloride

The excipients used are Lactose, Mannitol, Micro Crystalline Cellulose, Colour Lake Sunset Yellow FCF, Acetone, Ethyl Cellulose, Isopropyl Alcohol, Talcum, Flavour Mix Fruit DC 130 PH, Aspartame, Croscarmellose Sodium, Magnesium Stearate.

ZISPER FORTE is available in Blister strip of 10 Tablets

10. Details of manufacturer

Manufactured in India by:
Uni Medicolabs
21-22 Pharmacity, Selaqui, Dehradun, Uttarakhand.

11. Details of permission or licence number with date

Mfg Licence No. 65/UA/2015 issued on 12.03.2019

12. Date of revision

Not applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

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Ahmedabad-380 009, INDIA

IN/ZISPER FORTE 4,2 mg/JUL-19/01/PI