Generic Name Risperidone and Trihexyphenidyl hydrochloride orodispersible tablets

Trade Name RIZ PLUS tablets

1. NAME OF THE MEDICINAL PRODUCT: Risperidone and Trihexyphenidyl hydrochloride orodispersible tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION:**

Each dispersible tablet contains:
Risperidone BP……..3 mg
Trihexyphenidyl hydrochloride IP..... 2 mg
Excipeients……q.s.

3. **PHARMACEUTICAL FORM:** Dispersible tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications:

Risperidone is indicated for the treatment of schizophrenia.
Risperidone monotherapy is indicated for the treatment of acute manic or mixed episodes associated with Bipolar I Disorder.
Risperidone adjunctive therapy is indicated along with lithium or valproate for the treatment of acute manic or mixed episodes associated with Bipolar I Disorder.
Trihexyphenidyl is indicated to control associated extra pyramidal disorders caused due to central nervous system drugs such as antipsychotics.

4.2 Posology and Method of Administration

The initial dosing of risperidone is generally 2 mg/day. Dose increases should then occur at intervals not less than 24 hours, in increments of 1–2 mg/day, as tolerated, to a recommended dose of 4–8 mg/day.

The usual doses of trihexyphenidyl for drug-induced extra pyramidal symptoms lie within the range of 5- 15 mg daily in 2 to 3 divided doses.

Riz Plus can be administered once or twice daily when the patient is maintained at the dose of risperidone, 3mg/day or higher.

Dosage in Special Populations

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. The initial dose of trihexyphenidyl in elderly is 2mg. Subsequent doses of up to 20 mg can be given as recommended by the physician. Trihexyphenidyl is contraindicated in elderly with prostatic hypertrophy. Since the dose of risperidone in Riz Plus tablets is high for administration in elderly and the clinical experience of trihexyphenidyl in this population is limited, caution should be exercised while administering Riz Plus in the elderly with caution.

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.

Riz Plus should be used in caution in this group of patients.

4.3 Contraindications

Hypersensitivity: Hypersensitivity to risperidone, trihexyphenidyl or any of its ingredients.

Glaucoma: Anticholinergic drugs may cause papillary dilatation and paralysis of accommodation. Some people treated with anticholinergic drugs complain of blurring of vision as a result. Anticholinergic drugs are contraindicated in narrow-angle glaucoma, as they may precipitiate angle closure and raised intraocular pressure. Cases of blindness owing to this complication of trihexyphenidyl treatment have been reported. Riz Plus is therefore contraindicated in patients with glaucoma.

Prostatic hypertrophy: Prostatism may be exacerbated and occasionally acute retention precipitated, by the anticholinergic effect of trihexyphenidyl inhibiting detrusor muscle action. Riz Plus is therefore contraindicated in patients with prostatic hypertrophy.

Pyloric Stenosis: Trihexyphenidyl has an antispasmodic effect on the gastrointestinal system, decreasing gut motility. Pyloric stenosis and constipation may be made worse, and paralytic ileus may be precipitated, by trihexyphenidyl. Thus, Riz Plus is contraindicated in patients with Pyloric stenosis.

4.4 Special Warnings and Special Precautions for Use:

General

Food and Alcohol

Trihexyphenidyl is a weak base, and may interact with acidic foods such as citrous fruit and fruit juices, which will decrease the effect of a dose of trihexyphenidyl.

Alcohol will enhance the hepatic metabolism of trihexyphenidyl, and thus lower blood concentrations and decrease the therapeutic effect. Therefore, alcohol should be avoided when on Riz Plus treatment.

Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Risperidone is not approved for the treatment of dementia-related psychosis.

Concomitant Use with Furosemide in Elderly Patients with Dementia-Related Psychosis

In two of four placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone when compared to patients treated with risperidone alone or with placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed. An increase of mortality in elderly patients with dementia-related psychosis was seen with the use of risperidone, regardless of concomitant use with furosemide. Risperidoneis not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning).

Cerebrovascular Adverse Events (CVAE), Including Stroke, in Elderly Patients with Dementia-Related Psychosis

Cerebrovascular adverse events (e.g. stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age: 85 years; range: 73 to 97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. Risperidone is not approved for the treatment of patients with

dementia-related psychosis. 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.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity and altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g. pneumonia, systemic infection, etc.) and untreated or inadequately treated extra-pyramidal signs and symptoms. Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary CNS pathology.

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

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the

syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, risperidone should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Long-term antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require long-term treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with risperidone, drug discontinuation should be considered. However, some patients may require treatment with risperidone despite the presence of the syndrome.

Metabolic Changes

Hyperglycaemia and Diabetes Mellitus

Hyperglycaemia and diabetes mellitus, in some cases extreme, and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics including risperidone. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus, who are started on atypical antipsychotics, including risperidone, should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics, including risperidone, should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics, including risperidone, should be monitored for symptoms of hyperglycaemia, including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics, including risperidone, should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic, including risperidone, was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of risperidone.

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Hyperprolactinaemia

As with other drugs that antagonize dopamine D2 receptors, risperidone elevates prolactin levels and the elevation persists during continual administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents.

Hyperprolactinaemia may suppress hypothalamic GnRH (Gonadotropin Releasing Hormone), resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroid genesis in both female and male patients. Galactorrhoea, amenorrhoea, gynaecomastia and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinaemia, when associated with hypogonadism, may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. An increase in pituitary gland, mammary gland and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between continual administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Orthostatic Hypotension

Risperidone may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2,607) of risperidone - treated patients in Phase 2 and 3 studies in adults with schizophrenia. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either once daily or 1 mg twice daily) in normal adults and 0.5 mg twice daily in the elderly and patients with renal or hepatic impairment. Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. Risperidone should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure or conduction abnormalities), cerebrovascular disease and conditions which would predispose patients to hypotension, e.g. dehydration and hypovolaemia. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medication.

Leucopenia, Neutropenia and Agranulocytosis

In clinical trial and/or postmarketing experience, events of leucopenia/neutropenia have been reported temporally related to antipsychotic agents, including risperidone. Agranulocytosis has also been reported.

Possible risk factors for leucopenia/neutropenia include pre-existing low white blood cell counts (WBC) and history of drug-induced leucopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leucopenia/neutropenia should have their complete blood count (CBC) monitored frequently 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 <1,000/mm3) should discontinue risperidone and have their WBC followed until recovery.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with risperidone treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high-dose patients (risperidone 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of risperidone16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since risperidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that risperidone therapy does not affect them adversely.

Seizures

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

Dysphagia

Oesophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer’s dementia. Risperidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia

Priapism

Priapism may occur with risperidone treatment due to its alpha-adrenergic blocking effects.

Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28-year-old female patient receiving oral risperidone in a large, open premarketing experience (approximately 1,300 patients). She experienced jaundice, fever and bruising, but eventually recovered after receiving plasmapheresis. The relationship to risperidone therapy is unknown.

Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral risperidone use. Caution is advised when prescribing for patients who will be exposed to temperature extremes, e.g. exercising strenuously, exposure to extreme heat, receiving concomitant treatment with anticholinergic activity, or being subject to dehydration.

Anti-Emetic Effect

Risperidone has an anti-emetic effect in animals; this effect may also occur in humans and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome and brain tumour.

Suicide

The possibility of a suicide attempt is inherent in patients with schizophrenia and bipolar mania, including children and adolescent patients, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for risperidone should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.

Patients with Parkinson's disease or 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. Parkinson's disease may worsen with risperidone. Both groups may be at increased risk of NMS as well as having an increased sensitivity to antipsychotic medicinal products; these patients were excluded from clinical trials. Patients with Parkinson's disease or dementia with Lewy Bodies who receive antipsychotics, including risperidone are reported to have an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, and postural instability with frequent falls, extra-pyramidal symptoms and clinical features consistent with NMS.

Patients with Concomitant Illnesses

Caution is advisable in using risperidone in patients with diseases or conditions that could affect metabolism or haemodynamic responses. Risperidone has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing.

QT Prolongation

QT prolongation has very rarely been reported postmarketing. As with other antipsychotics, caution should be exercised when risperidone is prescribed in patients with known cardiovascular disease, a 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.

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.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction:

Centrally-Acting Drugs and Alcohol

Given the primary central nervous system (CNS) effects of risperidone, caution should be used when Riz Plus Tablets are taken in combination with other centrally-acting drugs such as opiates, antihistamines, benzodiazepines and alcohol due to the increased risk of sedation.

Drugs with Hypotensive Effects

Because of its potential for inducing hypotension, Riz Plus Tablets may enhance the hypotensive effects of other therapeutic agents with this potential.

Levodopa and Dopamine Agonists

Risperidone may antagonize the effects of levodopa and dopamine agonists. It may increase drug-induced involuntary movements in patients with parkinsonism treated with levodopa. There are also cases described of drug-induced choreiform movements occurring, with trihexyphenidyl as sole treatment, in Parkinson's disease and also in the treatment of dystonia.

Amitriptyline

Amitriptyline did not affect the pharmacokinetics of risperidone or risperidone and 9-hydroxyrisperidone combined.

Cimetidine and Ranitidine

Cimetidine and ranitidine increased the bioavailability of risperidone by 64% and 26%, respectively. However, cimetidine did not affect the area under the concentration curve (AUC) of risperidone and 9-hydroxyrisperidone combined, whereas ranitidine increased the AUC of risperidone and 9-hydroxyrisperidone combined by 20%.

Clozapine

Continued administration of clozapine with risperidone may decrease the clearance of risperidone.

Lithium

Repeated oral doses of risperidone (3 mg twice daily) did not affect the exposure (AUC) or peak plasma concentrations (Cmax) of lithium.

Valproate

In a trial, repeated oral doses of risperidone (4 mg once daily) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1,000 mg/day in three divided doses). However, there was a 20% increase in valproate peak plasma concentration (Cmax) after concomitant administration of risperidone.

Digoxin

Risperidone(0.25 mg twice daily) did not show a clinically relevant effect on the pharmacokinetics of digoxin.

Verapamil

Verapamil, an inhibitor of CYP 3A4 and P-gp, increases the plasma concentration of risperidone.

Phenothiazines, Tricyclic Antidepressants and Beta-Blockers

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

Psychostimulants

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

Furosemide

In a risperidone-placebo trial in the elderly with dementia, increased mortality was observed in patients concomitantly receiving furosemide.

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.

Fluoxetine and Paroxetine

Fluoxetine (20 mg once daily) and paroxetine (20 mg once daily) have been shown to increase the plasma concentration of risperidone 2.5- to 2.8-fold and 3- to 9-fold, respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of Riz Plus Tablets. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

Erythromycin

There were no significant interactions between risperidone and erythromycin.

Anticonvulsants

There have been suggestions that if patients adequately controlled epilepsy start to take anticholinergic drugs these may exacerbate seizures.

Drugs that Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs. Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness of the two groups has been made.

Studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism.

Carbamazepine and Other Enzyme Inducers

Carbamazepine co-administration decreased the steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known enzyme inducers (e.g. phenytoin, rifampin and phenobarbital) with Riz Plus Tablets may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment.

Drugs Metabolized by CYP 2D6

Studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, risperidone is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

Drugs Prolonging the QT Interval

Caution is advised when prescribing Riz Plus Tablets with drugs known to prolong the QT interval, e.g. class IAanti-arrhythmics (e.g. quinidine, dysopiramide, procainamide), class III anti-arrhythmics (e.g. amiodarone, sotalol), tricyclic antidepressant (i.e. amitriptyline), tetracyclic antidepressants (i.e. maprotiline), some antihistaminics, other antipsychotics, some antimalarials (i.e. chinice 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.

Potentially hazardous interactions with trihexyphenidyl

The unwanted peripheral anticholinergic effects of trihexyphenidyl may be worsened by simultaneous administration of other drugs with anticholinergic properties. In the past, trihexyphenidyl has been given prophylactically to prevent the development of drug-induced parkinsonism during neuroleptic drug therapy. However, the concurrent administration of a neuroleptic and an anticholinergic drug makes the subsequent development of tardive dyskinesia more likely. Anticholinergic drugs should therefore not be given prophylactically together with neuroleptics. They may however, be given with a neuroleptic drug when parkinsonism develops.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

There are no adequate data from the use of risperidone in pregnant women. According to postmarketing data reversible extra-pyramidal symptoms in the neonate were observed following the use of risperidone during the last trimester of pregnancy. Consequently, newborns should be monitored carefully. Risperidone was not teratogenic in animal studies, but other types of reproductive toxicity were seen. The potential risk for humans is unknown. Therefore, risperidone should not be used during pregnancy unless clearly necessary. If discontinuation during pregnancy is necessary, it should not be done abruptly.

Neonates exposed to antipsychotic drugs (including risperidone) during the third trimester of pregnancy are at risk for extra-pyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases, neonates have required intensive care unit support and prolonged hospitalization. Risperidone should be used during pregnancy

Animal studies on trihexyphenidyl 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.

Riz Plus should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation

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 breastfeeding infants. It is unknown whether trihexyphenidyl is excreted in human breast milk. The excretion of trihexyphenidyl in milk has not been studied in animals. Infants may be very sensitive to the effects of antimuscarinic medications. Therefore, it is recommended that nursing mothers receiving Riz Plus should not breastfeed, unless the advantages of breastfeeding weighs against the potential risks for the infant. Riz Plus should therefore not be used during breast feeding. for the child and the benefit of therapy for the mother.

4.7 Undesirable Effects

Risperidone

The most common adverse reactions in clinical trials (≥ 10%) were somnolence, increased appetite, fatigue, insomnia, sedation, parkinsonism, akathisia, vomiting, cough, constipation, nasopharyngitis, drooling, rhinorrhea, dry mouth, abdominal pain upper, dizziness, nausea, anxiety, headache, nasal congestion, rhinitis, tremor, and rash.

The most common adverse reactions that were associated with discontinuation from clinical trials (causing discontinuation in >1% of adults and/or >2% of pediatrics) were nausea, somnolence, sedation, vomiting, dizziness, akathisia, parkinsonism, dystonia, agitation, abdominal pain and orthostatic hypotension.

Discontinuation for extrapyramidal symptoms (including Parkinsonism, akathisia, dystonia, and tardive dyskinesia) was 1% in placebo-treated patients, and 3.4% in active control-treated patients in a double-blind, placebo- and active-controlled trial.

Adverse reactions are adverse events that were considered to be reasonably associated with the use of risperidone (adverse drug reactions) based on the comprehensive assessment of the available adverse event information. A causal association for risperidone often cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

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 [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], hypoglycemia, hyperinsulinaemia[c], blood triglycerides increased	diabetic ketoacidosis
Psychiatric disorders	insomnia[d]	sleep disorder, agitation, depression, anxiety	mania, confusional state, libido decreased, nervousness, nightmare	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 subcutaneous tissue disorders		rash, erythema	urticaria, pruritus, alopecia, hyperkeratosis, eczema, dry skin, skin discolouration, acne, seborrhoeic dermatitis, skin disorder, skin	drug eruption, dandruff	angioedema

			lesion		
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, vaginal discharge	priapism[c], menstruation delayed, breast engorgement, breast enlargement, breast 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		fall	procedural pain		

procedural complications					

Trihexyphenidyl

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties:

Risperidone

The clinical effect from risperidone results from the combined concentrations of risperidone and its major metabolite, 9-hydroxyrisperidone. The mechanism of action of risperidone with other drugs used to treat schizophrenia is unknown. However, it has been proposed that the drug's therapeutic activity in

schizophrenia is mediated through a combination of dopamine-type 2 (D2) and serotonin-type 2 (5HT2) receptor antagonism. Risperidone is a selective monoaminergic antagonist with a high affinity (Ki of 0.12 to 7.3 nM) for the serotonin type 2 (5HT2), dopamine type 2 (D2), alpha1and alpha2adrenergic, and H1 histaminergic receptors. Risperidone acts as an antagonist at other receptors, but with lower potency. Risperidone has low-to-moderate affinity (Ki of 47 to 253 nM) for the serotonin 5HT1C, 5HT1D, and 5HT1A receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D1 and haloperidol-sensitive sigma site, and no affinity(when tested at concentrations >10-5 M) for cholinergic muscarinic or beta1- and beta2-adrenergic 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 the extra-pyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

Trihexyphenidyl

Trihexyphenidyl is an anticholinergic used in the symptomatic treatment of all etiologic groups of parkinsonism and drug induced extrapyramidal reactions (except tardive dyskinesia). Trihexyphenidyl possesses both anticholinergic and antihistaminic effects, although only the former has been established as therapeutically significant in the management of parkinsonism.

Trihexyphenidyl is a selective M1 muscarinic acetylcholine receptor antagonist. It is able to discriminate between the M1 (cortical or neuronal) and the peripheral muscarinic subtypes (cardiac and glandular). Trihexyphenidyl partially blocks cholinergic activity in the CNS, which is responsible for the symptoms of Parkinson's disease. It is also thought to increase the availability of dopamine, a brain chemical that is critical in the initiation and smooth control of voluntary m
uscle movement.

5.2 Pharmacokinetic Properties:

Risperidone

Risperidone orodispersible tablets and oral solution are bio-equivalent to Risperidone film-coated tablets. 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 CYP 2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxy-risperidone form the active antipsychotic fraction. CYP 2D6 is subject to genetic polymorphism. Extensive CYP 2D6 metabolisers convert risperidone rapidly into 9-hydroxy-risperidone, whereas poor CYP 2D6 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 CYP 2D6.

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 CYP 1A2, CYP 2A6, CYP 2C8/9/10, CYP 2D6, CYP 2E1, CYP 3A4, and CYP 3A5. 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.

Trihexyphenidyl

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.

5.3 Preclinical Safety Data

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 D2-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 D2 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

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf-life: 36 Months

6.2 Special Precautions for Storage: Store in cool and dry place. Protect form light

6.3 Nature and Contents of Container: 10`s-blister pack

Marketed By
Alkem Laboratories Limited,
Alkem House, S.B. Road,
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