CIZOREST Tablets (Amisulpride)

Composition

CIZOREST 50mg Tablets

Each film-coated tablet contains:

Amisulpride……..50 mg

CIZOREST 100mg Tablets

Each film-coated tablet contains:

Amisulpride……..100 mg

CIZOREST 200mg Tablets

Each film-coated tablet contains:

Amisulpride……..200 mg

Dosage Form

Film-coated tablet

Pharmacology

Pharmacodynamics

Amisulpride binds selectively with a high affinity to human dopaminergic D_2/D_3 receptor subtypes whereas it is devoid of affinity for D_1, D_4 and D_5 receptor subtypes. Unlike classical and atypical neuroleptics, amisulpride has no affinity for serotonin, -adrenergic, histamine H_1 and cholinergic receptors. In addition, amisulpride does not bind to sigma sites.

In animal studies, at high doses, amisulpride blocks dopamine receptors located in the limbic structures in preference to those in the striatum. At low doses it preferentially blocks pre-synaptic D_2/D_3 receptors, producing dopamine release responsible for its disinhibitory effects.This pharmacological profile explains the clinical efficacy of amisulpride against both negative and positive symptoms of schizophrenia

Pharmacokinetics

In humans, amisulpride shows two absorption peaks: one which is attained rapidly, one hour post-dose and a second between 3 and 4 hours after administration. Corresponding plasma concentrations are 39 ± 3 and 54 ± 4 ng/ml after a 50 mg dose. The volume of distribution is 5.8 l/kg, plasma protein binding is low (16%) and no drug interactions are suspected.

Absolute bioavailability is 48%. Amisulpride is weakly metabolised: two inactive metabolites, accounting for approximately 4% of the dose, have been identified. There is no accumulation of amisulpride and its pharmacokinetics remain unchanged after the administration of repeated doses. The elimination half-life of amisulpride is approximately 12 hours after an oral dose.

Amisulpride is eliminated unchanged in the urine. Fifty percent of an intravenous dose is excreted via the urine, of which 90% is eliminated in the first 24 hours. Renal clearance is in the order of 20 l/h or 330 ml/min.

A carbohydrate rich meal (containing 68% fluids) significantly decreases the AUCs, Tmax and Cmax of amisulpride but no changes were seen after a high fat meal. However, the significance of these findings in routine clinical use is not known.

Special Populations

Hepatic Insufficiency

Since the drug is weakly metabolised a dosage reduction should not be necessary in patients with hepatic insufficiency.

Renal Insufficiency

The elimination half-life is unchanged in patients with renal insufficiency while systemic clearance is reduced by a factor of 2.5 to 3. The AUC of amisulpride in mild renal failure increased two fold and almost tenfold in moderate renal failure (see chapter 4.2). Experience is however limited and there is no data with doses greater than 50 mg.Amisulpride is very weakly dialysed.

Elderly:

Limited pharmacokinetic data in elderly subjects (> 65 years) show that a 10-30 % rise occurs in Cmax, T1/2 and AUC after a single oral dose of 50 mg. No data are available after repeat dosing.

Indications

CIZOREST is indicated for the treatment of acute and chronic schizophrenic disorders, in which positive symptoms (such as delusions, hallucinations, and thought disorders) and/or negative symptoms (such as blunted affect, emotional and social withdrawal) are prominent, including patients characterised by predominant negative symptoms.

Dosage and Administration

For acute psychotic episodes, oral doses between 400 mg/day and 800 mg/day are recommended. In individual cases, the daily dose may be increased up to 1200 mg/day. Doses above 1200 mg/day have not been extensively evaluated for safety and therefore should not be used. No specific titration is required when initiating the treatment with **CIZOREST**. Doses should be adjusted according to individual response.

For patients with mixed positive and negative symptoms, doses should be adjusted to obtain optimal control of positive symptoms.

Maintenance treatment should be established individually with the minimally effective dose.

For patients characterised by predominant negative symptoms, oral doses between 50 mg/day and 300 mg/day are recommended. Doses should be adjusted individually.

CIZOREST can be administered once daily at oral doses up to 300 mg, higher doses should be administered bid.

The minimum effective dose should be used.

CIZOREST can be administered once daily at oral doses up to 300 mg, higher doses should be administered bid.

Special Populations

Elderly

The safety of amisulpride has been examined in a limited number of elderly patients. **CIZOREST** should be used with particular caution because of a possible risk of hypotension and sedation. Reduction in dosage may also be required because of renal insufficiency.

Children

The efficacy and safety of **CIZOREST** from puberty to the age of 18 years have not been established. There are limited data available on the use of amisulpride in adolescents in schizophrenia. Therefore, the use of **CIZOREST** from puberty to the age of 18 years is not recommended; in children up to puberty amisulpride is contraindicated, as its safety has not yet been established.

Renal insufficiency

CIZOREST is eliminated by the renal route. In renal insufficiency, the dose should be reduced to half in patients with creatinine clearance (CRCL) between 30-60 ml/min and to a third in patients with CRCL between 10-30 ml/min. As there is no experience in patients with severe renal impairment (CRCL < 10 ml/min) particular care is recommended in these patients.

Hepatic Impairment

Dosage reduction is not necessary in patients with hepatic insufficiency since the drug is weakly metabolised.

Contraindications

Hypersensitivity to the active ingredient or to other ingredients of the medicinal product

Concomitant prolactin-dependent tumours (e.g. pituitary gland prolactinomas or breast cancer), phaeochromocytoma, children before the onset of puberty, lactation and combination with levodopa

Warnings and Precautions

Drug interactions

Contraindicated combinations

Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics. Amisulpride may oppose the effect of dopamine agonists e.g. bromocriptine, ropinirole.

Combinations not recommended

Amisulpride may enhance the central effects of alcohol.

Combinations to be taken into account

CNS depressants including narcotics, anaesthetics, analgesics, sedative H1 antihistamines, barbiturates, benzodiazepines and other anxiolytic drugs, clonidine and derivatives

Antihypertensive drugs and other hypotensive medications

Caution is advised when prescribing amisulpride with medicines known to prolong the QT interval, e.g., class IA antiarrythmics (e.g., quinidine, disopyramide) and class III antiarrhythmics (e.g. amiodarone, sotalol), some antihistaminics, some other antipsychotics and antimalarials (e.g., mefloquine)

Prolongation of the QT interval

Caution should be exercised when amisulpride is prescribed in patients with known cardiovascular disease or family history of QT prolongation and concomitant use with neuroleptics should be avoided.

Stroke

In randomized clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic drugs, a 3-fold increase of the risk of cerebrovascular events has been observed. The mechanism of such risk increase is not known. An increase in the risk with other antipsychotic drugs, or other populations of patients cannot be excluded. Amisulpride should be used with caution in patients with stroke risk factors.

Elderly Patients with Dementia

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death in clinical trials with atypical antipsychotics were varied, most of the deaths appeared to be either cardiovascular (e.g., hearth failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality.

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.

Amisulpride is not licensed for the treatment of dementia-related behavioural disturbances.

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 amisulpride and preventive

measures undertaken.

Breast cancer

Amisulpride may increase prolactin levels. Therefore, caution should be exercised and patients with a history or a family history of breast cancer should be closely monitored during amisulpride therapy.

Blood dyscrasias

Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics, including amisulpride. Unexplained infections or fever may be evidence of blood dyscrasia and requires immediate haematological investigation.

Glucose Intolerance

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Pregnancy

In animals, amisulpride did not show reproductive toxicity. A decrease in fertility linked to the pharmacological effects of the drug (prolactin mediated effect) was observed. No teratogenic effects of amisulpride were noted.

Very limited clinical data on exposed pregnancies are available. Therefore, the safety of amisulpride during human pregnancy has not been established.

Use of the drug is not recommended during pregnancy unless the benefits justify the potential risks. For women of childbearing potential, effective contraception should be fully discussed with the physician prior to treatment.

Neonates exposed to antipsychotics (including amisulpride) 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.

Lactation

It is not known whether amisulpride is excreted in breast milk, breast-feeding is therefore contra-indicated.

Effects on Ability to Drive and Use Machines

Even used as recommended, amisulpride may cause somnolence so that the ability to drive vehicles or operate machinery can be impaired.

Undesirable Effects

Adverse effects have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100; <1/10); uncommon (≥1/1,000 ;< 1/100); rare (≥1/10,000 ;<

1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data).

The following adverse effects have been observed in controlled clinical trials. It should be noted that in some instances it can be difficult to differentiate adverse events from symptoms of the underlying disease.

Nervous system disorders

Very common: Extrapyramidal symptoms may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia, and dyskinesia. These symptoms are generally mild at optimal dosages and partially reversible without discontinuation of amisulpride upon administration of antiparkinsonian medication. The incidence of extrapyramidal symptoms which is dose related, remains very low in the treatment of patients with predominantly negative symptoms with doses of 50-300 mg/day.

Common: Acute dystonia (spasm torticollis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon treatment with an antiparkinsonian agent. Somnolence.

Uncommon: Tardive dyskinesia characterized by rhythmic, involuntary movements primarily of the tongue and/or face have been reported, usually after long term administration. Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms. Seizures.

Psychiatric disorders

Common: Insomnia, anxiety, agitation, orgasmic dysfunction

Gastrointestinal disorders

Common: Constipation, nausea, vomiting, dry mouth

Endocrine disorders

Common: Amisulpride causes an increase in plasma prolactin levels which is reversible after drug discontinuation. This may result in galactorrhoea, amenorrhoea, gynaecomastia, breast pain, and erectile dysfunction.

Metabolism and nutrition disorders

Uncommon: Hyperglycaemia

Cardiovascular disorders

Common: Hypotension

Uncommon: Bradycardia

Investigations

Common: Weight gain

Uncommon: Elevations of hepatic enzymes, mainly transaminases

Immune system disorders

Uncommon: Allergic reaction

Post-Marketing Data

In addition, cases of the following adverse reactions have been reported through spontaneous reporting only:

Blood and Lymphatic system disorders

Frequency not known: Leukopenia, neutropenia and agranulocytosis

Metabolism and nutrition disorders

Frequency not known: hypertriglyceridemia and hypercholesterolemia

Psychiatric disorders

Frequency not known: confusion

Nervous system disorders

Frequency not known: Neuroleptic Malignant Syndrome, which is a potentially fatal complication.

Cardiac disorders

Frequency not known: QT interval prolongation and ventricular arrhythmias such as torsade de pointes, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, sudden death.

Vascular disorders

Frequency not known: Cases of venous thromboembolism, including cases of pulmonary embolism, sometimes fatal, and cases of deep vein thrombosis have been reported with antipsychotic drugs.

Skin and subcutaneous tissue disorders:

Frequency not known: Angioedema, urticaria

Pregnancy, puerperium and perinatal conditions:

Frequency not known: Drug withdrawal syndrome neonatal

Overdosage

Experience with amisulpride in overdosage is limited. Exaggeration of the known pharmacological effects of the drug have been reported. These include drowsiness and sedation, coma, hypotension and extrapyramidal symptoms. Fatal outcomes have been reported mainly in combination with other psychotropic agents.

In cases of acute overdosage, the possibility of multiple drug intake should be considered. Since amisulpride is weakly dialysed, haemodialysis is of no use to eliminate the drug.

There is no specific antidote to amisulpride.

Appropriate supportive measures should therefore be instituted with close supervision of vital functions including continuous cardiac monitoring due to the risk of prolongation of the QT interval

until the patient recovers.

If severe extrapyramidal symptoms occur, anticholinergic agents should be administered.

Shelf-life

24 months

Storage and Handling

Store below 30°C away from light and moisture.

Packaging Information

CIZOREST 50 mg: Blister Pack of 10 Tablets

CIZOREST 100mg: Blister Pack of 10 Tablets

CIZOREST 200mg: Blister Pack of 10 Tablets

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