xxxxxxxx-8883

For the use of a Psychiatrist or a Hospital only

AMAZEO

(Amisulpride Tablets 50 mg,100 mg, 200 mg, 300 mg & 400 mg)

COMPOSITION :

AMAZEO 50

Each film coated tablet contains :

Amisulpride B.P.	50 mg
Excipients	q.s.
Colour : Titanium Dioxide	

AMAZEO 100

Each film coated tablet contains :

Amisulpride B.P.	100 mg
Excipients	q.s.
Colour : Titanium Dioxide	

AMAZEO 200

Each film coated tablet contains :

Amisulpride B.P.	200 mg
Excipients	q.s.
Colour : Titanium Dioxide	

AMAZEO 300

Each film coated tablet contains :

Amisulpride B.P.	300 mg
Excipients	q.s.
Colour : Titanium Dioxide	

AMAZEO 400

Each film coated tablet contains :

Amisulpride B.P.	400 mg
Excipients	q.s.
Colour : Titanium Dioxide	

PROPERTIES

Class: Neuroleptic of the benzamide class

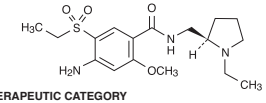
Chemical Name :

4-Amino-*N*-[[(2RS)-1-ethylpyrrolidin-2-yl]methyl]-5-(ethyl sulphonyl)- 2-methoxybenzamide.

Molecular Weight : 369.5

Molecular Formula : $C_{17}H_{27}N_3O_4S$

Amisulpride is a white or almost white, crystalline powder which is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in anhydrous ethanol. Amisulpride has the following structural formula :



THERAPEUTIC CATEGORY

Neuroleptic

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMICS :

Amisulpride binds selectively to the human dopaminergic D_2 (Ki 2.8 nM) and D_3 (Ki 3.2 nM) receptor subtypes without any affinity for D_1, D_4 and D_5 receptor subtypes (Ki > 1 μM). Unlike classical and atypical neuroleptics, amisulpride displays low affinity for serotonin, α-adrenergic, histamine H_1 receptor subtypes, muscarinic receptors and sigma sites. In the rodent, it preferentially blocks post-synaptic D_2 receptors located in the limbic structures as compared to those in the striatum as indicated by its reversal of d-amphetamine- induced hyperactivity without affecting stereotypies. In addition, it does not induce catalepsy and it does not produce D_2 hypersensitivity after repeated treatment. Moreover, it preferentially blocks pre-synaptic D_2/D_3 dopamine receptors, producing dopamine release responsible for its disinhibitory effects. This atypical pharmacological profile may explain amisulpride's antipsychotic effect at higher doses through post-synaptic dopamine receptor blockade located in the limbic areas and its efficacy against negative symptoms, at lower doses, through presynaptic dopamine receptor blockade. In addition, the reduced tendency of amisulpride to produce extra pyramidal side effects may be related to its preferential limbic activity.

PHARMACOKINETICS :

In man, 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. As plasma protein binding is low (16%), drug interactions due to displacement are unlikely.

The absolute bioavailability of amisulpride is 48%.

Amisulpride is weakly metabolised: two inactive metabolites, accounting for approximately 4% of the dose, have been identified. The elimination half-life of amisulpride is approximately 12 hours after an oral dose. Fifty percent of an intravenous dose is excreted via the urine, the majority as unchanged drug. Ninety percent of the intravenous dose is eliminated in the first 24 hours. Renal clearance is in the order of 20 L/h or 330 ml/min.

Following a single intravenous dose, about 20% of the dose was recovered from the faeces, about 70% of which was as unchanged amisulpride. Hepatic metabolism has a limited role in healthy patients.

A high-carbohydrate low-fat meal (14 g protein, 8 g fat, 108 g CHO) significantly decreases the AUC, T_{max} and C_{max} 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 POPULATION

Renal insufficiency: In patients with renal insufficiency 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. Experience is, however, limited and there is no data with doses greater than 50 mg. Amisulpride is very weakly dialysed. Limited Pharmacokinetic data in elderly subjects (> 65 years) show that a 10-30% rise occurs in C_{max}, T½ and AUC after a single oral dose of 50 mg. No data are available after repeat dosing.

THERAPEUTIC INDICATION :

For acute and chronic schizophrenic disorders, in which positive and negative symptoms are prominent, including patients characterised by predominant negative symptoms.

CONTRAINDICATIONS :

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

Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer.

Phaeochromocytoma.

Children up to puberty.

Combination with levodopa.

WARNINGS AND PRECAUTIONS:

As with other neuroleptics, Neuroleptic Malignant Syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK, may occur. In the event of hyperthermia, particularly with high daily doses, all antipsychotic drugs including amisulpride should be discontinued.

Hyperglycaemia has been reported in patients treated with some atypical antipsychotic agents, including amisulpride, therefore patients with an established diagnosis of diabetes mellitus or with risk factors for diabetes who are started on amisulpride, should get appropriate glycaemic monitoring.

Amisulpride is eliminated by the renal route. In cases of severe renal insufficiency, the dose could be decreased or intermittent treatment should be considered.

Amisulpride may lower the seizure threshold. Therefore patients with a history of epilepsy should be closely monitored during amisulpride therapy.

In elderly patients, amisulpride, like other neuroleptics, should be used with particular caution because of a possible risk of hypotension or sedation.

As with other antidopaminergic agents, caution should be also exercised when prescribing amisulpride to patients with Parkinson's disease since it may cause worsening of the disease. Amisulpride should be used only if neuroleptic treatment cannot be avoided.

Withdrawal symptoms have been described after abrupt cessation of high therapeutic doses of antipsychotic drugs. The emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported with amisulpride. Therefore, gradual withdrawal of amisulpride is advisable.

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.

Increased Mortality in Elderly people with Dementia:

Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are 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. 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.

Pregnancy and lactation

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. If amisulpride is used during pregnancy, neonates may show adverse effects of amisulpride and thus appropriate monitoring should be considered.

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.

Preclinical safety data

An overall review of the completed safety studies indicates that amisulpride is devoid of any general, organ-specific, teratogenic, mutagenic or carcinogenic risk. Changes observed in rats and dogs at doses below the maximum tolerated dose are either pharmacological effects or are devoid of major toxicological significance under these conditions.

Compared with the maximum recommended dosages in man, maximum tolerated doses are 2 and 7 times greater in the rat (200 mg/kg/d) and dog (120 mg/kg/d) respectively in terms of AUC. No carcinogenic risk, relevant to man, was identified in the rat at up to 1.5 to 4.5 times the expected human AUC.

A mouse carcinogenicity study (120 mg/kg/d) and reproductive studies (160, 300 and 500 mg/kg/d respectively in rat, rabbit and mouse) were performed. The exposure of the animals to amisulpride during these latter studies was not evaluated.

ADVERSE REACTION

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).

• Nervous system disorders :

Very common: Extrapyramidal symptoms may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia, 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: Hyperglycemia

• 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:

• Nervous system disorders :

Frequency not known: Neuroleptic Malignant Syndrome

• 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 thrombo- embolism, including cases of pulmonary embolism 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

DRUG INTERACTIONS :

COMBINATIONS WHICH ARE CONTRAINDICATED

Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics.

COMBINATIONS WHICH ARE 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 antiarrhythmics (e.g., quinidine, disopyramide) and class III antiarrhythmics (e.g., amiodarone, sotalol), some antihistaminics, some other antipsychotics and some antimalarials (e.g., mefloquine)
- Drugs causing electrolyte imbalance

DOSE AND ROUTE OF ADMINISTRATION

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

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/d and 300 mg/d are recommended. Doses should be adjusted individually.

Amisulpride 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.

Elderly:

Amisulpride should be used with particular caution because of a possible risk of hypotension or sedation.

Children:

Amisulpride is contra-indicated in children up to puberty as its safety has not yet been established.

Renal insufficiency:

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

Hepatic insufficiency:

Since the drug is weakly metabolised, a dosage reduction should not be necessary.

OVERDOSE AND TOXICITY:

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.

In cases of acute overdose, the possibility of multiple drug intake should be considered. Since amisulpride is weakly dialysed, haemodialysis should not be used to eliminate the drug. There is no specific antidote to amisulpride. Appropriate supportive measure should therefore be instituted : close supervision of vital functions and, because of the risk of prolongation of QT interval, continuous cardiac monitoring until the patient recovers. If severe extrapyramidal symptoms occur, anticho- linergic agents should be administered.

EXPIRY DATE :

Do not use after the date of expiry.

STORAGE :

Store below 30ºC.

Keep out of reach of children

PRESENTATION :

Amazeo 50,100, 200, 300 and 400 are available in blister strips of 10 tablets.

torrent PHARMA

Manufactured by :

TORRENT PHARMACEUTICALS LTD.

Baddi-173 205, Dist : Solan (H.P.), INDIA.