For the use of a Psychiatrist or a Hospital only

AMAZEO OD

(Amisulpride Sustained Release Tablets 100, 200 & 400 mg)

COMPOSITION

AMAZEO OD 100

Each uncoated sustained release bilayered tablet contains :
Amisulpride I.P. 100 mg
Color : Red oxide of Iron

AMAZEO OD 200

Each uncoated sustained release bilayered tablet contains :
Amisulpride I.P. 200 mg
Color : Red oxide of Iron

AMAZEO OD 400

Each uncoated sustained release bilayered tablet contains :
Amisulpride I.P. 400 mg
Color : Red oxide of Iron

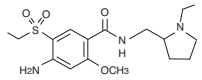
DESCRIPTION

Amisulpride is a white or almost white, crystalline powder which is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol.

Chemical Name: 4-Amino-N-[[(2RS)-1-ethylpyrrolidin-2-yl]methyl]-5-(ethylsulphonyl)-2-methoxybenzamide.

Molecular Weight: 369.5

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



INDICATIONS

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

DOSE AND METHOD OF ADMINISTRATION

Amisulpride SR should be administered once daily. For acute psychotic episodes, oral doses between 400mg/d and 800mg/d are recommended. In individual cases, the daily dose may be increased up to 1200 mg/d. No specific titration is required when initiating the treatment with amisulpride. Doses should be adjusted according to individual response. Doses are to be taken with or after meals. Amisulpride SR Tablets should be swallowed whole and not split, chewed or crushed.

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.

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 should be use cautiously in patients with renal insufficiency.

Hepatic insufficiency:

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

DIRECTION OF USE:

Amisulpride SR Tablets should be swallowed whole and not split, chewed or crushed.

CONTRAINDICATIONS

- Hypersensitivity to the active ingredient or to other ingredients of the product
- Concomitant prolacti- dependent tumors e.g. pituitary gland prolactinomas and breast cancer
- Phaeochromocytoma
- Children under 15 years of age
- Pregnancy or Lactation
- In combination with the following medication which could induce *torsades de pointes* :
  * Class Ia antiarrhythmic agents such as quinidine and disopyramide
  * Class III antiarrhythmic agents such as amiodarone and sotalol
  * Other medications such as cisapride, intravenous erythromycin, pentamidine
- Levodopa; reciprocal antagonism between levodopa and neuroleptics

WARNINGS

As with other neuroleptics, Neuroleptic Malignant Syndrome, characterized by hyper-thermia, muscle rigidity, autonomic instability and elevated CPK, may occur. In the event of hyperthermia, particularly with high daily doses, all antipsychotic drugs including Amisulpride should be discontinued.

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

Amisulpride can lower the seizure threshold. Therefore patients with a history of seizures 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. Reduction in dosage may also be required because of renal insufficiency.

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.

Amisulpride should be prescribed with caution in patients with cardiovascular disorders which may predispose to prolongation of the QT interval. Avoid concomitant prescription of other antipsychotics.

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

PRECAUTIONS

General

Neuroleptic Malignant Syndrome (NMS) is a potentially fatal syndrome that has been reported in association with anti-psychotic drugs, including amisulpride. Neuroleptic malignant syndrome is characterised by hyperthermia, muscle rigidity, autonomic instability, and elevated CPK, may occur. In the event of any symptoms which could suggest NMS, in particular hyperthermia, particularly with high daily doses, all antipsychotic drugs including amisulpride should be discontinued.

There are limited data on the potential for renally-cleared drugs to interfere with the clearance of amisulpride. Therefore, amisulpride should be used with caution with other renally-excreted drugs, including lithium.

The impact of hepatic impairment on hepatic metabolism and hepato-biliary excretion of amisulpride has not been studied. Amisulpride should be used with caution in patients with moderate or severe hepatic impairment.

Amisulpride can lower the seizure threshold. Therefore patients with a history of seizures should be closely monitored during amisulpride therapy. In elderly patients, amisulpride therapy, like other neuroleptics, should be used with particular caution because of a possible risk of hypotension or sedation.

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.

Amisulpride causes an increase in plasma prolactin levels which is reversible after drug discontinuation. This may result in galac torrhoea, amenorrhoea, gynaecomastia, breast pain, orgasmic dysfunction and impotence.

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

Extrapyramidal symptoms may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia. 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 are dose related.

Tardive dyskinesia characterised 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.

DRUG INTERACTIONS

A number of drugs can increase the risk of ventricular arrhythmias including *torsades de pointes*. The use of the following drugs is contraindicated:

- Class Ia antiarrhythmic agents such as quinidine and disopyramide.
- Class III antiarrhythmic agents such as amiodarone and sotalol.
- Other medications such as cisapride, intravenous erythromycin, pentamidine.

Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics Caution is required with the use of the following drugs:

- Drugs which induce bradycardia, such as bradycardia - inducing calcium channel blockers (diltiazem, verapamil), beta-blockers, clonidine, digitalis.
- Drugs which can cause hypokalaemia, such as diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactides.
- Neuroleptics such as pimozide, haloperidol
- Imipramine antidepressants
- lithium

Concomitant use of amisulpride with other anti-psychotics may increase the risk of developing neuroleptic malignant syndrome.

Amisulpride may enhance the effects of alcohol.

Amisulpride may enhance the effects of the following drugs:

- CNS depressants including narcotics, anaesthetics, analgesics, sedative H_1-antihistamines, barbiturates, benzodiazepines and other anxiolytic drugs, clonidine and derivatives
- Antihypertensive drugs and other hypotensive medications

UNDESIRABLE EFFECTS

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

Common adverse effects (5-10 %):

Insomnia, anxiety, agitation

Less common adverse effects (0.1-5 %):

Somnolence, gastrointestinal disorders such as constipation, nausea, vomiting, dry mouth.

As with other neuroleptics:

Amisulpride causes an increase in plasma prolactin levels which is reversible after drug discontinuation. This may result in galactorrhoea, amenorrhoea, gynaecomastia, breast pain, orgasmic dysfunction and impotence. Weight gain may occur under therapy with Amisulpride.

Acute dystonia (spasm torticolis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of Amisulpride upon treatment with an antiparkinsonian agent.

Extrapyramidal symptoms may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia. 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 50-300mg/day.

Tardive dyskinesia characterised 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. Hypotension and bradycardia have been reported occasionally.

Cases of QT prolongation and very rare cases of torsades de pointes have been reported. Acute withdrawal reactions have very rarely been reported. Allergic reactions, elevations of hepatic enzymes, mainly transaminases and cases of seizures have been very rarely reported. Very rare cases of Neuroleptic Malignant Syndrome have been reported.

OVERDOSAGE

Experience with amisulpride in overdosage is limited. Exaggeration of the known pharmacological effects of the drug has 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, anticholinergic agents should be administered.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Mechanism of Action

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 receptor subtypes, muscarinic receptors and sigma sites.

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 extrapyramidal side effects may be related to its preferential limbic activity.

Pharmacokinetics

In man, amisulpride SR formulation achieves Tmax around 4-4.5 hrs after single dose administration. Corresponding Cmax and AUC values after single dose administration in fed conditions are 560.48 ng/ml and 8564.736 ng.hr/ml respectively. As compared to fasting condition Amisulpride SR formulation achieves lower Cmax but comparable AUC in fed condition.

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 tablets 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 SR 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.

Expiry Date

Do not use later than the date of expiry.

Storage

Store at a temperature not exceeding 30°C, protected from moisture.
Keep out of reach of children.

Presentation

AMAZEO OD 100, 200 and 400 are available in strips of 10 tablets.

MARKETED BY

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