

PRODUCT INFORMATION

SOLIAN[®] TABLETS and SOLUTION

NAME OF THE DRUG

SOLIAN 100

SOLIAN 200

SOLIAN 400

SOLIAN Solution 100mg/mL

Active Ingredient: Amisulpride

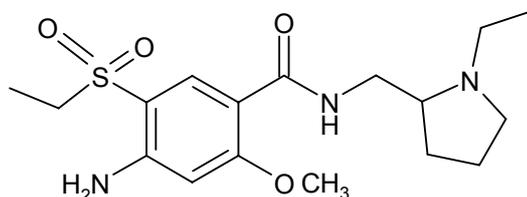
Class: Neuroleptic of the benzamide class

Chemical Name: (R, S)-4-Amino-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-ethylsulfonyl-2-methoxybenzamide

Molecular Weight: 369.48

Molecular Formula: C₁₇H₂₇N₃O₄S

Chemical Abstracts Number: 71675-85-9



DESCRIPTION

Amisulpride is a white to off-white powder which is practically insoluble in water, sparingly soluble in ethanol, soluble in methanol and freely soluble in dichloromethane.

SOLIAN Tablets contain amisulpride (100 mg, 200 mg and 400 mg) and the following excipients:

100 and 200 mg tablets: sodium starch glycollate type A, lactose, microcrystalline cellulose, hypromellose, magnesium stearate.

400 mg tablets: sodium starch glycollate type A, lactose, cellulose-microcrystalline, hypromellose, magnesium stearate, Peg-40 stearate, titanium dioxide.

SOLIAN SOLUTION contains amisulpride 100mg/mL and the following excipients:

hydrochloric acid, methyl hydroxybenzoate, propyl hydroxybenzoate, potassium sorbate and water-purified.

and the following proprietary ingredients:

Gesweet® Sweetener (ARTG No 10553): vanillin, ethanol, propylene glycol and acetoin and Caramel Flavour® E9422058 (ARTG No 10645): saccharin, gluconolactone and sodium gluconate.

PHARMACOLOGY

Pharmacodynamic Properties

Amisulpride binds selectively to the human dopaminergic D₂ (K_i 2.8 nM) and D₃ (K_i 3.2 nM) receptor subtypes without any affinity for D₁, D₄ and D₅ receptor subtypes (K_i > 1 µM). Unlike classical and atypical neuroleptics, amisulpride displays low affinity for serotonin, α-adrenergic, histamine receptor subtypes, muscarinic receptors and sigma sites.

In the rodent, it preferentially blocks post-synaptic D₂ 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 D₂ hypersensitivity after repeated treatment.

Moreover, it preferentially blocks pre-synaptic D₂/D₃ 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.

Pharmacokinetic Properties

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 tablets is 48%.

Bioequivalence between the solution and the 200 mg tablet has been demonstrated (C_{max} mean ratio 0.95, 90% confidence interval 0.81-1.12; AUC_{0-∞} mean ratio 0.89, 90% confidence interval 0.81-0.97). However, bioequivalence has not been demonstrated between the solution and the 400 mg tablet (C_{max} mean ratio 0.88, 90% confidence interval 0.75-1.04; AUC_{0-∞} mean ratio 0.86, 90% confidence interval 0.78-0.94).

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.

Hepatic insufficiency: See **PRECAUTIONS**.

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} , $T_{1/2}$ and AUC after a single oral dose of 50 mg. No data are available after repeat dosing.

Clinical Trials

The efficacy of amisulpride in the treatment of schizophrenia has been established on the basis of eleven phase II and III studies conducted in 20 countries and involving 1933 patients (1247 treated with amisulpride) belonging to two distinct populations:

- patients with acute exacerbations of schizophrenia
- patients with predominant negative schizophrenia

These studies form the basis of the registration documentation for amisulpride. Seven of them are considered pivotal for efficacy and their results are summarized below.

Acute exacerbations of schizophrenia

In four well-controlled double-blind studies versus reference drugs in patients with acute schizophrenia according to DSM III-R and DSM-IV criteria, amisulpride was at least as effective as haloperidol, flupenthixol and risperidone. In addition to its global antipsychotic activity, amisulpride significantly alleviated secondary negative symptoms as well as affective symptoms such as depressed mood and retardation.

1. A 4-week double-blind active-controlled trial (n=319) compared four fixed doses of amisulpride (100 mg/d, 400 mg/d, 800 mg/d and 1200 mg/d) and a fixed dose of haloperidol (16 mg/d). A dose response relationship was clearly established in comparison to 100 mg/d, chosen as a potentially subtherapeutic dose in acute schizophrenia. Amisulpride at doses of 400 and 800 mg/d statistically significantly improved positive symptoms (BPRS total score, PANSS positive symptoms subscale) compared with amisulpride 100 mg/d. 800 mg/d of amisulpride was also statistically significantly superior to 100 mg/d for response rates based on the CGI.
2. Efficacy results were similar in the three other short-term controlled studies where 800 mg/d of amisulpride was compared with 20 mg/d of haloperidol (n=191), 1000 mg/d of amisulpride with 25 mg/d of flupenthixol (n=132) and 800 mg/d of amisulpride with 8 mg of risperidone (n=228). On BPRS total score and PANSS positive subcale, amisulpride was not found to be different from haloperidol and flupenthixol and showed equivalent efficacy to risperidone. Additionally, amisulpride significantly improved the response rate with CGI versus haloperidol.

Predominant negative schizophrenia

Three pivotal trials were conducted versus placebo in schizophrenic patients with predominant negative symptoms according to DSM III and DSM III-R, showing that low doses of amisulpride are active against negative symptoms.

1. In a six-week dose finding study (n=104), amisulpride 100 mg/d and 300 mg/d were significantly better than placebo on the basis of the SANS total score.
2. In an additional 3-month dose finding study (n=242) testing two fixed dose of amisulpride (50 mg/d and 100 mg/d) versus placebo, both doses of amisulpride were significantly more active in improving the negative symptoms than placebo on the SANS total score. Additionally, there was a significant improvement of the MADRS scores in the two amisulpride groups.
3. A medium-/long-term placebo controlled study with amisulpride 100 mg/d over 6 months with the possibility of extension up to 12 months was conducted to demonstrate the maintenance of efficacy over time. Amisulpride improved negative symptoms (SANS total score) significantly compared with placebo, and the response rate with CGI was significantly higher in the amisulpride group versus placebo. The results were confirmed by the significant improvement of global functioning measured with the GAF. SANS total score remained stable over time up to 12 months, indicating that 100 mg/d not only maintains the improvement of negative symptoms but has also an effect on preventing the recurrence of positive symptoms.

INDICATIONS

Amisulpride is indicated for the treatment of acute and chronic schizophrenic disorders, in which positive symptoms (such as delusions, hallucinations, thought disorders) and/or negative symptoms (such as blunted affect, emotional and social withdrawal) 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 eg pituitary gland prolactinomas and breast cancer.

Phaeochromocytoma.

Children up to puberty.

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 (See **Interactions**).

In hepatic impairment, amisulpride may be contraindicated to avoid the possible risk of adverse events due to an influence of the disease on amisulpride metabolism.

PRECAUTIONS

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.

Amisulpride is eliminated by the renal route. In cases of severe renal insufficiency, the dose should be decreased and intermittent treatment should be considered (see **DOSAGE AND ADMINISTRATION**).

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 (see **Interactions**).

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 galactorrhoea, 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 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.

Prolongation of QT Interval

Amisulpride produces a dose-dependent prolongation of the QT interval. This effect, known to potentiate the risk of occurrence of serious ventricular arrhythmias such as *torsades de pointes*, is enhanced by the existence of bradycardia, hypokalaemia, congenital or acquired long QT interval. Before any administration, and if possible according to the patient's clinical status, it is recommended to rule out factors which could favour the onset of this rhythm disorder:

- Bradycardia less than 55 bpm

- Hypokalaemia
- Congenital prolongation of the QT interval
- On-going treatment with a medication likely to produce pronounced bradycardia (<55 bpm), hypokalaemia, slowing of the intracardiac conduction, or prolongation of the QT_c interval (see **Interactions**).

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 mouse (up to 120 mg/kg/d) and in the rat (up to 240 mg/kg/d), corresponding for the rat to 1.5 to 4.5 times the expected human AUC.

Reproductive studies performed in the rat, rabbit and mouse did not show any teratogenic potential.

Carcinogenicity, Mutagenicity and Impairment of Fertility

In carcinogenicity studies, amisulpride was administered in the diet of mice and rats for up to two years. Treatment of mice was associated with increases in malignant mammary gland tumours and pituitary adenomas in females at all dose levels, but there was no tumourigenic response in males (doses were equivalent to 0.1, 0.2 and 0.5 times the maximum human dose of 1200 mg/day on a body surface area basis). Treatment of rats resulted in increased incidences of malignant mammary gland tumours in both sexes, malignant pituitary tumours and adrenal medullary pheochromocytomas in males, and malignant pancreatic islet cell tumours in both sexes, at doses achieving lower systemic drug exposure (plasma AUC) than in humans at the maximal recommended dose. Increases in mammary gland, pituitary, adrenal and pancreatic endocrine tumours in rodents have been reported for other antipsychotic drugs, and are considered to result from increased prolactin secretion.

The relevance of prolactin-mediated endocrine tumours in rodents for human risk is unknown. In clinical trials, amisulpride substantially elevated plasma prolactin concentrations, although to date neither clinical nor epidemiological studies have shown an association between chronic administration of neuroleptic drugs and mammary tumourigenesis. However, since tissue culture experiments indicate that about one-third of human breast cancers are prolactin-dependent *in vitro*, amisulpride should be used cautiously in patients with previously-detected breast cancer or in patients with pituitary tumours (see **CONTRAINDICATIONS**).

Amisulpride showed no genotoxicity in *in vitro* tests for bacterial gene mutation, or in *in vitro* and *in vivo* tests for clastogenic activity.

Male rat fertility was unaffected by an amisulpride oral dose resulting in systemic drug exposure (plasma AUC) similar to that in humans, when treatment was carried out prior to mating. Female rat mating was reduced by concurrent amisulpride treatment, but it was normalised within days of cessation of dosing with overall fertility being unaffected, although some adverse effects were observed (see **Use in Pregnancy**).

Use in Pregnancy (Category B3)

There was no evidence of teratogenicity in embryofoetal development studies in mice and rabbits following oral doses of up to 2 (mice) and 4 (rabbits) times the maximum recommended human dose based on body surface area, administered daily during the period of organogenesis. Oral treatment of female rats from prior to mating to late gestation or weaning, achieving systemic drug exposure (plasma AUC) similar to that in humans at the maximum dose, was associated with increased preimplantation loss, slight impairment of ossification and reduced pup weight gain to weaning. Teratogenicity was not observed. The safety of amisulpride during human pregnancy has not been established, and therefore use of this drug is not recommended during pregnancy unless the benefits justify the potential risks.

Use in Lactation

It is not known whether amisulpride or its metabolites are excreted in animal or human breast milk. Breast-feeding is therefore contraindicated during amisulpride treatment.

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 thioridazine, chlorpromazine, trifluoperazine, 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 H₁-antihistamines, barbiturates, benzodiazepines and other anxiolytic drugs, clonidine and derivatives.
- Antihypertensive drugs and other hypotensive medications.

A placebo-controlled study of concomitant use of lithium carbonate 500 mg twice daily and a low dose of amisulpride (100 mg) twice daily in healthy young male volunteers showed no effect of amisulpride on the pharmacokinetics of lithium. A small trend towards prolongation of the QT_c interval was observed when lithium and amisulpride were co-administered but is not regarded as clinically important.

A study of the effect of concomitant use of cimetidine on amisulpride excretion has not been conducted.

In vitro studies using human liver microsomes and cryopreserved human hepatocytes did not show evidence of significant amisulpride metabolism. Based on these results, it is unlikely that drug interactions involving amisulpride would occur due to inhibition or induction of cytochrome P450 –mediated metabolism.

Effects on ability to drive and use machines

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

ADVERSE REACTIONS

Clinical Trial Data

The following adverse effects have been observed in controlled clinical trials in at least 1% of treated patients (see Table). It should be noted that, in some instances, it can be difficult to differentiate adverse events from symptoms of the underlying disease.

Amisulpride – Negative & Positive Schizophrenia Clinical Studies

Adverse events reported with an incidence of 1% or greater in the amisulpride group.

	Amisulpride (n = 921) %	Placebo (n = 202) %	Haloperidol (n=245) %	Flupentixol/Risperidone (n=62) %
CNS Disorder				
Extrapyramidal disorder	11	2	33	12
Insomnia	10	7	11	7
Anxiety	7	5	9	6
Agitation	5	3	5	4
Tremor	3	6	4	7
Somnolence	3	0	4	4
Headache	3	4	3	10
Rigidity	2	2	5	5
Hypersalivation	2	0	2	4
Dyskinesia	2	0	6	0
Nervousness	2	1	2	1
Dystonia	1	0	3	1
Oculogyric crisis	1	0	1	2
Depression	1	0	2	1
Dizziness	1	1	0	3
Aggressive reaction	1	1	1	0
Suicide attempt	1	0	2	3
Gastro-intestinal disorders				
Constipation	3	1	4	1
Vomiting	2	3	2	4
Nausea	2	2	2	2
Dry mouth	1	1	2	0
Diarrhoea	1	1	1	0
Abdominal pain	1	1	1	3

	Amisulpride (n = 921) %	Placebo (n = 202) %	Haloperidol (n=245) %	Flupentixol/Risperidone (n=62) %
Dyspepsia	1	0	0	0
Body as a whole disorders				
Weight increase	6	5	2	5
Weight decrease	2	2	1	0
Sweating increased	1	1	0	0
Fatigue	1	1	1	4
Reproductive disorders				
Amenorrhoea	4	0	0	0
Galactorrhoea	3	0	1	13
Menstrual disorder	1	0	0	2
Vaginitis	1	0	1	0
Cardiovascular disorders				
Hypotension	1	0	1	3
Hypotension postural	1	0	0	3
Hypertension	1	0	0	2
Cutaneous disorders				
Pruritis	1	1	0	1

Central and Peripheral Nervous System Disorders. Tardive dyskinesia characterised by rhythmic, involuntary movements primarily of the tongue and/or face have been rarely reported, usually after long-term administration. Anti-parkinsonian medication is ineffective or may induce aggravation of the symptoms.

Seizures have been reported rarely.

Cardiovascular Disorders. Bradycardia has been rarely reported.

Body as a Whole – General Disorders. Allergic reactions have been reported rarely.

Hepatic System. Elevations of hepatic enzymes, mainly transaminases, have been very rarely reported.

Post-Marketing Data

Very rare cases of Neuroleptic Malignant Syndrome have been reported (see **PRECAUTIONS**).

Cases of QT prolongation and very rare cases of *Torsades de pointes* have also been reported.

Very common	≥10%
Common	>1% - <10%
Uncommon	≥0.1% - <1%
Rare	≥0.01% - <0.1%
Very rare	<0.01%

DOSAGE AND 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. Doses above 800 mg/d have not been shown to be superior to lower doses and may increase the incidence of adverse events. No specific titration is required when initiating the treatment with amisulpride. Doses should be adjusted according to individual response.

Doses should preferably be administered before meals.

Amisulpride should be administered bid for doses above 400 mg.

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.

A graduated dosage syringe (pipette) is supplied for dispensing SOLIAN SOLUTION. Each one mL graduation is equivalent to 100mg amisulpride.

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 (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 ($CR_{CL} < 10$ mL/min) particular care is recommended in these patients (see **PRECAUTIONS**).

Hepatic insufficiency:

Since the drug is weakly metabolised, a dosage reduction should not be necessary (see **PRECAUTIONS**).

OVERDOSAGE

Experience with amisulpride in overdose 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, anticholinergic agents should be administered.

PRESENTATIONS

SOLIAN 100: white to off white, flat-faced breakable tablet, engraved "AMI 100".

SOLIAN 200: white to off white, flat-faced breakable tablet, engraved "AMI 200".

SOLIAN 400: white, film-coated, breakable, oblong tablet, engraved "AMI 400".

Packed in blister packs.

SOLIAN SOLUTION 100mg/mL: a clear, pale yellow coloured liquid, is packed in 60mL brown glass bottles.

STORAGE

SOLIAN Tablets: Store below 30°C.

SOLIAN Solution: Store below 25°C. Once opened, discard after two months.

SPONSOR

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