SOLIAN
100mg & 400mg
Amisulpride scored Tablets

AVAILABILITY
Solian 100 mg scored tablet
Amisulpride (INN) ............................................100 mg
Solian 400 mg scored film coated tablet ......................400 mg

PHARMACODYNAMIC PROPERTIES
Anti psychotic (N: Central Nervous System)

Amisulpride is an antipsychotic in the class of substituted benzamides.
Its pharmacodynamic profile is characterised by selective and predominant affinity for D2 and D3 dopaminergic receptors in the limbic system. Amisulpride has no affinity for serotonergic receptors or other neuroreceptors of histamine, cholinergic or adrenergic types.

At high doses in animal studies, amisulpride preferentially blocked the dopaminergic neurones of the mesolimbic system rather than those in the striatal system. The specific affinity may explain the antipsychotic effects of amisulpride which predominate over its extrapyramidal effects.

At low doses, amisulpride preferentially blocks presynaptic D2/D3 dopaminergic receptors, which may explain its action on negative symptoms.

During a controlled, double-blind study versus haloperidol, including 191 patients with acute schizophrenia, the use of amisulpride was associated with an improvement in secondary negative symptoms which was significantly superior to that achieved by comparator.

PHARMACOKINETIC PROPERTIES
In man, amisulpride exhibits two peaks of absorption: the first is reached rapidly, one hour after dosing, and the second is reached three or four hours after administration.

The corresponding plasma levels are 39 ± 3 and 54 ± 4 ng/ml, respectively, following the administration of a 50mg dose.

The distribution volume is 5.8 l/kg. Plasma protein binding is weak (16%) and no drug interactions are anticipated with respect to binding on these proteins. The absolute bioavailability reaches 48%.
Amisulpride is weakly metabolised: two inactive metabolites have been identified and represent 4% of the total quantity excreted.

Following repeated doses amisulpride does not accumulate, and the pharmacokinetic parameters are unchanged.

The elimination half-life is approximately 12 hours after oral administration.
Amisulpride is excreted in an unchanged form in the urine, 50% of the dose administered via the IV route is excreted in the urine, mainly during the first 24 hours (90% of urinary excretion).

Renal clearance is about 330ml/minute.

A high carbohydrate meal significantly reduces the AUC, Tmax and Cmax values of amisulpride,
while a meal with a high fat content does not effect these parameters. The effect of these results during treatment with amisulpride is not unknown.

Liver failure
Because amisulpride is little metabolised, a reduction in dosage is not necessary in patients with liver failure.

Renal failure
The elimination half-life is not modified in patients with renal failure, but total clearance is reduced by a factor of 2.5 to 3.
The AUC of amisulpride is multiple two-fold in patients with mild renal failure, and nearly 10 fold in dose with moderate renal failure.
However, experiment is limited no data are available for doses higher than 50mg.
Amisulpride is weakly dialyzable.

Elderly subjects
The pharmacokinetic data available in elderly subjects over the age of 65 years show a 10 to 30% increase in Cmax, T1/2 and AUC values following a single dose of 50mg.
No data are available following repeated doses.

PRECLINICAL SAFETY DATA
The toxicological profile of amisulpride is dominated by the pharmacological effects of the compound. No target organ seems to have been revealed by toxicity studies following repeated administration. The compound is devoid of teratogenic and genotoxic potential. Studies of carcinogenesis have demonstrated hormone dependent tumours in rodents. These are not any clinical relevance in man.

THERAPEUTIC INDICATIONS
Solian is indicated for the treatment of psychoses, particularly acute or chronic schizophrenic disorders characterised by a positive symptoms (such as delusion, hallucination, thought disorders) and/or negative symptoms (such as blunted effect, emotional and social withdrawal), including when negative symptoms predominate.

CONTRA–INDICATIONS
This medicine MUST NOT BE USED in the following cases:
- Known hypersensitivity to amisulpride or another component of the product.
  Serious hypertensive accidents have been reported in patients with pheochromocytoma using antidopaminergic drugs, including some benzamides.
  It is therefore wise to abstain from prescribing this product in known or suspected sufferers of pheochromocytoma.
- Children below the age of 15 years, because no clinical data are available on this age group.
- Lactation.
- Known or suspected prolactin-dependent tumour, e.g., prolactin secreting pituitary adenoma and breast cancer.
- Severe renal insufficiency (CICr < 10ml/min).
- In combination with:
  - sultopride
- dopaminergic agonists (amantadine, apomorphine, bromocriptine, cabergoline, antacapone, lisuride, pergolide, priribedil, pramipexole, quinagolide, ropinirole), except in the case of patients with Parkinson's disease. (see interactions with other medicinal products and other forms of interaction).
Use of this medicinal product is GENERALLY INADVISABLE in the following cases:

- In combination with:
  - alcohol
  - levodopa
  - medicines which may cause torsades de pointes: class la (quinidine, hydroquinidine, disopyramide) and class III (amiodarone, sotalol, dofetilide, ibutilide) anti-arrhythmics, some neuroleptics (thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, tiapride, pimozide, haloperidol, droperidol).
  - and other medicines such as: bepidril, cisapride, diphenamid, IV erythromycin, mizolastine, IV vincamine, halofantrine, pentamidine, sparflaxacin, moxifloxacin, etc.
  - dopaminergic agonist (amantadine, apomorphine, bromocriptine, cabergoline, entacapone, lisuride, pergolide, priribedil, pramipexole, quinagolide, ropinirole), in patients with Parkinson's disease.

(see interaction with other medicinal products and other forms of interaction).

**WARNINGS AND SPECIAL PRECAUTION FOR USE**

**Warnings**

- **Neuroleptic Malignant syndrome**
  As with other neuroleptics, the onset of malignant syndrome (hyperthermia, muscle rigidity, neurovegetative disorders, impaired consciousness, elevation of CPK) is possible. In the event of hyperthermia, particularly in patients receiving high daily doses, any antipsychotic therapy should be discontinued.

- **Prolongation of the QT interval**
  Amisulpride prolongs the QT interval in a dose-dependent way. This effect, known to potentize the risk of onset of severe ventricular rhythm disorders such as torsades de pointes, is enhanced by the existence of bradycardia, hypokaliemia, congenital or acquired long QT interval (combination with a drug increasing the QTc interval)
  If the clinical status so permits, it is necessary to verify the absence of factors, which may favour the onset of the arrhythmia before any administration:
  - Bradycardia slower than 55 bpm.
  - Hypokaliemia.
  - Congenital prolongation of the QT interval.
  - Current treatment with a drug likely to cause marked bradycardia (<55bpm), hypokaliemia, slowing of intracardiac conduction or prolongation of the QTc interval.

An ECG is recommended as part of the initial assessment of patients who are to receive long-term neuroleptic therapy.

Because it contains lactose, this medicine is contraindicated in the event of congenital galactosemia, glucose or galactose malabsorption syndrome or lactase deficiency.

**Precaution for use**

- Because of the renal excretion of this product, a reduction in dosage is recommended in patient with renal insufficiency (Cf, Dosage and Administration). No data are available concerning patients with severe renal insufficiency (Cf, Contraindications).
Neuroleptics are known to lower the epileptogenic threshold. Patients with a history of convulsive attacks should therefore be monitored closely during treatment with Solian.

Caution should be exercised in elderly subjects, because of their high sensitivity (sedation and hypotension).

Caution should be exercised in patient with Parkinson’s disease, in whom this product should only be used if neuroleptic therapy is absolutely necessary.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

**Contraindicated combination**

+ Dopaminergic agonists (amantadine, apomorphine, bromocriptine, cabergoline, entacapone, lisuride, pergolide, piribedil, pramipexole, quinagolide, ropinirole), except in the case of patients with Parkinson’s disease.
  Reciprocal antagonism of the dopaminergic agonist and neuroleptics.
  In the event of an extrapyramidal syndrome induced by the neuroleptic, do not treat with a dopaminergic agonist but use an anticholinergic.
  + Sultopride
    Increased risk of ventricular arrhythmia, particularly torsades de pointes.

**Inadvisable combination**

+ Drugs which may cause torsades de pointes: class la (quinidine, hydroquinidine, disopyramide) and class III (amiodarone, sotalol, dofetilide, ibutilide) anti-arrhythmics, some neuroleptics 9thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, tiapride, pimozide, haloperidol, droperidol), bepridil, cisapride, diphemanil, IV erythromycin, mizolastine, IV vincamine etc.
  Increased risk of ventricular arrhythmia, particularly torsades de pointes.
  + Alcohol
    Alcohol enhances the sedative effect of neuroleptics.
    Impaired alertness may render driving or machine operation dangerous.
    Avoid the consumption of alcoholic drinks and medicines containing alcohol.
  + Levodopa
    Reciprocal antagonism of levodopa and neuroleptics.
    In patients with Parkinson’s disease, use the minimum effective dose of both medicines.
  + Dopaminergic agonists (amantadine, apomorphine, bromocriptine, cabergoline, entacapone, lisuride, pergolide, piribedil, pramipexole, quinagolide, ropinirole), in patients with Parkinson’s disease. Reciprocal antagonism of the dopaminergic agonist and neuroleptics.
    The dopaminergic agonist may cause or aggravate the psychotic disorders.
    If treatment with a neuroleptic is necessary in patients with Parkinson’s disease receiving a dopaminergic agonist, the latter should be tapered gradually to discontinuation (the abrupt withdrawal of dopaminergics may expose the patient to a risk of neuroleptic malignant syndrome).
  + Halofantrine, pentamidine, sparfloxacin, moxifloxacin:
    Increased risk of ventricular arrhythmia, particularly torsades de pointes.
    If possible, discontinue the non anti-infectious drug causing torsades de pointes.
    If the combination cannot be avoided, prior verification of the QT interval and monitored ECG surveillance.

**Combination requiring precautions for use.**
+ **Bradycardiac medicines** (calcium channel blockers with bradycardiac effects: diltiazem, verapamil; beta-blockers; clonidine; guanfacine; digitalis; anticholinesterase agents: donezepil, rivastigmine, tacrine, ambemonium, galantamine, pyridostigmine, neostigmine)
  Increased risk of ventricular arrhythmia particularly torsades de pointes Clinical and ECG monitoring.

+ **Potassium-lowering medicines** (potassium-lowering diuretics, stimulant laxatives, amphotericin B (IV route), glucocorticosteroids, tetracosactide).
  Increased risk of ventricular arrhythmia, particularly torsades de pointes.
  Correct any hypokaliemia before administering the product, and ensure the monitoring of clinical, electrolyte and electrocardiographical parameters.

**Combination to be taken into account**
+ **Antihypertensive (all):**
  Antihypertensive effect and increased risk of orthostatic hypotension (additive effect).

+ **Other central nervous system depressant:**
  Morphine derivatives (analgesic, antitussive and replacement therapies); barbiturates, benzodiazepines, anxiolytics other than benzodiazepines; hypnotics, sedative antidepressant; sedative H1 antihistaminic agents; central antihypertensives; baclofen; thalidomide.
  Increase in central depression. Impaired alertness may render driving or machine operation dangerous.

**ADVERSE EFFECTS**

**EFFECT ON ABILITY TO DRIVE AND USE MACHINES**
Drivers and machine operators are warned of the risk of drowsiness associated with to the use of this medicine.

**Pregnancy**
Animal studies have not demonstrated any teratogenic effect. In the absence of any teratogenic effect in animal, a malformative effect is not anticipated in humans. Indeed, to date, substances causing malformations in humans have proved to be teratogenic in animals during well-conducted clinical studies in two species.

In clinical use, insufficient relevant data are available at present to assess any malformative or foetotoxic effect of amisulpride when it is administered during pregnancy.

Consequently, as a precaution, preference should be given to not using amisulpride during pregnancy.

**Lactation:** in the absence of data on passage into breast milk, breast feeding is contraindicated.

**Undesirable effects**

**Common :**
- Elevation of serum prolactin levels, reversible on treatment discontinuation, which may cause the following clinical symptoms: galactorrhea, amenorrhea, gynecomastia, swollen breast, impotence, frigidity.
- Weight gain
- Extrapyramidal symptoms (tremor, hypertonia, hypersalivation, akathisia, hypokinesia) may occur. These are usually of moderate intensity at maintenance doses and partially reversible, without discontinuation of Solian, using anticholinergic antiparkinsonian therapy.
The frequency of extrapyramidal symptoms (which are dose-dependent) is very low in patients receiving doses of between 50 and 300 mg/day to treat of predominantly negative symptoms.

During clinical studies, the patients treated with amisulpride presented a lower incidence of extrapyramidal symptoms than those receiving haloperidol.

**Occasionally :**
- Drowsiness.
- Gastrointestinal disorders such as constipation, nausea, vomiting, dry mouth.

**Very rarely :**
- Acute dystonia (spasmodic torticollis, oculogyric crisis, trismus, etc) may occur. This is reversible without discontinuing treatment, under the effect of an anticholinergic, antiparkinsonian agent.
- Tardive dyskinesia, characterised by involuntary movements of the tongue and/or face has been reported, particularly after prolonged administration. Anticholinergic antiparkinsonians have not effect or may worsen the symptoms.
- Cases of hypotension and bradycardia have been reported.
- Cases of increase in the QT interval, and very rare cases of torsades de pointes, have been described (see: Warnings and Precaution for Use).
- Allergic reactions.
- Convulsive episodes.
- Cases of neuroleptic malignant syndrome (see: Warnings and Precaution for Use).
- Cases of hypotension and bradycardia have been reported.
- Cases of a prolongation of the QT interval, and very rare cases of torsades de pointes, have been reported (Cf. Warnings and Precaution for Use).

**POSOLOGY**

**DOSAGE AND METHOD OF ADMINISTRATION**

As a general rule, if the daily dose is £ 400 mg, administration should be in a single daily intake; above 400 mg, the medicine should be administered in two daily intakes.

**Predominant negative episodes**

The recommended dosage is 50 to 300mg/day. Dosage should be adjusted on an individual basis. The optimum dosage is around 100 mg/day.

Mixed episodes with positive and negative symptoms.

At the beginning of treatment, the dosage should be that which enables to control of the positive symptoms, or 400 to 800 mg/day. The dosage should then be adjusted individually as a function of the patient’s response, so as to attain the minimum effective dose.

**Acute psychotic episodes**

At the beginning of treatment, the recommended dosage via the oral route is 400 to 800 mg; the maximum dosage should
never exceed 1200mg.
Thereafter
·the dosage should be maintained or adjusted as a function of the patient’s response.

In all cases, the dosage of maintenance therapy should be established individually using the minimum effective dose.

Renal insufficiency: because amisulpride is excreted via the kidneys, the dosage in patients with renal insufficiency should be reduced by half in those whose creatinine clearance (ClCr) is between 30 and 60ml/minute, and by a third if the creatinine clearance is between 10 and 30ml/min. If no data are available on patients presenting with severe renal insufficiency (ClCr < 10 ml/min), amisulpride is contraindicated (see Contraindications).

Liver insufficiency: because amisulpride is only slightly metabolised, a dosage reduction is not necessary in patients with liver failure.

OVERDOSAGE

To date, the data concerning acute overdose with Solian are limited. The signs and symptoms which have been reported usually resulted from an increase in the pharmacological effects of the medicine, producing clinical symptoms such as: drowsiness, sedation, coma, hypotension and extrapyramidal symptoms.

There is no known, specific antidote to amisulpride. In the event of an acute overdose, a combination with other medicine should be determined and appropriate measures implemented:
- Close monitoring of the vital signs.
- Cardiac monitoring (risk of increase in QT interval), which should be maintained until the patient has recovered.
- If severe extrapyramidal symptoms appear, anticholinergic therapy should be initiated.
- Amisulpride is weakly dialysable.

SHELF LIFE
3 years

Store temperature below 250

Package:
Box of 3 blisters of 10 scored film coated tablets.

Harus dengan resep dokter

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