For the use only of a Registered Medical Practitioner (Psychiatrist) or a Hospital or a Laboratory

This package insert is continually updated: Please read carefully before using a new pack.

Amisulpride Tablets I.P.
SOLIAN®
50mg, 100mg, 200mg and 400 mg

Composition

Solian®50
Each uncoated tablet contains:
Amisulpride IP.... 50 mg

Solian® 100
Each uncoated tablet contains:
Amisulpride IP.... 100 mg

Solian® 200
Each uncoated tablet contains:
Amisulpride IP.... 200 mg

Solian®400
Each film coated tablet contains:
Amisulpride IP.... 400 mg

INDICATIONS

Solian® 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 effect, emotional and social withdrawal) are prominent, including patients characterised by predominant negative symptoms.

DOSAGE AND METHOD OF ADMINISTRATION

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

Solian® 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.

USE IN SPECIFIC POPULATIONS

Pediatric patients: The efficacy and safety of amisulpride 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 amisulpride from puberty to the age of 18 years is not recommended; in children up to puberty amisulpride is contraindicated (see section ContraIndications).

Elderly patients: Solian® should be used with particular caution because of a possible risk of hypotension or sedation.

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

Renal impairment: Amisulpride is eliminated by 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 (see section Precautions).

CONTRAINDICATIONS

- Hypersensitivity to the active ingredient or to other ingredients of the medicinal product
- Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer (see section Warnings and section, Adverse reactions)
- Phaeochromocytoma
- Children up to puberty
- Lactation (See Section Lactation)
- Combination with the following medications which could induce torsade de pointes:
    - Class Ia antiarrhythmic agents such as quinidine, disopyramide.
    - Class III antiarrhythmic agents such as amiodarone, sotalol.
    - Others medications such as bepridil, cisapride, sultopride, thioridazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin (see section Interactions).
- Combination with levodopa (see section Interactions).

WARNINGS

- As with other neuroleptics, Neuroleptic Malignant Syndrome, a potentially fatal complication characterized by hyperthermia, muscle rigidity and autonomic instability, rhabdomylosis and elevated CPK (creatinine phosphokinase) may occur. In the event of hyperthermia particularly with high daily doses, all antipsychotic drugs including amisulpride should be discontinued.

  Rhabdomyolysis has also been observed in patients without Neuroleptic Malignant Syndrome

- 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.

- **Prolongation of the QT interval:** Amisulpride induces a dose-dependent prolongation of the QT interval (see Adverse reactions). This effect is known to potentiate the risk of serious ventricular arrhythmias such as torsade de pointes. Before any administration, and if possible according to the patient's clinical status, it is recommended to monitor factors which could favour the occurrence of this rhythm disorder, such as for example:
    - bradycardia less than 55 bpm,
    - electrolyte imbalance, in particular hypokalemia,

- congenital prolongation of the QT interval,
- on-going treatment with a medication likely to produce pronounced bradycardia (< 55 bpm), hypokalemia, decreased intracardiac conduction, or prolongation of the QT interval (see section Interactions).

- **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 anti-psychotics were varied, most of the deaths appeared to be either cardiovascular (e.g., heart 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.

- **Venous thromboembolism:**
  Cases of venous thromboembolism, sometimes fatal, have been reported with antipsychotic drugs. Therefore, Solian® should be used with caution in patients with risk factors for thromboembolism (see Section Adverse Reactions.)

- **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.

- **Benign pituitary tumour**:
  Amisulpride may increase prolactin levels. Cases of benign pituitary tumours such as prolactinoma have been observed during amisulpride therapy. (see section Adverse reaction). In case of very high levels of prolactin or clinical signs of pituitary tumour (such as visual field defect and headache), pituitary imaging should be performed. If the diagnosis of pituitary tumour is confirmed, the treatment with amisulpride must be stopped (see section Contraindications)

PRECAUTIONS

- Hyperglycemia 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 may lower the seizure threshold. Therefore, patients with a history of epilepsy should be closely monitored during amisulpride therapy.
- Amisulpride is eliminated by the renal route. In cases of renal insufficiency, the dose should be decreased or intermittent treatment could be considered (see section Dosage and Administration).

- In elderly patients, amisulpride, like other neuroleptics, should be used with particular caution because of a possible risk of hypotension or sedation.
- 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.
- Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics, including Solian®. Unexplained infections or fever may be evidence of blood dyscrasia (section Adverse Reactions) and requires immediate hematological investigation.

PREGNANCY

Animal studies do not indicate direct or indirect harmful effects with respect to teratogenicity and embryofetotoxicity. Animal studies are insufficient with respect to neurodevelopmental disorders in pups.
Amisulpride crosses the placenta.
Very limited clinical data on exposed pregnancies are available. Therefore, the safety of amisulpride during human pregnancy has not been established. The use of Amisulpride is not recommended during pregnancy and in women of childbearing potential not using effective contraception, unless the benefits justify the potential risks.
Neonates exposed to antipsychotics, including Solian® 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 (section Adverse Reactions). There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Fertility
A decrease in fertility linked to the pharmacological effects of the drug (prolactin-mediated effect) was observed in treated animals.

LACTATION
Amisulpride has been found in milk in treated women. Breast-feeding is contra-indicated.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS
Even when used as recommended, amisulpride may cause somnolence and blurred vision so that the ability to drive vehicles or operate machinery can be impaired (see section Adverse Reactions).

INTERACTIONS
Contraindicated combinations
- Medications which could induce torsade de pointes:
  - Class Ia antiarrhythmic agents such as quinidine, disopyramide.
  - Class III antiarrhythmic agents such as amiodarone, sotalol.
  - Others medications such as bepridil, cisapride, sultopride, thioridazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin.

- Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics.

Combinations not recommended
- Amisulpride may enhance the central effects of alcohol.
- Medications which enhance the risk of torsade de pointes or could prolong the QT interval:
  - Bradycardia-inducing medications such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine, guanfacine; digitalis.
  - Medications which induce hypokalemia: hypokalemic diuretics, stimulant laxatives, IV amphotericin B, glucocorticoids, tetracosactides. Hypokalemia should be corrected.
  - Neuroleptics such as pimozide, haloperidol; imipramine antidepressants; lithium.

Combinations to be taken into account

- CNS depressants including narcotics, analgesics, sedative H1 antihistamines, barbiturates, benzodiazepines and other anxiolytics, clonidine and derivatives.
- Antihypertensive drugs and other hypotensive medications.
- Co-administration of amisulpride and clozapine may lead to an increase in plasma levels of amisulpride

ADVERSE REACTIONS

The following CIOMS frequency rating is used, when applicable:
Very common ≥ 10%; common ≥1 and <10%; Uncommon ≥0.1 and <1%; Rare ≥ 0.01 and <0.1%; Very rare <0.01%, Not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:
Uncommon: leukopenia, neutropenia (see Section Precautions)
Rare: agranulocytosis (see Section Precautions)

Immune system disorders:
Uncommon: allergic reaction

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.
Rare: benign pituitary tumour such as prolactinoma (see Section Contraindications and Section Warnings)

Metabolism and nutrition disorders:
Uncommon: hyperglycemia (see Section Precautions), hypertriglyceridemia and hypercholesterolemia
Rare: hyponatraemia, syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Psychiatric disorders:
Common: insomnia, anxiety, agitation, orgasmic dysfunction
Uncommon: confusion

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
Rare: Neuroleptic Malignant Syndrome (see Section Warnings), which is a potentially fatal complication
Not known: restless legs syndrome with or without a context of akathisia

Eye disorders:
Common: blurred vision (see Section Driving a vehicle or performing other hazardous tasks)

Cardiac disorders:

Uncommon: bradycardia
Rare: QT interval prolongation, ventricular arrhythmias such as torsade de pointes, ventricular tachycardia, ventricular fibrillation, cardiac arrest, sudden death (see Section Warnings)

Vascular disorders:
Common: hypotension
Uncommon: increase in blood pressure
Rare: venous thromboembolism, including pulmonary embolism, sometimes fatal, and deep vein thrombosis (see Section Warnings)
Respiratory, thoracic and mediastinal disorders: Uncommon: nasal congestion, pneumonia aspiration (mainly in association with other antipsychotics and CNS depressants).

Gastrointestinal disorders
Common: constipation, nausea, vomiting, dry mouth

Hepatobiliary disorders
Uncommon: hepatocellular injury

Skin and subcutaneous tissue disorders:
Rare: angioedema, urticaria
Not known: photosensitivity reaction

Musculoskeletal and connective tissue disorders:
Uncommon: osteopenia, osteoporosis
Not known: rhabdomyolysis,

Renal and urinary disorders
Uncommon: urinary retention

Injury, poisoning and procedural complications:
Not known: Fall as a consequence of adverse reactions compromising body balance

Pregnancy, puerperium and perinatal conditions:
Frequency not known: drug withdrawal syndrome neonatal (see Section Pregnancy)

Investigations:
Common: weight gain
Uncommon: elevations of hepatic enzymes, mainly transaminases
Not known: blood creatine phosphokinase

OVERDOSAGE
Signs and Symptoms:
Exaggerations of the known pharmacological effects of the drug have been reported. These include drowsiness, sedation, hypotension, extrapyramidal symptoms and coma. Fatal outcomes have been reported mainly in combination with other psychotropic agents.

Management:
In cases of acute overdose, the possibility of multiple drug intakes should be considered. Since amisulpride is weakly dialyzed, hemodialysis is of no use to eliminate the drug. There is no specific antidote to amisulpride. Appropriate supportive measures should therefore be instituted: close supervision of vital functions and continuous cardiac monitoring (risk of prolongation of QT interval)

until the patient recovers. If severe extra-pyramidal symptoms occur, anti-cholinergic agents should be administered.

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