SOLIAN® Abridged Prescribing Information

1-NAME AND PRESENTATION: Solian tablets contains amisulpride in the form of :
50 mg tablets and 200 mg scored tablets
2. THERAPEUTIC INDICATIONS: Treatment of schizophrenia.

3. POSOLOGY AND METHOD OF ADMINISTRATION:
Posology
if the daily dose does not exceed 400 mg, it should be administered once daily;
if the daily dose exceeds 400 mg, it should be administered as two divided doses.
Acute psychotic episodes
It is possible to start via the IM route for a few days, at a maximum dose of 400 mg/day, switching thereafter to oral treatment. Doses between 400 mg/day and 800 mg/day are recommended for oral administration. The maximum daily dose should never exceed 1 200 mg. Given that there has been no large-scale safety assessment of doses higher than 1 200 mg/day, these doses should not be used.
The dosage should then be maintained or adjusted depending on the patient's individual response.
In all cases, the maintenance treatment should be established individually with the minimum effective dose.
Predominantly negative episodes
Doses between 50 mg/day and 300 mg/day are recommended. Doses should be adjusted individually. The optimum dose is about 100 mg/day.
Children and adolescents
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. Amisulpride is contraindicated in children under 15 years of age, since the safety of the drug has not been established .
Elderly patients
The safety of amisulpride has been assessed in a limited number of elderly subjects. The medicinal product should be used with particular caution in this patient population due to the risk of hypotension and sedation. Dose reduction may also be required in patients with kidney failure.
4. **CONTRA-INDICATIONS**: This medicinal product MUST NOT BE USED in the following situations:
This medicinal product MUST NOT BE USED in the following situations:
Hypersensitivity to amisulpride or any of the excipients listed in section 6.1,
Serious hypertensive events have been reported in patients with pheochromocytoma using antidopaminergic drugs, including some benzamides. This medicinal product should therefore not be prescribed to known or suspected pheochromocytoma carriers,
 Children under 15 years of age, because no clinical data are available,
 Known or suspected prolactin-dependent tumors, e.g. pituitary gland prolactinomas and breast cancer (see sections 4.4 and 4.8),
 In combination with:
o non-antiparkinsonian dopamine agonists (cabergoline, quinagolide),
o citalopram, escitalopram, domperidone, hydroxyzine, piperaquine
5. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
As with other neuroleptics, Neuroleptic Malignant Syndrome, a potentially fatal complication, characterized by hyperthermia, muscle rigidity and autonomic instability, consciousness disturbances and elevated creatine phosphokinase (CPK) may occur. In the event of hyperthermia particularly with high daily doses, all antipsychotic drugs including amisulpride should be discontinued.
Prolongation of the QT interval
Amisulpride induces a dose-dependent prolongation of the QT interval. This effect, known to potentiate the risk of serious ventricular arrhythmias, particularly torsades de pointes, is worsened in patients with bradycardia, hypokalemia, or congenital or acquired prolonged QT interval (use in combination with a drug increasing the QTc interval) (see section 4.8).
Prior to administration and depending on the patient’s clinical status, it is necessary to rule out any risk factors for arrhythmias, such as:
 bradycardia less than 55 bpm,
 hypokalemia,
 congenital prolongation of the QT interval,

 ongoing treatment with a medication likely to produce pronounced bradycardia (< 55 bpm), hypokalemia, decreased intracardiac conduction or prolongation of the QTc interval (see sections 4.3 and 4.5).

An ECG should be performed as part of the initial assessment of patients requiring long-term treatment with a neuroleptic.

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 in 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. This medicinal product should be used with caution in patients with stroke risk factors.

Elderly patients with dementia

There is an increased risk of mortality in elderly patients with dementia-related psychosis treated with antipsychotic drugs. Analyses of seventeen placebo-controlled trials (mean duration of 10 weeks1), largely in patients taking atypical antipsychotic drugs, revealed a risk of mortality in drug-treated patients of between 1.6 to 1.7 times the risk of mortality in placebo-treated patients.

Over the course of a typical 10-week treatment period, the risk of mortality2 in drug-treated patients was approximately 4.5%, compared to approximately 2.6% in the placebo group.

Although the causes of death in clinical trials with atypical antipsychotics 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.

It is unclear how much the antipsychotic drug and patient characteristics contribute to the increase in mortality found in the epidemiological studies.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotic drugs often have acquired risk factors for VTE, any potential risk factors for VTE must be identified before and during treatment with Solian and preventive measures should be taken if needed (see section 4.8).

Hyperglycemia/Metabolic syndrome

Cases of hyperglycemia or glucose intolerance and onset or exacerbation of diabetes have been reported in patients treated with certain atypical antipsychotic drugs, including amisulpride (see section 4.8).

Clinical and laboratory monitoring should be performed in patients receiving treatment with Solian in compliance with current recommendations. Particular caution should be exercised in patients with diabetes mellitus or with risk factors for diabetes.

Seizures

Amisulpride may lower the seizure threshold. Therefore, patients with a history of seizures should be closely monitored during treatment with Solian.

Special populations

As amisulpride is eliminated by the renal route, the dose should be decreased in patients with renal failure or another treatment may be considered (see section 4.2). There are no data concerning patients with serious renal failure (see section 4.2).

Amisulpride, like all antipsychotics, should be used with particular caution in elderly patients due to the potential risk of sedation and hypotension. A dose reduction may also be required in elderly patients with renal failure (see section 4.2).

As with other antidopaminergic agents, caution should be exercised when administering amisulpride in 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 syndrome

Withdrawal symptoms including nausea, vomiting and insomnia have been described following sudden discontinuation of high doses of antipsychotics. Recurrence of psychotic symptoms may also be observed and involuntary movement disorders (such as akathisia, dystonia and dyskinesia) have been reported with amisulpride. Therefore, gradual withdrawal of amisulpride is advisable.

Hyperprolactinemia

Amisulpride may increase prolactin levels (see section 4.8). Patients with a history of hyperprolactinemia or of a potentially prolactin-dependent tumor should be closely monitored during amisulpride treatment (see section 4.3).

Benign pituitary tumor

Amisulpride may increase prolactin levels. Cases of benign pituitary tumors such as prolactinoma have been observed during amisulpride therapy (see section 4.8). In case of very high levels of prolactin or clinical signs of pituitary tumor (such as visual field defect and headache), pituitary imaging should be performed. If the diagnosis of pituitary tumor is confirmed, amisulpride treatment must be stopped

6. DRUG INTERACTIONS

+ Sedative drugs

Many drugs or substances can have additive depressant effects on the central nervous system and contribute to decreased alertness. This must be taken into account for patients using amisulpride. These drugs/substances include morphine derivatives (analgesics, cough suppressants and replacement therapies), neuroleptics, barbiturates, benzodiazepines, anxiolytics other than benzodiazepines (e.g. meprobamate), hypnotics, sedative antidepressants (amitriptyline, doxepin, mianserin, mirtazapine, trimipramine), sedative H1 antihistamines, centrally acting antihypertensive agents, baclofen and thalidomide.

+ Medications likely to induce torsades de pointes

This serious cardiac rhythm disorder can be caused by a number of antiarrhythmic and non-antiarrhythmic drugs. Hypokalemia (see Potassium-depleting agents) is a promoting factor, as is bradycardia (see Bradycardia-inducing drugs) or pre-existing congenital or acquired QT interval prolongation.

Medicines likely to cause this adverse effect include class Ia and III antiarrhythmic agents and certain neuroleptics.

Other agents not belonging to these classes are also involved.

For dolasetron, erythromycin, spiramycin and vincamine, only intravenously administered forms are concerned by this interaction.

Coadministration of two torsadogenic drugs is generally contraindicated.

However, some of these torsadogenic drugs are exceptions to this as they are considered essential. In this case, coadministration is simply not recommended. These torsadogenic drugs include methadone, hydroxychloroquine, antiparasitic agents (chloroquine, halofantrine, lumefantrine, pentamidine), neuroleptics.

However, citalopram, escitalopram, domperidone, hydroxyzine and piperaquine are not among these exceptions, and are therefore contraindicated when coadministered with all torsadogenic drugs.

Contraindicated combinations

+ Non-antiparkinsonian dopamine agonists (cabergoline, quinagolide)

There is mutual antagonism between dopamine agonists and neuroleptics.

+ Citalopram, escitalopram, domperidone, hydroxyzine, piperaquine

There is an increased risk of ventricular arrhythmias, especially torsades de pointes.

Inadvisable combinations

+ Antiparasitics likely to induce torsades de pointes (chloroquine, halofantrine, lumefantrine, pentamidine)

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

If possible, one of the two treatments should be discontinued.

If coadministration cannot be avoided, a preliminary QT examination should be carried out and ECG monitoring performed.

+ Antiparkinsonian dopamine agonists (amantadine, apomorphine, bromocriptine, entacapone, lisuride, pergolide, piribedil, pramipexole, rasagiline, ropinirole, rotigotine, selegiline, tolcapone)

There is mutual antagonism between dopamine agonists and neuroleptics.

Dopamine agonists can cause or worsen psychotic disorders. If treatment with neuroleptics is required in patients with Parkinson's disease treated with dopamine agonists, these dopamine agents should be tapered off gradually (sudden discontinuation exposes the patient to a risk of "neuroleptic malignant syndrome").

+ Other medications likely to induce torsades de pointes: class Ia antiarrhythmic agents (quinidine, hydroquinidine, disopyramide) and class III antiarrhythmics (amiodarone, dronedarone, sotalol, dofetilide, ibutilide), and other drugs such as arsenic compounds, diphemanil, dolasetron IV, erythromycin IV, levofloxacin, mequitazine, mizolastine, prucalopride, vincamine IV, moxifloxacin, spiramycin IV, toremifene, vandetanib

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

+ Other neuroleptics which could induce torsades de pointes (chlorpromazine, cyamemazine, droperidol, flupenthixol, fluphenazine, haloperidol, levomepromazine, pimozide, pipamperone, pipotiazine, sulpiride, sultopride, tiapride, zuclopenthixol)

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

7. PREGNANCY AND LACTATION: Pregnancy

Pregnancy

Available data on the use of amisulpride in pregnant women are limited. Therefore, the safety of amisulpride during human pregnancy has not been established.

Amisulpride crosses the placenta.

Animal studies have shown reproductive toxicity (see section 5.3).

The use of amisulpride is not recommended during pregnancy and in women of child-bearing potential not using effective contraception, unless the benefits of such treatment outweigh 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 (see section 4.8). There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress or feeding disorder. Consequently, newborns should be monitored carefully.

Breast-feeding
Amisulpride has been found in milk in treated women.
A significant amount of amisulpride is excreted in breast milk. In some cases the amount exceeds the accepted value of 10% of the mother's weight-adjusted dose, however blood concentrations in breast-fed infants have not been evaluated. There are inadequate data on the effects of amisulpride in neonates/infants.
The benefit of breast-feeding for the infant should be weighed against the benefit of amisulpride treatment when deciding to stop breast-feeding or to not take amisulpride.
8. EFFECTS ON ABILITY TO DRIVE: Patients, especially those who drive and use machines, should be warned of the risk of drowsiness or blurred vision associated with the use of this drug.

9. UNDESIRABLE EFFECTS: Undesirable effects have been grouped by frequency using the following convention: very common ≥ 1/10; common ≥ 1/100 to < 1/10; uncommon ≥ 1/1000 to < 1/100; rare ≥ 1/10 000 to < 1/1000; very rare < 1/10 000, not known (frequency cannot be estimated from the available data).
Blood and lymphatic system disorders , Immune system disorders, Endocrine disorders, Metabolism and nutrition disorders, Psychiatric disorders, Nervous system disorders,, Eye disorders, Vascular disorders, Respiratory, thoracic and mediastinal disorders, Gastrointestinal disorders, Hepatobiliary disorders, Skin and subcutaneous tissue disorders, Musculoskeletal and systemic disorders, Renal and urinary disorders, Pregnancy, puerperium and perinatal conditions,

10. OVERDOSAGE: To date, available data on acute amisulpride overdose are limited. The signs and symptoms reported generally result from exaggeration of the pharmacological effects of the medicinal product, clinically presenting as: drowsiness, sedation, coma, hypotension and extrapyramidal symptoms. Fatal outcomes have been reported, mainly in combination with other antipsychotic agents.
There is no known specific antidote to amisulpride. In the event of acute overdose, use of this drug in combination with other medicinal products should be considered and appropriate measures taken:
- Close monitoring of vital functions.
- Cardiac monitoring (risk of prolongation of the QT interval) until the patient recovers.
- If severe extrapyramidal symptoms occur, anticholinergic agents should be administered.
- Since amisulpride is poorly dialyzed, hemodialysis is of limited use to eliminate the drug.

11.PHARMACODYNAMIC PROPERTIES: Amisulpride is an antipsychotic drug, which belongs to the class of substituted benzamides.
The pharmacodynamic profile of the drug is characterized by a selective and predominant affinity for dopamine D2 and D3 receptors in the limbic system. Amisulpride has no affinity for serotonin receptors, or other neuroreceptors such as histamine, cholinergic and adrenergic receptors.
In animal studies, at high doses, amisulpride preferentially blocks the dopaminergic neurons of the mesolimbic system compared to those in the striatal system. This specific affinity could explain the predominant antipsychotic effects of amisulpride compared with its extrapyramidal effects.
At low doses, amisulpride preferentially blocks the presynaptic D2 / D3 dopaminergic receptors, which could explain its effects on negative symptoms.
In a controlled, double-blind study versus haloperidol conducted in 191 patients with acute schizophrenia, improvement of secondary negative symptoms was significantly greater with amisulpride compared to haloperidol.
12. MARKETING AUTHORISATION HOLDER : Sanofi aventis France , 82, avenue Raspail 94250 Gentilly, France.
Abbreviated Prescribing Information based on the SmPC as of Aprl 2019 . Always refer to the full Summary of Product Characteristics (SmPC) before prescribing.