Professional information for SOLIAN

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

SOLIAN® 50 mg tablets

SOLIAN® 200 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SOLIAN 50 mg: Each tablet contains 50 mg amisulpride.

SOLIAN 200 mg: Each tablet contains 200 mg amisulpride.

Excipients with known effect

SOLIAN 50 mg:

Contains sugar (lactose monohydrate): 34,80 mg per tablet.

SOLIAN 200 mg:

Contains sugar (lactose monohydrate): 139,20 mg per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

SOLIAN 50 mg:

Round, white to off-white, flat-faced tablet, engraved AMI 50 on one face of the tablet.

SOLIAN 200 mg:

Round, white to off-white, flat-faced, breakable tablet, engraved AMI 200 on one face and with a breakable bar on the other face of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SOLIAN is indicated for the treatment of patients with acute and chronic schizophrenia, including patients characterised by predominant negative symptoms.

4.2 Posology and method of administration

Posology

No specific titration is required when initiating the treatment with SOLIAN and doses should be adjusted according to the individual response.

SOLIAN can be administered once daily at oral doses up to 400 mg, higher doses should be administered twice daily.

The minimum effective dose should be used.

Adults

For acute schizophrenia:

Oral doses between 400 – 800 mg/day are recommended. In individual cases, the dose may be increased up to 1 200 mg/day. Doses above 1 200 mg/day have not been evaluated for safety and therefore should not be used.

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 minimum effective dose.

For patients characterised by predominant negative symptoms:

Doses between 50 – 100 mg/day are recommended. Doses should be adjusted individually.

Special populations

Paediatric population

The efficacy and safety of SOLIAN from puberty to the age of 18 years have not been established: there are limited data available on the use of SOLIAN in adolescents in schizophrenia. Therefore, the use of SOLIAN from puberty to age of 18 years is not recommended; in children up to puberty SOLIAN is contraindicated (see section 4.3).

Elderly

The safety of SOLIAN has been examined in a limited number of elderly patients. Particular caution should be exercised due to a possible risk of hypotension or sedation. Reduction in dosage may also be required in the presence of renal insufficiency.

Hepatic insufficiency

Since amisulpride, as contained in SOLIAN, is weakly metabolised, a dosage reduction should not be necessary.

Renal impairment

Amisulpride, as contained in SOLIAN, is eliminated by the 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), these patients should not use SOLIAN (see section 4.4).

4.3 Contraindications

- Hypersensitivity to amisulpride or to any of the constituents of the formulation (see section 6.1).
- Concomitant use of other medicines that could induce or enhance the risk of torsades de pointes and/or prolong the QT-interval (see sections 4.4 and 4.5).

- Congenital QT-interval prolongation.
- Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer (see sections 4.4 and 4.8).
- Phaeochromocytoma.
- Children before the onset of puberty (under 15 years of age).
- Pregnancy and lactation (see section 4.6).
- Women of childbearing potential unless using adequate contraception (see section 4.6).
- Severe renal function impairment (see section 4.2).
- Combination with the following medications which could induce torsades de pointes:
    - Class Ia antidysrhythmic medicines, such as quinidine, disopyramide.
    - Class III antidysrhythmic medicines, such as amiodarone, sotalol.
    - Other medications, such as bepridil, cisapride, sultopride, thioridazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin (see section 4.5).
- Combination with levodopa (see section 4.5).

4.4 Special warnings and precautions for use

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported with some atypical antipsychotic medicines, including SOLIAN. Patients with an established diagnosis of diabetes mellitus, who are started on SOLIAN, should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with SOLIAN should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with SOLIAN should undergo fasting blood glucose testing. In some cases, hyperglycaemia may resolve when SOLIAN is discontinued. However, some patients could require continuation of anti-diabetic treatment despite discontinuation of the suspect medicine.

SOLIAN contains lactose, which may have an effect on the glycaemic control of patients with

diabetes mellitus. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take SOLIAN.

Neuroleptic malignant syndrome: a potentially fatal complication, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness, rhabdomyolysis and elevated creatinine phosphokinase (CPK) may occur. In the event of hyperthermia, particularly with high daily doses, all antipsychotic medicines, including SOLIAN, should be discontinued.

Rhabdomyolysis has also been observed in patients without neuroleptic malignant syndrome.

SOLIAN is eliminated by the renal route. In cases of renal insufficiency, the dose should be decreased, or intermittent treatment could be considered (see section 4.2).

SOLIAN may lower the seizure threshold. Therefore, patients with a history of epilepsy should be closely monitored during SOLIAN therapy.

Caution should be exercised when prescribing SOLIAN in patients with Parkinson's disease since it may cause worsening of the disease. SOLIAN should be used only if neuroleptic treatment cannot be avoided.

Prolongation of the QT-interval

SOLIAN induces a dose-dependent prolongation of the QT-interval (see sections 4.4 and 4.8). This effect is known to potentiate the risk of serious ventricular dysrhythmias 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,
- patients with known cardiovascular disease or family history of sudden death or QT prolongation,
- electrolyte imbalance, in particular hypokalaemia,
- congenital prolongation of the QT-interval,
- on-going treatment with a medication likely to produce pronounced bradycardia (< 55 bpm), hypokalaemia, decreased intracardiac conduction, or prolongation of the QT-interval.

Stroke

In randomized clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic medicines, 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 medicines, or other populations of patients cannot be excluded. SOLIAN should be used with caution in patients with stroke risk factors.

Elderly patients with dementia

Elderly patients with dementia-related psychosis treated with antipsychotic medicines are at an increased risk of death. Although the cause 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 medicines, treatment with conventional antipsychotic medicines, such as SOLIAN, may increase mortality.

The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic medicine as opposed to some characteristic(s) of the patients is not clear.

In elderly patients, SOLIAN should be used with particular caution because of a possible risk of hypotension or sedation.

Venous thromboembolism (VTE)

Cases of VTE, sometimes fatal, have been reported with antipsychotic medicines. Therefore, SOLIAN should be used with caution in patients with risk factors for thromboembolism. All possible risk factors for VTE should be identified before and during treatment with SOLIAN and preventive measures undertaken (see section 4.8).

Breast cancer

SOLIAN 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 SOLIAN therapy (see section 4.3).

Benign pituitary tumour

SOLIAN may increase prolactin levels. Cases of benign pituitary tumours such as prolactinoma have been observed during SOLIAN therapy (see section 4.8). 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 SOLIAN must be stopped (see section 4.3).

Acute withdrawal symptoms including nausea, vomiting and insomnia have been described after abrupt cessation of high doses of antipsychotic medicines. 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 of SOLIAN is advisable.

Leucopenia, neutropenia and agranulocytosis have been reported with antipsychotics, including SOLIAN. Unexplained infections or fever may be evidence of blood dyscrasia and requires immediate haematological investigation (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

Combinations, which are contraindicated (see section 4.3)

Medications which could induce torsade de pointes:

- Class Ia antidysrhythmic medicines, such as quinidine, disopyramide.
- Class III antidysrhythmic medicines, such as amiodarone, sotalol.
- Other 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

- SOLIAN 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, digoxin.
- Medications, which induce hypokalaemia: hypokalaemic diuretics, stimulant laxatives, IV amphotericin B, glucocorticoids, tetracosactide. Hypokalaemia should be corrected.
- Neuroleptics, such as pimozide, haloperidol, imipramine antidepressants, lithium.

Combinations to be taken into account

- Central nervous system (CNS) depressants including narcotics, anaesthetics, analgesics, sedative H_1 antihistamines, barbiturates, benzodiazepines and other anxiolytic medicines, clonidine and derivatives.
- Antihypertensive medicines and other hypotensive medications.
- Co-administration of amisulpride and clozapine may lead to an increase in plasma levels of amisulpride.

4.6 Fertility, pregnancy and lactation

Pregnancy

Amisulpride crosses the placenta.

The use of SOLIAN is not recommended during pregnancy and in women of childbearing potential not using effective contraception (see section 4.3).

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.

Breastfeeding

Amisulpride is excreted in treated women. Breastfeeding is contraindicated (see section 4.3).

Fertility

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

4.7 Effects on ability to drive and use machines

Even when used as recommended, SOLIAN may cause somnolence and blurred vision; therefore, the ability to drive vehicles or operate machines may be impaired (see section 4.8).

4.8 Undesirable effects

Side effects have been ranked under headings of frequency using the following convention:

Very common: (≥ 1/10); Common: (≥ 1/100; < 1/10); Uncommon (≥ 1/1 000; < 1/100); Rare: (≥ 1/10 000; < 1/1 000); Very Rare: (< 1/10 000); frequency not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Uncommon: leucopenia, neutropenia (see section 4.4).

Rare: agranulocytosis (see section 4.4).

Immune system disorders

Uncommon: allergic reactions.

Endocrine disorders

Common: increase in plasma prolactin levels, which is reversible after SOLIAN discontinuation. This may result in galactorrhoea, amenorrhoea, gynaecomastia, breast pain or enlargement and erectile dysfunction.

Rare: benign pituitary tumour such as prolactinoma (see section 4.3 and section 4.4).

Metabolism and nutrition disorders

Uncommon: hyperglycaemia (see section 4.4), hypertriglyceridaemia and hypercholesterolaemia.

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 (tremor, rigidity, hypersalivation, akathisia, hypokinesia, dyskinesia) may occur. These symptoms are generally mild at optimal dosages and partially reversible without discontinuation of SOLIAN upon administration of antiparkinsonian medicine. The incidence of extrapyramidal symptoms is dose related.

Common: somnolence, acute dystonia (spasm torticollis, oculogyric crisis, trismus). This is reversible without discontinuation of SOLIAN upon treatment with an antiparkinsonian medicine.

Uncommon: tardive dyskinesia, characterised by rhythmic, involuntary movements primarily of the tongue and/or face has been reported. Antiparkinsonian medication may induce aggravation of these symptoms. Seizures.

Rare: neuroleptic malignant syndrome, which is a potentially fatal complication (see section 4.4).

Frequency not known: restless legs syndrome with or without a context of akathisia.

Eye disorders

Common: blurred vision (see section 4.7).

Cardiac disorders

Uncommon: bradycardia.

Rare: QT interval prolongation, ventricular dysrhythmias, such as torsade de pointes, ventricular tachycardia, ventricular fibrillation, cardiac arrest, sudden death (see section 4.4).

Vascular disorders

Common: hypotension.

Uncommon: increase in blood pressure.

Rare: venous thromboembolism, including pulmonary embolism, sometimes fatal, and deep vein thrombosis (see section 4.4).

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.

Frequency not known: photosensitivity reaction.

Musculoskeletal and connective tissue disorders

Uncommon: osteopenia, osteoporosis.

Frequency not known: rhabdomyolysis (see section 4.4).

Renal and urinary disorders

Uncommon: urinary retention

Pregnancy, puerperium and perinatal conditions

Frequency not known: neonatal medicine withdrawal syndrome (see section 4.6)

Investigations

Common: weight gain

Uncommon: elevations of hepatic enzymes, mainly transaminases

Frequency not known: blood creatine phosphokinase increased (see section 4.4).

Injury, poisoning and procedural complications

Frequency not known: fall as a consequence of adverse reactions compromising body balance.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of SOLIAN is important. It allows continued monitoring of the benefit/risk balance of SOLIAN. Health care providers are asked to

report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi:

  za.drugsafety@sanofi.com (email) or 011 256-3700 (tel.), or
- SAHPRA via the **6.04 Adverse Drug Reaction Reporting Form**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Experience with SOLIAN in overdosage is limited. Exaggeration of the known pharmacological effects of SOLIAN has been reported, including drowsiness and sedation, coma, hypotension and extrapyramidal symptoms. Fatal outcomes have been reported mainly in combination with other psychotropics.

In case of acute overdosage, the possibility of multiple medicine intake should be considered.

Since SOLIAN is weakly dialysed, haemodialysis should not be used to eliminate the medicine.

There is no specific antidote. 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 extrapyramidal symptoms occur, anticholinergic medicines should be administered.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 2.6.5 Tranquilizers, miscellaneous structures

Pharmacotherapeutic group: Antipsychotics, ATC code: N05AL05

5.1 Pharmacodynamic properties

Amisulpride binds selectively with a high affinity to human dopaminergic D_2/D_3 receptor subtypes

whereas it is devoid of affinity for D_1, D_4 and D_5 receptor subtypes.

Amisulpride has no affinity for serotonin, α-adrenergic, histamine H_1 and cholinergic receptors. In addition, amisulpride does not bind to sigma sites.

In animal studies, at high doses, amisulpride preferentially blocks the dopamine receptors located in the limbic structures as compared with those in the striatum. At low doses, it selectively blocks the pre-synaptic D_2/D_3 receptors, producing dopamine release, responsible for its disinhibitory effects.

5.2 Pharmacokinetic properties

Absorption

In young healthy adults, after oral administration of a 50 mg dose, there are two plasma peaks, one at about one hour and one at 3 to 4 hours post dose. The oral bioavailability is about 48 %.

The bioavailability of amisulpride was significantly decreased after a carbohydrate rich meal. A carbohydrate rich meal (containing 68 % fluids) significantly decreases the AUCs, T_{max} and C_{max} of amisulpride.

Distribution

The volume of distribution is 5,8 L/kg and plasma protein binding is low (16 %).

Biotransformation

Amisulpride is weakly metabolised; two metabolites which account for approximately 4 % of the dose have been identified. There is no accumulation of amisulpride and its pharmacokinetic profile remains unchanged following repeated administration.

Elimination

Amisulpride is excreted unchanged in the urine, renal clearance is in the order of 20 L/h or 330 mL/min.

Its elimination half-life is approximately 12 hours after oral administration.

Characteristics in specific groups of subjects or patients

The AUC of amisulpride in renal impairment is significantly increased after a single dose of 50 mg while the elimination is prolonged. No information is available at higher doses or at steady state.

There is limited information on kinetics in the elderly, C_{max}, $t_{½}$, AUC are increased after a single dose of 50 mg.

Amisulpride is very weakly dialysed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SOLIAN 50 mg and SOLIAN 200 mg:

Hypromellose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycolate.

6.2 Incompatibilities

None known.

6.3 Shelf life

SOLIAN 50 mg:

36 months.

Store at or below 25 °C in a dry place.

SOLIAN 200 mg:

36 months.

Store at or below 25 °C in a dry place.

6.4 Special precautions for storage

SOLIAN does not require any special storage conditions.

6.5 Nature and contents of container

SOLIAN 50 mg and SOLIAN 200 mg:

PVC/aluminium blisters of 10 tablets packed in cartons of 30 and 150 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building I, 5th Floor

90 Bekker Road

Vorna Valley, Midrand, 2196

South Africa

8. REGISTRATION NUMBERS

SOLIAN 50 mg: 34/2.6.5/0116

SOLIAN 200 mg: 34/2.6.5/0117

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

SOLIAN 50 mg: 15 June 2001

SOLIAN 200 mg: 15 June 2001

10. DATE OF REVISION OF THE TEXT

31 March 2023

NAMIBIA

Scheduling status: NS3

Registration numbers:

Solian 50 mg: 05/2.6.5/0022

Solian 200 mg: 05/2.6.5/0023