**PACKAGE INSERT**

**SCHEDULING STATUS:** **S5**

**PROPRIETARY NAME (**and dosage form):

**SOLIAN ® 50 mg** (tablets)

**SOLIAN ® 200 mg** (tablets)

**COMPOSITION:**

SOLIAN 50 mg: Each tablet contains 50 mg Amisulpride.

SOLIAN 200 mg: Each tablet contains 200 mg Amisulpride.

The excipients are hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

**PHARMACOLOGICAL CLASSIFICATION:**

A 2.6.5 Tranquilizers, miscellaneous structures

**PHARMACOLOGICAL ACTION:**

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, $\alpha$-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.

**Pharmacokinetics:**

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. The oral bioavailability is about 48 %.

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

Amisulpride is weakly metabolised and there is no accumulation of amisulpride and its pharmacokinetic profile remains unchanged following repeated administration.

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.

The bioavailability of amisulpride was significantly decreased after a carbohydrate rich meal.

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.

**INDICATIONS:**

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

**CONTRA-INDICATIONS:**

- Hypersensitivity to amisulpride or to any of the constituents of the formulation.
- Concomitant use of other medicines that could induce or enhance the risk of Torsades de Pointes and/or prolong the QT-interval (See “WARNINGS” and “INTERACTIONS”).
- Congenital QT-interval prolongation.
- Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer.
- Phaeochromocytoma.
- Children under 15 years of age.
- Pregnancy and lactation. (See “PREGNANCY AND LACTATION”).
- Women of childbearing potential unless using adequate contraception.
- Severe renal function impairment. (See “DOSAGE AND DIRECTIONS”)
- Combination with the following medications which could induce Torsades de Pointes:
    - Class Ia antidysrhythmic agents such as quinidine disopyramide.
    - Class III antidysrhythmic agents such as amiodarone, sotalol.
    - Other medications such as bepridil, cisapride, sultopride, thioridazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin (See “INTERACTIONS”).
    - Combination with Levodopa (“SEE INTERACTIONS”).

**WARNINGS:**

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported with some atypical antipsychotic

agents. 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.

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

Patients with a history of epilepsy should be closely monitored during the treatment period as SOLIAN can lower the seizure threshold.

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 "Side-effects and Special Precautions"). This effect is known to potentiate the risk of serious ventricular dysrhythmias such as Torsades 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 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.

**Venous thromboembolism**

Cases of venous thromboembolism, sometimes fatal, have been reported with antipsychotic medicines. Therefore, SOLIAN should be used with caution in patients with risk factors for thromboembolism (See “SIDE EFFECTS AND SPECIAL PRECAUTIONS”)

**INTERACTIONS*:***

**Combinations, which are contra-indicated:**

Medications, which could induce Torsades de Pointes:

- Class Ia antidysrhythmic agents such as quinidine, disopyramide.
- Class III antidysrhythmic agents 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 Torsades de Pointes or could prolong the QT intervals:

- 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, tetracosactides. Hypokalaemia should be corrected.
- Neuroleptics such as pimozide, haloperidol, imipramine antidepressants, lithium.

**Combinations to be taken into account:**

- 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.

**PREGNANCY AND LACTATION**

**Pregnancy**

Safety in pregnancy has not been established (See “CONTRAINDICATIONS”).

If SOLIAN is used during pregnancy, neonates may show adverse effects of amisulpiride.

**Lactation**

It is not known whether amisulpiride is excreted in breast milk, therefore breastfeeding is contraindicated.

**DOSAGE AND DIRECTIONS FOR USE:**

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.

**For acute schizophrenia:**

Oral doses between 400 - 800 mg/day are recommended. In individual cases, the dose may be increased up to 1200 mg/day. Doses above 1200 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.

**Elderly:**

Particular caution should be used due to a possible risk of hypotension or sedation.

**Hepatic insufficiency:**

Since SOLIAN is weakly metabolised, a dosage reduction should not be necessary.

**Renal impairment:**

SOLIAN 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), these patients should not receive SOLIAN. (See “Special Precautions”).

**SIDE EFFECTS AND SPECIAL PRECAUTIONS:**

**Side 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)

Clinical trial data:

***Central and Peripheral Nervous system disorders:***

Very Common: Extrapyramidal symptoms (tremor, rigidity, hypersalivation, akathisia, hypokinesia, dyskinesia) may occur. The incidence of extrapyramidal symptoms is dose related.

Common: Acute dystonia (spasm torticollis, oculogyric crisis, trismus), [~~may occur~~] somnolence

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.

***Psychiatric disorders:***

Common: insomnia, somnolence, anxiety, agitation, orgasmic dysfunction

***Endocrine disorders:***

Common: Increase in serum prolactin levels, which is reversible after the drug discontinuation. This may result in galactorrhoea, gynaecomastia, swollen breasts and erectile dysfunction.

***Gastrointestinal disorders:***

Common: constipation, nausea, vomiting, dry mouth

***Cardiovascular disorders:***

Common: hypotension

Uncommon: bradycardia

**Investigations:**

Common: weight gain

Uncommon: elevation of hepatic enzymes, mainly transaminases

***Metabolism and nutrition disorders:***

Uncommon: hyperglycaemia (See “Precautions”)

***Immune system disorders:***

Uncommon: allergic reactions

***Post marketing:***

Cases of the following adverse reactions have been reported through spontaneous reporting only:

***Nervous system disorders:***

Frequency not known: neuroleptic malignant syndrome (see “WARNINGS”).

***Cardiac disorders:***

Frequency not known: QT interval prolongation and ventricular dysrhythmias such as Torsade de Pointes ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, sudden death (See “WARNINGS”)

***Vascular disorders:***

Frequency not known: venous thromboembolism, including pulmonary embolism, sometimes fatal, and deep vein thrombosis (See “WARNINGS”)

**Special precautions:**

Hyperglycaemia has been reported in patients treated with some atypical antipsychotic agents, including SOLIAN, therefore patients with an established diagnosis of diabetes mellitus or with risk factors for diabetes who are started on SOLIAN should get appropriate glycaemic monitoring. See “WARNINGS”.

SOLIAN may lower the seizure threshold. Therefore patients with a history of epilepsy should be monitored during SOLIAN therapy. SOLIAN is eliminated by the renal route. In cases of renal insufficiency, the dose should be decreased or intermittent treatment could be considered (See “DOSAGE AND DIRECTIONS FOR USE”).

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

**Effects on ability to drive or to use machines:**

Even when used as recommended, SOLIAN may cause somnolence so that the ability to drive vehicles or operate machinery can be impaired. (See “Side effects”)

**Lactose:** Since SOLIAN tablets contain lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicine.

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**

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.

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

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

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 agents should be administered.

**IDENTIFICATION:**

SOLIAN 50 mg: Round, white, flat-faced breakable tablet with a scored line on one side and a mark AMI 50 on the other side.

SOLIAN 200 mg: Round, white, flat-faced breakable tablet with a scored line on one side and a mark AMI 200 on the other side.

**PRESENTATION:**

Blisters of 10 tablets packed in cartons of 30 and 150.

**STORAGE INSTRUCTIONS:**

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

KEEP OUT OF REACH OF CHILDREN.

**REGISTRATION NUMBERS:**

SOLIAN 50 mg: 34/2.6.5/0116

SOLIAN 200 mg: 34/2.6.5/0117

**PACKAGE INSERT**

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:**

**sanofi-aventis south africa (pty) ltd**

2 Bond Street

MIDRAND

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**DATE OF PUBLICATION OF THIS PACKAGE INSERT:**

25 October 2012