1. NAME OF THE MEDICINAL PRODUCT

Solian 100mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Amisulpride 100 mg per tablet

Also contains lactose monohydrate 69.6mg per tablet.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet
White to off white, round flat-faced, breakable tablet engraved 'AMI100' on one face and with a breakable bar on the other face. The scoreline/breakline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Amisulpride is indicated for the treatment of acute and chronic schizophrenic disorders, in which positive symptoms (such as delusions, hallucinations, thought disorders) and/or negative symptoms (such as blunted affect, emotional and social withdrawal) are prominent, including patients characterised by predominant negative symptoms.

Amisulpride also regulates secondary negative symptoms in productive state, as well as affective disorders such as depressive mood.

4.2 Posology and method of administration

For acute psychotic episodes, oral doses between 400 mg/day and 800 mg/day are recommended. In individual cases, the daily dose may be increased up to 1200 mg/day. Doses above 1200 mg/day have not been extensively evaluated for safety and therefore should not be used. No specific titration is required when initiating the treatment. 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 (deficit syndrome)**,** oral doses between 50 mg/day and 300 mg/day are recommended. Doses should be adjusted individually.

Amisulpride can be administered once a day at oral doses up to 400mg, higher dose should be split into two separate doses.

Elderly: The safety of amisulpride has been examined in a limited number of elderly patients. Amisulpride should be used with particular caution because of a possible risk of hypotension and sedation. Reduction in dosage may also be required because of renal insufficiency.

Children: 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 amilsulpride is contraindicated as its safety has not yet been established.

Renal insufficiency: Amisulpride 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) particular care is recommended in these patients (see section 4.4 Special Warnings and Special Precautions for Use).

Hepatic insufficiency: since the drug is weakly metabolised a dosage reduction should not be necessary.

4.3 Contraindications

Hypersensitivity to the active ingredient or to other ingredients of the product.

Concomitant prolactin-dependent tumours (e.g. pituitary gland prolactinomas or breast cancer) (see section 4.4 and section 4.8).

Phaeochromocytoma.

Children up to puberty.

Combination with levodopa (see section 4.5 Interactions with other medicinal products and other forms of interactions).

4.4 Special warnings and precautions for use

As with other neuroleptics, neuroleptic malignant syndrome (NMS) may occur. This condition is characterised by high fever, muscle rigidity, autonomic dysfunction, clouding of consciousness, rhabdomyolysis and elevated CPK values, and it is

potentially fatal. If a patient develops signs and symptoms indicative for NMS or presents with unexplained hyperthermia, particularly at high daily doses, all antipsychotic agents including amisulpride must be discontinued.
Rhabdomyolysis has also been observed in patients without Neuroleptic Malignant Syndrome.

Hyperglycaemia 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 glycemic monitoring.

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 4.2 Posology and method of administration).

Severe liver toxicity has been reported with amisulpride use. Patients should be instructed to report immediately signs such as asthenia, anorexia, nausea, vomiting, abdominal pain or icterus to a physician. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately (see section 4.8)

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

In elderly patients, amisulpride, like other neuroleptics, should be used with particular caution because of a possible risk of hypotension and sedation. Reduction in dosage may also be required because of renal insufficiency.

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
Caution should be exercised when amisulpride is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and concomitant use with neuroleptics should be avoided.

Stroke:
In randomised 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 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.

Withdrawal symptoms including nausea, vomiting and insomnia have been described after abrupt cessation of high therapeutic doses of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement

disorders (such as akathisia, dystonia and dyskinsia) 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 (see Section 4.8), and requires immediate haematological investigation.

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 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.
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.

Breast cancer:
Amisulpride causes an increase in plasma 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. Amisulpride is contraindicated in patients with breast cancer (see section 4.3 and 4.8).

Venous thromboembolism:
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with amisulpride and preventative measures undertaken.

Benign pituitary tumour:
Amisulpride may increase prolactin levels. Cases of benign pituitary tumours such as prolactinoma have been observed during amisulpride therapy. 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium:
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

CONTRAINDICATED COMBINATIONS
Levodopa reciprocal antagonism of effects between levodopa and neuroleptics.

COMBINATIONS NOT RECOMMENDED
Amisulpride may enhance the central effects of alcohol.

COMBINATIONS TO BE TAKEN INTO ACCOUNT
- CNS depressants including narcotics, anaesthetics, 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.
- Caution is advised when prescribing amisulpride with medicines known to prolong the QT interval, e.g., class IA antiarrythmics (e.g., quinidine, disopyramide) and class III antiarrhytmics (e.g., amiodarone, sotalol), some antihistaminics, some other antipsychotics and some antimalarials (e.g., mefloquine) (see section 4.4)

Amisulpride may oppose the effect of dopamine agonists e.g. bromocriptine, ropirinole.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are only limited data available from the use of amisulpride in pregnant women. The safety of amisulpride during human pregnancy has not been established.

Amisulpride crosses the placenta.

Studies in animals 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 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 (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 is excreted into breastmilk in rather large amounts above the accepted value of 10% of the maternal weight-adjusted dosage in some cases, but blood concentrations in breastfed infants have not been evaluated. There is insufficient information on the effects of amisulpride in newborns/infants. A decision must be made whether to discontinue breast-feeding or to abstain from amisulpride therapy

taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

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

4.7 Effects on ability to drive and use machines

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 4.8 Undesirable Effects).

4.8 Undesirable effects

Adverse 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: leukopenia, neutropenia (see Section 4.4).
Rare: agranulocytosis.

- **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 4.4).

- **Metabolism and nutrition disorders:**

Uncommon: hyperglycemia, 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 4.4), which is a potentially fatal complication.
Not known: restless legs syndrome.

- **Eye disorders:**

Common: blurred vision.

- **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 4.4).

- **Vascular disorders:**

Common: hypotension.
Uncommon: increase in blood pressure.
Rare: venous thromboembolism, including pulmonary embolism, sometimes fatal, and deep vein thrombosis

- **Respiratory, thoracic and mediastinal disorders:**

Uncommon: nasal congestion, aspiration pneumonia (mainly in association with other antipsychotics and CNS depressants).

- **Gastrointestinal disorders:**

Common: constipation, nausea, vomiting, dry mouth.

- **Hepatobilary 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

-- **Pregnancy, puerperium and perinatal conditions**
Frequency not known: drug withdrawal syndrome neonatal (see Section 4.6)

- **Injury, poisoning and procedural complications:**
Not known: fall as a consequence of adverse reactions compromising body balance.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

Experience with amisulpride in overdosage is limited. Exaggeration of the known pharmacological effects of the drug has been reported. These include drowsiness, sedation, hypotension, extrapyramidal symptoms and coma. Fatal outcomes have been reported mainly in combination with other psychotropic agents.

In cases of acute overdosage, the possibility of multiple drug intake should be considered. Since amisulpride is weakly dialysed, haemodialysis 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 cardiac monitoring (risk of prolongation of QT interval) until the patient recovers.

If severe extrapyramidal symptoms occur, anticholinergic agents should be administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics, psychopharmaca, neuroleptics
ATC code: N05A L05

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.

Unlike classical and atypical neuroleptics, amisulpride has no affinity for serotonin, ∝-adrenergic, histamine H_1 and cholinergic receptors. In addition, amisulpride does not bind to sigma sites.

In animals, at high doses it blocks post-synaptic D_2 receptors located in the limbic structures in preference to those in the striatum. Unlike classical neuroleptics it does not induce catalepsy and hypersensitivity of D_2 dopamine receptors does not develop after repeated treatment. At low doses it preferentially blocks pre-synaptic D_2/D_3 receptors, producing dopamine release responsible for its disinhibitory effects.

This atypical pharmacological profile may explain amisulpride's antipsychotic effect at higher doses through post-synaptic dopamine receptor blockade and its efficacy against negative symptoms, at lower doses, through pre-synaptic dopamine receptor blockade. In addition, the reduced tendency of amisulpride to produce extrapyramidal side effects may be related to its preferential limbic activity.

In clinical studies including schizophrenic patients with acute exacerbations, amisulpride significantly alleviated secondary negative symptoms as well as affective symptoms such as depressed mood.

5.2 Pharmacokinetic properties

In man, amisulpride shows two absorption peaks: one which is attained rapidly, one hour post-dose and a second between 3 and 4 hours after administration. Corresponding plasma concentrations are 39 ± 3 and 54 ± 4 ng/ml after a 50 mg dose.

The volume of distribution is 5.8 l/kg. A plasma protein binding is low (16%) drug interactions are unlikely.

Absolute bioavailability is 48%. Amisulpride is weakly metabolised : two inactive metabolites, accounting for approximately 4% of the dose, have been identified. There is no accumulation of amisulpride and its pharmacokinetics remain unchanged after the administration of repeated doses. The elimination half-life of amisulpride is approximately 12 hours after an oral dose.

Amisulpride is eliminated unchanged in the urine. Fifty percent of an intravenous dose is excreted via the urine, of which 90% is eliminated in the first 24 hours. Renal clearance is in the order of 20 l/h or 330 ml/min.
Kinetic profile of amisulpride is not influenced by diet.

A carbohydrate rich meal (containing 68% fluids) significantly decreases the AUC_s, T_{max} and C_{max} of amisulpride but no changes were seen after a high fat meal. However, the significance of these findings in routine clinical use is not known.

Hepatic insufficiency: since the drug is weakly metabolised a dosage reduction should not be necessary in patients with hepatic insufficiency.

Renal insufficiency: The elimination half-life is unchanged in patients with renal insufficiency while systemic clearance is reduced by a factor of 2.5 to 3. The AUC of amisulpride in mild renal failure increased two fold and almost tenfold in moderate renal failure (see section 4.2 for dosing recommendations). Experience is however limited and there is no data with doses greater than 50 mg.

Amisulpride is very weakly dialysed.

Limited pharmacokinetic data in elderly subjects (> 65 years) show that a 10-30 % rise occurs in C_{max}, $T_{1/2}$ and AUC after a single oral dose of 50 mg. No data are available after repeat dosing.

5.3 Preclinical safety data

An overall review of the completed safety studies indicates that amisulpride is devoid of any general, organ-specific, teratogenic, mutagenic or carcinogenic risk. Changes observed in rats and dogs at doses below the maximum tolerated dose are either pharmacological effects or are devoid of major toxicological significance under these conditions. Compared with the maximum recommended dosages in man, maximum tolerated doses are 2 and 7 times greater in the rat (200 mg/kg/day) and dog (120 mg/kg/day) respectively in terms of AUC. No carcinogenic risk, relevant to man, was identified in mice (up to 120mg/kg/day) and in rats (up to 240mg/kg/day), corresponding for the rat to 1.5 to 4.5 times the expected human AUC.

Reproductive studies performed in rats, rabbits and mice did not show any teratogenic potential.

In animal trials, amisulpride elicited an effect on foetal growth and development at doses corresponding to Human Equivalent Dose of 2000 mg/day and upwards for a 50-kg patient. There was no evidence for a teratogenic potential of amisulpride. Studies on the impact of amisulpride on the behaviour of the offspring have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium starch glycolate
Lactose monohydrate
Microcrystalline cellulose
Hypromellose
Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

No special precautions for storage

6.5 Nature and contents of container

PVC/aluminium foil blister packs containing 30, 60 or 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special precautions

7. MARKETING AUTHORISATION HOLDER

sanofi-aventis Ireland Ltd. T/A SANOFI
Citywest Business Campus
Dublin 24

8. MARKETING AUTHORISATION NUMBER

PA 540/158/2

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 27th July 1998
Date of last renewal: 1st September 2009

10. DATE OF REVISION OF THE TEXT

August 2022.