SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Solian 100 mg
Solian 400 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Solian 100mg tablet contains 100mg of the active substance, amisulpride
Also contains 69.6mg of lactose monohydrate

Each Solian 400mg tablet contains 400mg of the active substance, amisulpride
Also contains 130.25mg of lactose monohydrate

For the complete list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solian 100 mg tablet.
White to off-white, round, flat-faced tablet engraved AMI 100 on one face and with a breakable bar on the other face.

Solian 400mg film coated tablet
White, film coated, scored oblong tablet, engraved 'AMI 400' on one face.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of schizophrenia

4.2. Posology and method of administration

Usually, if the daily dose is ≤ 400 mg, it is to be administered as a once-daily dose. If the daily dose exceeds 400 mg, it is to be administered as two divided doses.

Predominantly negative episodes:

Doses between 50 mg/day and 300 mg/day are recommended. Doses should be adjusted individually. The optimum dosage is about 100 mg/day.

For patients with mixed positive and negative symptoms, doses should be adjusted to obtain optimal control of positive symptoms.

Acute psychotic episodes:

When initiating treatment

- 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,
- oral doses between 400 mg/day and 800 mg/day are recommended. The maximum dose should never exceed 1200 mg. Given that there has been no large-scale safety assessment of doses higher than 1200 mg/day, these doses should not be used.

Thereafter

- the dosage should then be maintained or adjusted according to the patient's individual response.

In all cases, the maintenance treatment should be established individually with the minimum effective dose.

Elderly:

The safety of Amisulpride has been examined in a limited number of elderly patients. Amisulpiride should be used with particular caution in this patients population due to the risk of hypotension or sedation (see section 4.4). Reduction in dosage may also be required because of renal insufficiency.

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; in children up to puberty amisulpride is contraindicated, as its safety has not yet been established (see section 4.3).

Renal insufficiency

Amisulpride is eliminated via the renal route. In patients with renal insufficiency, the dose should be reduced by half when creatinine clearance (CR_{CL}) is between 30-60 ml/min and to a third in patients with CR_{CL} between 10-30 ml/min.

Because of the lack of data on patients with severe renal insufficiency (CR_{CL} <10 ml/min), careful monitoring is recommended in this population (see Section 4.4).

Hepatic insufficiency

Since amisulpride is weakly metabolized, a dosage reduction is not necessary in patients with hepatic insufficiency.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Concomitant prolactin-dependent tumours (e.g. pituitary gland prolactinomas or breast cancer) (see sections 4.4 and 4.8).
- Pheochromocytoma.

- Children before the onset of puberty.
- Combination with levodopa, bromocriptine, ropinirole (see section 4.5).

4.4. Special warnings and precautions for use

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

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.

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.

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

As with other antidopaminergic agents, caution should be also exercised when prescribing Solian to patients with Parkinson's disease since it may cause worsening of the disease. Solian should be used only if neuroleptic treatment cannot be avoided.

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

(such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal of amisulpride is advisable.

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 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. 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 drugs are at an increased risk of death. Analysis 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 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 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.

Solian is not licensed for the treatment of dementia-related behavioural disturbances.

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 Solian and preventive measures undertaken.

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.

Benign pituitary tumour

Amisulpride may increase prolactin levels. Cases of benign pituitary tumours 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 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 4.3).

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.

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

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).

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

Combinations not recommended

• Solian 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 anxiolytic drugs, 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 antiarrhythmics (e.g. amiodarone, sotalol), some antihistaminics, some other antipsychotics and antimalarials (e.g. mefloquine) (see Section 4.4).

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 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 (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 used as recommended, Solian may cause somnolence and blurred vision so that the ability to drive vehicles or operate machinery can be impaired (see section 4.8).

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 (≥ 1/1000; < 1/100); rare (≥ 1/10 000; < 1/1000); very rare (< 1/10 000); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:

Uncommon: leukopenia, neutropenia (see Section 4.4)

Rare: agranulocytosis (see Section 4.4)

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 sections 4.3 and 4.4)

Metabolism and nutrition disorders:

Uncommon: hyperglycaemia (see Section 4.4), hypertriglyceridemia 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 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: somnolence, acute dystonia (spasm torticollis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon treatment with an antiparkinsonian agent.

Uncommon: seizures, tardive dyskinesia characterized by rhythmic, involuntary movements primarily of the tongue and/or face have been reported, usually after longterm administration.

Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms.

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Rare: Neuroleptic Malignant Syndrome (see section 4.4), which is a potentially fatal complication

Not known: restless legs syndrome

Eye disorders:

Common: blurred vision (see section 4.7)

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 (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
Not known: photosensitivity reaction

Musculoskeletal and connective tissue disorders:
Uncommon: osteopenia, osteoporosis

Renal and urinary disorders:
Uncommon: urinary retention

Pregnancy, puerperium and perinatal conditions:
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.

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form at https://sideeffects.health.gov.il.

4.9. Overdose

Experience with Solian in overdosage is limited. Exaggerations of the known pharmacological effects of the drug have been reported. These include drowsiness and sedation, coma, hypotension and extrapyramidal symptoms. 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 Solian is weakly dialysed, hemodialysis is of no use to eliminate the drug.

There is no specific antidote to Solian.

Appropriate supportive measures should therefore be instituted with close supervision of vital functions including continuous cardiac monitoring due to the risk of prolongation of the 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: Antipsychotic**,** ATC code: N05AL05

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, α-adrenergic, histamine H_1 and cholinergic receptors. In addition, amisulpride does not bind to sigma sites.

In animal studies, at high doses, amisulpride blocks dopamine receptors located in the limbic structures in preference to those in the striatum.

At low doses, it preferentially blocks the pre-synaptic D2 / D3 receptors, producing dopamine release responsible for its disinhibitory effects.

This pharmacological profile explains the clinical efficacy of Solian against both negative and positive symptoms of schizophrenia.

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, plasma protein binding is low (16%) and no drug interactions are suspected. Absolute bioavailability is 48%.

Amisulpride is weakly metabolized: 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.

A carbohydrate rich meal (containing 68% fluids) significantly decreases the AUCs, Tmax and Cmax 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 metabolized 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 ten fold in moderate renal failure (see section 4.2).

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 Cmax, T1/2 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 Solian 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/d) and dog (120 mg/kg/d) respectively in terms of AUC. No carcinogenic risk, relevant to man, was identified in the rat at up to 1.5 to 4.5 times the expected human AUC.

A mouse carcinogenicity study (120 mg/kg/d) and reproductive studies (160, 300 and 500 mg/kg/d respectively in rat, rabbit and mouse) were performed. The exposure of the animals to amisulpride during these latter studies was not evaluated.

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 behavior of the offspring have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Solian 100: Lactose Monohydrate (69.6mg), Microcrystalline Cellulose, Sodium Starch glycolate (type A),-Hypromellose, Magnesium Stearate.

Solian 400: Lactose monohydrate (130.25mg), Microcrystalline Cellulose, Sodium Starch glycollate (type A), Hypromellose, Magnesium Strearate, Titanium dioxide (E 171), Polyoxyl 40 stearate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life
The expiry date of the product is indicated on the packaging materials.

6.4. Special precautions for storage
Do not store above 25^0C.

6.5. Special precautions for disposal
No special precautions

7. MARKETING AUTHORIZATION HOLDER
Sanofi-aventis Israel ltd, 10 Beni Gaon, POB 8090, Netanya, Israel.

8. MANUFACTURER
Delpharm Dijon, Quetigny, France.

Revised in November 2021 according to MoH guidelines.