

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0540/158/005

Case No: 2053368

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

sanofi-aventis Ireland Limited

Citywest Business Campus, Dublin 24, Ireland

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Solian 100mg/ml Oral Solution 100 Micromol Oral Solution

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **08/07/2008** until **31/08/2009**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Solian 100mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Amisulpride 100 mg/ml.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Oral solution

A clear yellow liquid with an odour of caramel.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Solian 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.

4.2 Posology and method of administration

For acute psychotic episodes: oral doses between 400 mg/day and 800 mg/day are recommended. Doses above 800 mg/d have not been associated with greater efficacy and have induced higher rates of extrapyramidal symptoms. No specific titration is required when initiating the treatment with Solian. 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: oral doses between 50 mg/day and 300 mg/day are recommended. Doses should be adjusted individually.

Amisulpride should be administered b.i.d.(twice a day) for doses above 400 mg.

Elderly: The safety of Solian has been examined in a limited number of elderly patients. Solian 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.

Children: Solian is contra-indicated in children up to puberty, 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.

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

Method of administration: The graduations on the dosage pipette measure the milligrams of active ingredient. After introducing the measuring syringe into the bottle, draw the plunger of the measuring syringe up to the graduation mark corresponding to the number of milligrams to be administered. The oral solution should be drunk with a liquid, which does not contain alcohol.

4.3 Contraindications

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

Concomitant prolactin-dependant tumours e.g. pituitary gland prolactinomas and breast cancer.

Phaeochromocytoma.

Children up to puberty.

Lactation.

Combinations with the following medications which could introduce torsades de pointes.

- Class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide.
- Class III antiarrhythmic agents such as amiodarone, sotalol.
- Other medications such as bepridil, cisapride, sultopride, thioradazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin.

This list is not exhaustive.

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, 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.

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 severe renal insufficiency or renal dialysis, the dose should be decreased or intermittent treatment could be considered (see section 4.2 Posology and method of administration).

Amisulpride 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.

Prolongation of the QT interval

Amisulpride induces a dose-dependant prolongation of the QT interval (see section 4.8 Undesirable effects). This effect is known to potentiate the risk of serious ventricular arrhythmias such as torsades de pointes.

Before any administration, and if possible according to the patients 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 imbalances (hypomagnesaemia, hypocalcaemia and especially 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 QTc interval (see Section 4.5 Interaction with other medicinal products and other forms of interactions).

Amisulpride should be prescribed with caution in patients presenting with these factors and patients with cardiovascular disorders which may predispose to prolongation of QT interval.

Avoid concomitant prescription of other antipsychotics.

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.

Acute withdrawal symptoms including nausea, vomiting and insomnia have been rarely 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) have been reported. Therefore , gradual withdrawal is advisable.

This product contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216), which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

COMBINATIONS WHICH ARE CONTRAINDICATED

(See Section 4.3 Contra-indications).

Combination with the following medications which could induce torsades de pointes or prolong the QT interval:
(see Section 4.4 Warnings).

- Class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide.
- Class III antiarrhythmic agents such as amiodarone, sotalol.
- Other medications such as bepridil, cisapride, sultopride, thioridazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin.

This list is not exhaustive.

Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics.

COMBINATIONS WHICH ARE NOT RECOMMENDED

Solian may enhance the central effects of alcohol.

Medications which enhance the risk of torsades de pointes or prolongation of QT interval (see Section 4.4 Special warnings and special precautions for use):

- Bradycardia-inducing medications such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine, guanfacine; digitalis.
- Medications which induce electrolyte imbalance, in particular those causing hypokalaemia: hypokalaemic diuretics, stimulant laxatives, IV amphotericin B, glucocorticoids, tetracosactides. Electrolyte imbalance (hyperkalaemia) should be corrected.
- Neuroleptics such as pimozide, haloperidol; imipramine antidepressants; lithium.

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

4.6 Pregnancy and lactation

4.6.1 Pregnancy

In animals, amisulpride did not show direct reproductive toxicity. A decrease in fertility linked to the pharmacological effects of the drug (prolactin mediated effect) was observed. No teratogenic effects of amisulpride were noted.

Very limited clinical data on exposed pregnancies are available. Therefore the safety of amisulpride during human pregnancy has not been established. Use of the drug is not recommended during pregnancy unless the benefits justify the potential risks. If amisulpride is used during pregnancy, neonates may show adverse effects of amisulpride and thus appropriate monitoring should be considered.

4.6.2 Lactation

It is not known whether amisulpride is excreted in breast milk, breast-feeding is therefore contra-indicated.

4.7 Effects on ability to drive and use machines

Even used as recommended, Solian may cause somnolence 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).

Clinical Trial date

The following adverse effects have been observed in controlled clinical trials. It should be noted that in some instances it can be difficult to differentiate adverse events from symptoms of the underlying disease.

- **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: Tardiva 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.

- **Psychiatric disorders:**

Common: Insomnia, anxiety, agitation, orgasmic dysfunction.

- **Gastrointestinal disorders:**

Common: Constipation, nausea, vomiting, dry mouth.

- **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.

- **Metabolism and nutrition disorders:**

Uncommon: Hyperglycemia (see section 4.4 Special Warnings and Special Precautions for Use).

- **Cardiovascular disorders:**

Common: Hypotension.

Uncommon: Bradycardia.

- **Investigations:**

Common: Weight gain may occur under therapy with amisulpride.

Uncommon: Elevations of hepatic enzymes, mainly transaminases.

- **Immune system disorders:**

Uncommon: Allergic reaction.

Post Marketing date:

In addition, cases of the following adverse reactions have been reported through spontaneous reporting only:

- **Nervous system disorders:**

Frequency not known: Neuroleptic Malignant Syndrome (see Section 4.4 Special Warnings and Precautions for Use).

- **Cardiac disorders:**

Frequency not known: QT interval prolongation and ventricular arrhythmias such as torsade de pointes, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, sudden death (see section 4.4 Special Warnings and Special Precautions for Use).

4.9 Overdose

Experience with amisulpride in overdosage is limited. Exaggeration of the known pharmacological effects of the drug have been reported. These include drowsiness and sedation, coma, hypotension and extrapyramidal symptoms.

In cases of acute overdosage, the possibility of multiple drug intake should be considered. Since amisulpride is weakly

dialysed, haemodialysis should not be used 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 is recommended (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

Amisulpride binds selectively with a high affinity to human dopaminergic D₂/D₃ receptor subtypes whereas it is devoid of affinity for D₁, D₄ and D₅ receptor subtypes.

Unlike classical and atypical neuroleptics, amisulpride has no affinity for serotonin, α -adrenergic, histamine H₁ and cholinergic receptors. In addition, amisulpride does not bind to sigma sites.

In animals, at high doses it blocks post-synaptic D₂ receptors located in the limbic structures in preference to those in the striatum. Unlike classical neuroleptics it does not induce catalepsy and hypersensitivity of D₂ dopamine receptors does not develop after repeated treatment. At low doses it preferentially blocks pre-synaptic D₂/D₃ 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.

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. As 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 remains 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, 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 chapter 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 the mouse (up to 120mg/kg/day) and in the rat (up to 240mg/kg/day), corresponding for the rat to 1.5 to 4.5 times the expected human AUC.

Reproductive studies performed in the rat, rabbit and mouse did not show any teratogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gesweet® (saccharin sodium, sodium gluconate and glucono delta- lactone)
 Hydrochloric acid
 Methyl Parahydroxybenzoate (E218)
 Propyl Parahydroxybenzoate (E216)
 Potassium sorbate
 Caramel flavour
 Purified water

6.2 Incompatibilities

None known.

6.3 Shelf Life

Unopened: 3 years.

After first opening: Any remaining product must be discarded two months after first opening.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

60 ml brown glass bottle (type III) with a dosage pipette graduated to 4 ml.

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

Dispose of following two months after opening.

7 MARKETING AUTHORISATION HOLDER

sanofi-aventis Ireland Ltd
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 540/158/5

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 March 2001

Date of last renewal: 01 September 2004

10 DATE OF REVISION OF THE TEXT

June 2008