AUSTRALIAN PRODUCT INFORMATION – SOLIAN (AMISULPRIDE) TABLETS AND SOLUTION

1 NAME OF THE MEDICINE

Amisulpride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets

SOLIAN Tablets contain amisulpride (50 mg, 100 mg, 200 mg and 400 mg).

Excipient with known effect: Lactose monohydrate

For the full list of excipients, see Section 6.1 List of excipients.

Solution

SOLIAN SOLUTION contains amisulpride 100mg/mL.

Excipients with known effect: methyl hydroxybenzoate, potassium sorbate, and propyl hydroxybenzoate,

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Tablets

SOLIAN 50: white to off white, flat-faced breakable tablet, engraved “AMI 50”.

SOLIAN 100: white to off white, flat-faced breakable tablet, engraved “AMI 100”.

SOLIAN 200: white to off white, flat-faced breakable tablet, engraved “AMI 200”.

SOLIAN 400: white, film-coated, breakable, oblong tablet, engraved “AMI 400”.

Solution

SOLIAN SOLUTION 100mg/mL: a clear, yellow to yellow-brown coloured liquid.

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.

4.2 DOSE AND METHOD OF ADMINISTRATION

For acute psychotic episodes, oral doses between 400 mg/d and 800 mg/d are recommended. In individual cases, the daily dose may be increased up to 1200 mg/d. Doses above 1200 mg/d have not been extensively evaluated for safety and therefore should not be used. Doses above 800 mg/d have not been shown to be superior to lower doses and may increase the incidence of adverse events. No specific titration is required when initiating the treatment with amisulpride. Doses should be adjusted according to individual response.

Doses should preferably be administered before meals.

Amisulpride should be administered twice daily for doses above 400 mg.

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/d and 300 mg/d are recommended. Doses should be adjusted individually.

A graduated dosage syringe (pipette) is supplied for dispensing SOLIAN SOLUTION. Each one mL graduation is equivalent to 100mg amisulpride.

Elderly:

Amisulpride should be used with particular caution because of a possible risk of hypotension or sedation.

Children:

Amisulpride 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 (see Section 4.4 Special warnings and precautions for use).

Hepatic Insufficiency:

Since amisulpride is weakly metabolised, a dosage reduction should not be necessary (see Section 4.4 Special warnings and precautions for use).

4.3 CONTRAINDICATIONS

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

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

Phaeochromocytoma.

Children up to puberty.

Lactation.

Comment: Editorial change – addition of cross-reference.

In combination with the following medication which could induce *torsades de pointes*:

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

Levodopa; reciprocal antagonism between levodopa and neuroleptics (See Section 4.5 Interactions with other medicines and other forms of interactions).

In hepatic impairment, amisulpride may be contraindicated to avoid the possible risk of adverse events due to an influence of the disease on amisulpride metabolism.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Neuroleptic Malignant Syndrome (NMS) is a potentially fatal syndrome that has been reported in association with anti-psychotic medicines, including amisulpride. Neuroleptic malignant syndrome is characterised by hyperthermia, muscle rigidity, autonomic instability, and elevated CPK, may occur. In the event of any symptoms which could suggest NMS, in particular hyperthermia, particularly with high daily doses, all antipsychotic medicines including amisulpride should be discontinued.

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

Withdrawal symptoms have been described after abrupt cessation of high therapeutic doses of antipsychotic drugs. The emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported with amisulpride. Therefore, gradual withdrawal of amisulpride is advisable.

Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics, including amisulpride. Unexplained infections or fever may be evidence of blood dyscrasia and requires immediate haematological investigation.

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.

Amisulpride causes an increase in plasma prolactin levels which is reversible after discontinuation of the medicine. This may result in galactorrhoea, amenorrhoea, gynaecomastia, breast pain, orgasmic dysfunction and impotence.

Acute dystonia (spasm torticollis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon treatment with an antiparkinsonian agent.

Extrapyramidal symptoms may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia. 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 50-300mg/day.

The presentation of akathisia may be variable and comprises subjective complaints of restlessness and an overwhelming urge to move and either distress or motor phenomena such as pacing, swinging of the legs while seated, rocking from foot to foot, or both. Particular attention should be paid to the monitoring for such symptoms and signs as, left untreated, akathisia is associated with poor compliance and an increased risk of relapse.

Tardive dyskinesia characterised 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.

Hyperglycaemia and Diabetes Mellitus

Hyperglycaemia has been reported in patients treated with atypical antipsychotics including amisulpride. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increase background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics 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 atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

In patients with significant treatment-emergent hyperglycaemia, discontinuation of amisulpride should be considered.

Prolongation of QT Interval

Amisulpride produces a dose-dependent prolongation of the QT interval (see Section 4.8 Adverse effects (Undesirable effects)). This effect is known to potentiate the risk of occurrence of serious ventricular arrhythmias 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 onset of this rhythm disorder, 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, slowing of the intracardiac conduction, or prolongation of the QTc interval (See Section 4.5 Interactions with other medicines and other forms of interactions).

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. Amisulpride should be used with caution in patients with stroke risk factors.

Venous Thromboembolism

Cases of venous thromboembolism, sometimes fatal, have been reported with antipsychotic drugs. Therefore, amisulpride should be used with caution in patients with risk factors for thromboembolism (see Section 4.8 Adverse effects (Undesirable effects)).

Sleep Apnoea

No cases of sleep apnoea clearly attributed to amisulpride have been reported and no epidemiology studies can substantiate this. However, sleep apnoea and related disorders have been reported in patients treated with other antipsychotic medicines, with or without prior

history of sleep apnoea, in patients with or without concomitant weight-gain. Patients who have a history of or are at risk for sleep apnoea, or who are concomitantly using central nervous system depressants, should be medically monitored.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia and close supervision of high-risk patients should accompany therapy. Prescriptions for amisulpride should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Breast Cancer

Amisulpride 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 amisulpride therapy.

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 (see Section 4.3 Contraindications).

Use in hepatic impairment

The impact of hepatic impairment on hepatic metabolism and hepato-biliary excretion of amisulpride has not been studied. Amisulpride should be used with caution in patients with moderate or severe hepatic impairment.

Use in renal impairment

Amisulpride is eliminated by the renal route. In cases of renal insufficiency, the dose should be decreased and intermittent treatment should be considered (see Section 4.2 Dose and method of administration).

There are limited data on the potential for renally-cleared medicines to interfere with the clearance of amisulpride. Therefore, amisulpride should be used with caution with other renally-excreted medicines, including lithium (See Section 4.5 Interactions with other medicines and other forms of interactions).

Use in the elderly

In elderly patients, amisulpride therapy, like other neuroleptics, should be used with particular caution because of a possible risk of hypotension or sedation.

Elderly Patients with Dementia

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. 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.

Paediatric use

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, the use of amisulpride is contraindicated (see Section 4.3 Contraindications).

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

A number of medicines can increase the risk of ventricular arrhythmias including *torsades de pointes*.

Contraindicated combinations:

- Medications which could induce torsades de pointes:

Class Ia antiarrhythmic agents such as quinidine and disopyramide.

Class III antiarrhythmic agents such as amiodarone and sotalol.

Other medications such as bepridil, cisapride, sultopride, thioridazine, methadone, intravenous erythromycin, intravenous vincamine, halofantrine, pentamidine, sparfloxacin.

- Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics.

Combinations not recommended:

- Amisulpride may enhance the effects of alcohol.
- Medications which enhance the risk of *torsades de pointes* or could prolong the QT interval:
    - Medicines which induce bradycardia, such as bradycardia-inducing calcium channel blockers (diltiazem, verapamil), beta-blockers, clonidine, guanfacine, digitalis.

- Medicines which can cause hypokalaemia, such as diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactides. Hypokalaemia should be corrected.
- Neuroleptics such as thioridazine, chlorpromazine, trifluperazine, pimozide, haloperidol, imipramine antidepressants, lithium.

Combinations to be taken into account:

Concomitant use of amisulpride with other anti-psychotics may increase the risk of developing neuroleptic malignant syndrome.

Co-administration of amisulpride and clozapine may lead to an increase in plasma levels of amisulpride.

Amisulpride may enhance the effects of the following medicines:

- CNS depressants including narcotics, anaesthetics, analgesics, sedative H1-antihistamines, barbiturates, benzodiazepines and other anxiolytic medicines, clonidine and derivatives.
- Antihypertensive medicines and other hypotensive medications.

A placebo-controlled study of concomitant use of lithium carbonate 500 mg twice daily and a low dose of amisulpride (100 mg) twice daily in healthy young male volunteers showed no effect of amisulpride on the pharmacokinetics of lithium. A small trend towards prolongation of the QTc interval was observed when lithium and amisulpride were co-administered but is not regarded as clinically important.

A study of the effect of concomitant use of cimetidine on amisulpride excretion has not been conducted.

In vitro studies using human liver microsomes and cryopreserved human hepatocytes did not show evidence of significant amisulpride metabolism. Based on these results, it is unlikely that drug interactions involving amisulpride would occur due to inhibition or induction of cytochrome P450 –mediated metabolism.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Male rat fertility was unaffected by an amisulpride oral dose resulting in systemic drug exposure (plasma AUC) similar to that in humans, when treatment was carried out prior to mating. Female rat mating was reduced by concurrent amisulpride treatment, but it was normalised within days of cessation of dosing with overall fertility being unaffected, although some adverse effects were observed (see Use in pregnancy).

Use in pregnancy

Category C

Neonates exposed to antipsychotic drugs (including amisulpride) during the third trimester of pregnancy are at risk of experiencing extrapyramidial neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required additional medical treatment or monitoring. All newborns should be carefully monitored to assess the severity of adverse effects.

There was no evidence of teratogenicity in embryofoetal development studies in mice and rabbits following oral doses of up to 2 (mice) and 4 (rabbits) times the maximum recommended human dose based on body surface area, administered daily during the period of organogenesis. Oral treatment of female rats from prior to mating to late gestation or weaning, achieving systemic drug exposure (plasma AUC) similar to that in humans at the maximum dose, was associated with increased preimplantation loss, slight impairment of ossification and reduced pup weight gain to weaning. Teratogenicity was not observed.

Amisulpride crosses the placenta.

The safety of amisulpride during human pregnancy has not been established, and therefore 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 and the administered dose and duration of treatment should be as low and as short as possible.

Use in lactation

Amisulpride has been found in breast milk of treated women. Breast-feeding is contraindicated.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Even used as recommended, amisulpride may affect reaction time and/or cause somnolence and blurred vision so that the ability to drive vehicles or operate machinery can be impaired.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data

The following adverse effects have been observed in controlled clinical trials in at least 1% of treated patients (see Table 1). It should be noted that, in some instances, it can be difficult to differentiate adverse events from symptoms of the underlying disease.

Table 1 - Amisulpride – Negative & Positive Schizophrenia Clinical Studies pre-1997

Adverse events reported with an incidence of 1% or greater in the amisulpride group.

	Amisulpride (n = 921) %	Placebo (n = 202) %	Haloperidol (n=245) %	Flupentixol/Risperidone (n=62) %
CNS Disorder				
Extrapyramidal disorder	11	2	33	12

	Amisulpride (n = 921) %	Placebo (n = 202) %	Haloperidol (n=245) %	Flupentixol/Risperidone (n=62) %
Insomnia	10	7	11	7
Anxiety	7	5	9	6
Agitation	5	3	5	4
Tremor	3	6	4	7
Somnolence	3	0	4	4
Headache	3	4	3	10
Rigidity	2	2	5	5
Hypersalivation	2	0	2	4
Dyskinesia	2	0	6	0
Nervousness	2	1	2	1
Dystonia	1	0	3	1
Oculogyric crisis	1	0	1	2
Depression	1	0	2	1
Dizziness	1	1	0	3
Aggressive reaction	1	1	1	0
Suicide attempt	1	0	2	3
Gastro-intestinal disorders				
Constipation	3	1	4	1
Vomiting	2	3	2	4
Nausea	2	2	2	2
Dry mouth	1	1	2	0
Diarrhoea	1	1	1	0
Abdominal pain	1	1	1	3
Dyspepsia	1	0	0	0
Body as a whole disorders				
Weight increase	6	5	2	5
Weight decrease	2	2	1	0
Sweating increased	1	1	0	0
Fatigue	1	1	1	4
Reproductive disorders				
Amenorrhoea	4	0	0	0
Galactorrhoea	3	0	1	13
Menstrual disorder	1	0	0	2
Vaginitis	1	0	1	0
Cardiovascular disorders				
Hypotension	1	0	1	3
Hypotension postural	1	0	0	3
Hypertension	1	0	0	2
Cutaneous disorders				
Pruritis	1	1	0	1

The following CIOMS frequency rating is used, when applicable:

Very common ≥10%; Common ≥1 and <10%; Uncommon ≥0.1 and <1%; Rare ≥0.01 and <0.1%; Very rare <0.01%; Not known (cannot be estimated from available data).

The following adverse reactions have been observed in controlled clinical trials and through spontaneous reporting:

Blood and Lymphatic System Disorders:

Uncommon: leukopenia, neutropenia

Rare: agranulocytosis

Immune System Disorders:

Uncommon Allergic reactions

Endocrine Disorders:

Common Amisulpride causes an increase in plasma prolactin levels which is reversible after drug discontinuation. This may lead to galactorrhoea, amenorrhoea, gynaecomastia, breast pain, erectile dysfunction

Rare Benign pituitary tumour, such as prolactinoma (see Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use)

Metabolism and Nutrition Disorders:

Uncommon Hyperglycaemia (see Section 4.4 Special warnings and precautions for use), hypertriglyceridaemia and hypercholesterolaemia

Rare Hyponatraemia and 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 anti-parkinson medication

Common Acute dystonia (spasm torticollis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon treatment with an anti-parkinson agent

Solmnolence

Uncommon Tardive dyskinesia characterised by rhythmic, involuntary movements primarily of the tongue and/or face have been reported, usually after long-term administration. Anti-parkinsonian medication is ineffective or may induce aggravation of the symptoms

Seizures

Rare Neuroleptic Malignant Syndrome, which is a potentially fatal complication (see Section 4.4 Special warnings and precautions for use)

	Somnambulism (sleepwalking) and related behaviours including sleep-related eating disorder have been reported with the use of atypical antipsychotic medicines, including amisulpride.
Not known	Restless legs syndrome with or without a context of akathisia

Eye Disorders:

Common:	Blurred vision

Cardiac Disorders:

Common	QT interval prolongation (see Section 4.4 Special warnings and precautions for use)
Uncommon	Bradycardia
Rare	Ventricular arrhythmias such as torsades de pointes, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, sudden death (see Section 4.4 Special warnings and precautions for use)

Vascular Disorders:

Common	Hypotension
Uncommon	Increase in blood pressure
Rare	Venous thromboembolism, including pulmonary embolism, sometimes fatal, and deep vein thrombosis have been reported (see Section 4.4 Special warnings and precautions for use).

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 and urticaria
Not known	Photosensitivity reaction

Musculoskeletal and Connective Tissue Disorders:

Uncommon	Osteopenia and osteoporosis

Renal and Urinary Disorders:

Uncommon Urinary retention

Injury, poisoning and procedural complications:

Not known Fall as a consequence of adverse reactions compromising body balance

Pregnancy, Puerperium and Perinatal Conditions:

Frequency not known: Neonatal drug withdrawal syndrome

Investigations:

Common Weight gain

Uncommon Elevations of hepatic enzymes, mainly transaminases

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

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

Fatal outcomes have been reported mainly in combination with other psychotropic agents.

Treatment

In cases of acute overdose, the possibility of multiple drug intake should be considered.

There is no specific antidote to amisulpride. Appropriate supportive measure should therefore be instituted: close supervision of vital functions and, because of the risk of prolongation of QT interval, continuous cardiac monitoring until the patient recovers.

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

Since amisulpride is weakly dialysed, haemodialysis is not recommended as a method of elimination.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Neuroleptic of the benzamide class

Mechanism of action

Amisulpride binds selectively to the human dopaminergic D_2 (Ki 2.8 nM) and D_3 (Ki 3.2 nM) receptor subtypes without any affinity for D_1, D_4 and D_5 receptor subtypes (Ki > 1 μM). Unlike classical and atypical neuroleptics, amisulpride displays low affinity for serotonin, α-adrenergic, histamine receptor subtypes, muscarinic receptors and sigma sites.

In the rodent, it preferentially blocks post-synaptic D_2 receptors located in the limbic structures as compared to those in the striatum as indicated by its reversal of d-amphetamine-induced hyperactivity without affecting stereotypies. In addition, it does not induce catalepsy and it does not produce D_2 hypersensitivity after repeated treatment.

Moreover, it preferentially blocks pre-synaptic D_2/D_3 dopamine 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 located in the limbic areas and its efficacy against negative symptoms, at lower doses, through presynaptic dopamine receptor blockade. In addition, the reduced tendency of amisulpride to produce extrapyramidal side effects may be related to its preferential limbic activity.

Clinical trials

The efficacy of amisulpride in the treatment of schizophrenia has been established on the basis of eleven phase II and III studies conducted in 20 countries and involving 1933 patients (1247 treated with amisulpride) belonging to two distinct populations:

- patients with acute exacerbations of schizophrenia
- patients with predominant negative schizophrenia

These studies form the basis of the registration documentation for amisulpride. Seven of them are considered pivotal for efficacy and their results are summarized below.

<u>Acute exacerbations of schizophrenia</u>

In four well-controlled double-blind studies versus reference medicines in patients with acute schizophrenia according to DSM III-R and DSM-IV criteria, amisulpride was at least as effective as haloperidol, flupenthixol and risperidone. In addition to its global antipsychotic activity, amisulpride significantly alleviated secondary negative symptoms as well as affective symptoms such as depressed mood and retardation.

- A 4-week double-blind active-controlled trial (n=319) compared four fixed doses of amisulpride (100 mg/d, 400 mg/d, 800 mg/d and 1200 mg/d) and a fixed dose of haloperidol (16 mg/d). A dose response relationship was clearly established in

comparison to 100 mg/d, chosen as a potentially subtherapeutic dose in acute schizophrenia. Amisulpride at doses of 400 and 800 mg/d statistically significantly improved positive symptoms (BPRS total score, PANSS positive symptoms subscale) compared with amisulpride 100 mg/d. 800 mg/d of amisulpride was also statistically significantly superior to 100 mg/d for response rates based on the CGI.

- Efficacy results were similar in the three other short-term controlled studies where 800 mg/d of amisulpride was compared with 20 mg/d of haloperidol (n=191), 1000 mg/d of amisulpride with 25 mg/d of flupenthixol (n=132) and 800 mg/d of amisulpride with 8 mg of risperidone (n=228). On BPRS total score and PANSS positive subscale, amisulpride was not found to be different from haloperidol and flupenthixol and showed equivalent efficacy to risperidone. Additionally, amisulpride significantly improved the response rate with CGI versus haloperidol.

Predominant negative schizophrenia

Three pivotal trials were conducted versus placebo in schizophrenic patients with predominant negative symptoms according to DSM III and DSM III-R, showing that low doses of amisulpride are active against negative symptoms.

1. In a six-week dose finding study (n=104), amisulpride 100 mg/d and 300 mg/d were significantly better than placebo on the basis of the SANS total score.
2. In an additional 3-month dose finding study (n=242) testing two fixed dose of amisulpride (50 mg/d and 100 mg/d) versus placebo, both doses of amisulpride were significantly more active in improving the negative symptoms than placebo on the SANS total score. Additionally, there was a significant improvement of the MADRS scores in the two amisulpride groups.
3. A medium-/long-term placebo controlled study with amisulpride 100 mg/d over 6 months with the possibility of extension up to 12 months was conducted to demonstrate the maintenance of efficacy over time. Amisulpride improved negative symptoms (SANS total score) significantly compared with placebo, and the response rate with CGI was significantly higher in the amisulpride group versus placebo. The results were confirmed by the significant improvement of global functioning measured with the GAF. SANS total score remained stable over time up to 12 months, indicating that 100 mg/d not only maintains the improvement of negative symptoms but has also an effect on preventing the recurrence of positive symptoms.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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.

Distribution

The volume of distribution is 5.8 L/kg. As plasma protein binding is low (16%), drug interactions due to displacement are unlikely.

The absolute bioavailability of amisulpride tablets is 48%.

Bioequivalence between the solution and the 200 mg tablet has been demonstrated (C_{max} mean ratio 0.95, 90% confidence interval 0.81-1.12; $AUC_{0-\infty}$ mean ratio 0.89, 90% confidence interval 0.81-0.97). However, bioequivalence has not been demonstrated between the solution and the 400 mg tablet (C_{max} mean ratio 0.88, 90% confidence interval 0.75-1.04; $AUC_{0-\infty}$ mean ratio 0.86, 90% confidence interval 0.78-0.94).

Metabolism

Amisulpride is weakly metabolised: two inactive metabolites, accounting for approximately 4% of the dose, have been identified. The elimination half-life of amisulpride is approximately 12 hours after an oral dose.

Excretion

Fifty percent of an intravenous dose is excreted via the urine, the majority as unchanged drug. Ninety percent of the intravenous dose is eliminated in the first 24 hours. Renal clearance is in the order of 20 L/h or 330 mL/min.

Following a single intravenous dose, about 20% of the dose was recovered from the faeces, about 70% of which was as unchanged amisulpride. Hepatic metabolism has a limited role in healthy patients.

A high-carbohydrate low-fat meal (14 g protein, 8 g fat, 108 g CHO) significantly decreases the AUC, 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: See Section 4.4 Special warnings and precautions for use.

Renal insufficiency: In patients with renal insufficiency 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. 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}, $T_{½}$ 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/d) and dog (120 mg/kg/d) respectively in terms of AUC. No

carcinogenic risk, relevant to man, was identified in the mouse (up to 120 mg/kg/d) and in the rat (up to 240 mg/kg/d), corresponding for the rat to 1.5 to 5 times the expected human AUC.

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

Genotoxicity

Amisulpride showed no genotoxicity in *in vitro* tests for bacterial gene mutation, or in in vitro and in vivo tests for clastogenic activity.

Carcinogenicity

In carcinogenicity studies, amisulpride was administered in the diet of mice and rats for up to two years. Treatment of mice was associated with increases in malignant mammary gland tumours and pituitary adenomas in females at all dose levels, but there was no tumourigenic response in males (doses were equivalent to 0.1, 0.2 and 0.5 times the maximum human dose of 1200 mg/day on a body surface area basis). Treatment of rats resulted in increased incidences of malignant mammary gland tumours in both sexes, malignant pituitary tumours and adrenal medullary phaeochromocytomas in males, and malignant pancreatic islet cell tumours in both sexes, at doses achieving lower systemic drug exposure (plasma AUC) than in humans at the maximal recommended dose. Increases in mammary gland, pituitary, adrenal and pancreatic endocrine tumours in rodents have been reported for other antipsychotic medicines, and are considered to result from increased prolactin secretion.

The relevance of prolactin-mediated endocrine tumours in rodents for human risk is unknown. In clinical trials, amisulpride substantially elevated plasma prolactin concentrations, although to date neither clinical nor epidemiological studies have shown an association between chronic administration of neuroleptic medicines and mammary tumourigenesis. However, since tissue culture experiments indicate that about one-third of human breast cancers are prolactin-dependent in vitro, amisulpride should be used cautiously in patients with previously-detected breast cancer or in patients with pituitary tumours (see 4.3 Contraindications).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

SOLIAN Tablets contain the following excipients:

50, 100 and 200 mg tablets:	sodium starch glycollate type A, lactose monohydrate, microcrystalline cellulose, hypromellose, magnesium stearate.
400 mg tablets:	sodium starch glycollate type A, lactose monohydrate, microcrystalline cellulose, hypromellose, magnesium stearate, PEG-40 stearate, titanium dioxide.

SOLIAN SOLUTION contains the following excipients:

hydrochloric acid, methyl hydroxybenzoate, propyl hydroxybenzoate, potassium sorbate and purified water, and the following proprietary ingredients: Gesweet® 2023 (ARTG No 10553) and Caramel Flavour E9422058 (ARTG No 10645).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Tablets

Store below 30°C.

Solution

Store below 25°C. Once opened, discard after two months.

6.5 NATURE AND CONTENTS OF CONTAINER

SOLIAN 50: Packed in blister packs of 2, 5, 10, 15, 30, 50, 60, 90 and 100. (Not marketed)

SOLIAN 100: Packed in blister packs of 2, 5, 10, 15, 30♦, 50, 60, 90 and 100.

SOLIAN 200: Packed in blister packs of 2, 5, 10, 15, 30, 50, 60♦, 90 and 100.

SOLIAN 400: Packed in blister packs of 2, 5, 10, 15, 30, 50, 60♦, 90 and 100.

SOLIAN SOLUTION 100mg/mL: Packed in 60mL brown glass bottles.

♦ Marketed pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

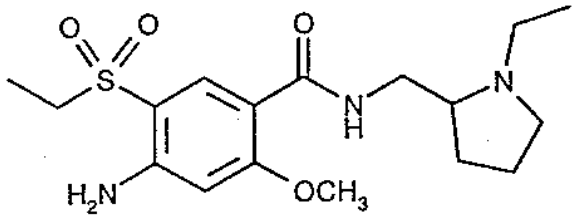
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Amisulpride is a white to off-white powder, which is practically insoluble in water, sparingly soluble in ethanol, soluble in methanol and freely soluble in dichloromethane.

Chemical Name:	(R, S)-4-Amino-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-ethylsulfonyl-2-methoxybenzamide
Molecular Weight:	369.48
Molecular Formula:	$C_{17}H_{27}N_3O_4S$

Chemical structure



CAS number

71675-85-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113
Australia
Toll Free Number (medical information): 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

1 February 2002

10 DATE OF REVISION

27 October 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Editorial changes included
4.8	Adverse Effects updated to include fall as a consequence of adverse reactions comprising body balance