QUALITATIVE AND QUANTITATIVE COMPOSITION

Solian® 100 mg, scored tablets
Amisulpride ……..……100 mg
Solian® 400 mg, scored film-coated tablets
Amisulpride …… 400 mg

PHARMACEUTICAL FORM

Solian® 100 mg, scored tablets
White to off-white scored tablet, engraved “AMI 100”.
Solian® 400 mg, scored film-coated tablets
White scored film-coated tablet, engraved “AMI 400”.

CLINICAL PARTICULARS

Therapeutic indications

Treatment of acute or chronic schizophrenic disorders, in which positive symptoms (such as delusions, hallucinations, thought disorders) and/or negative symptoms (such as blunted emotions, emotional and social withdrawal) are pronounced, including patients with predominantly negative symptoms.

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.

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

Children and adolescents

The efficacy and safety of amisulpride from the age of puberty up to 18 years has not been elucidated: available data on the use of amisulpride in adolescents with schizophrenia are limited. As a result, amisulpride is not recommended in patients from the age of puberty up to 18 years. Amisulpride is contraindicated for children under 15 years of age.

Elderly subjects

Amisulpride should be used with particular caution in this patient population due to the risk of hypotension and sedation. Dose reduction may also be required in patients with kidney failure.

Renal insufficiency
Amisulpride is eliminated via the renal route. In patients with renal insufficiency, the dose should be reduced by half when creatinine clearance (CrCl) is between 30-60 ml/min and to a third in patients with CrCl between 10-30 ml/min.
As no data on patients with serious renal insufficiency (CrCl <10 ml/min) are available, careful monitoring is recommended in this population.

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

Contraindications
This medicine MUST NOT BE USED in the following cases:

- hypersensitivity to amisulpride or to any of the ingredients of the medicinal product,
- serious hypertensive events have been reported in patients with pheochromocytoma using antidopaminergic drugs, including some benzamides. This medicinal product should therefore not be prescribed to known or suspected pheochromocytoma carriers,
- children under 15 years of age, because no clinical data are available,

- known or suspected prolactin-dependent tumors, e.g. pituitary gland prolactinomas and breast cancer,
- in combination with:
    - non-antiparkinsonian dopamine agonists (cabergoline, quinagolide)
    - citalopram, escitalopram, domperidone, hydroxyzine, piperaquine

Special warnings and precautions for use

Potentially fatal neuroleptic malignant syndrome
As with other neuroleptic agents, potentially fatal neuroleptic malignant syndrome (hyperthermia, muscle rigidity, autonomic disorders, consciousness disorders and elevated CPK levels) may occur. If patients suffer from hyperthermia, particularly with high daily doses, all antipsychotic agents, including amisulpride, should be discontinued.

Prolongation of the QT interval
Amisulpride induces a dose-dependent prolongation of the QT interval. This effect, known to potentiate the risk of serious ventricular arrhythmias, particularly of the torsades de pointes type, is enhanced in patients with bradycardia, hypokalemia, or congenital or acquired prolonged QT interval (combination with a medicinal product which prolongs the QTc interval).

It is therefore recommended, when the clinical situation permits, that checks be made before administration to ensure that there are no factors which could promote the occurrence of this rhythm disorder, i.e.:

- bradycardia less than 55 bpm,
- hypokalemia,
- congenital prolongation of the QT interval,
- ongoing treatment with a medicinal product likely to cause marked bradycardia (<55 bpm), hypokalemia, delayed intracardiac conduction, or prolongation of the QTc interval.

An ECG should be performed as part of the initial assessment of patients requiring long-term treatment with a neuroleptic agent.

Stroke
In randomized, placebo-controlled clinical studies in elderly patients with dementia and treated with certain atypical antipsychotic agents, a three-fold risk of stroke was observed versus placebo. The mechanism underlying this increased risk is unknown. Increased risk with other antipsychotic agents or in other patient populations cannot be ruled out. This medicinal product must be used with caution in patients with risk factors for stroke.

Elderly patients with dementia
The risk of mortality increases in elderly patients suffering from dementia-related psychosis and treated with antipsychotic drugs.

Analysis of 17 placebo-controlled studies (mean duration of 10 weeks), conducted in patients mainly taking atypical antipsychotic drugs, showed that the risk of mortality increased 1.6- to 1.7-fold in patients treated with these medicinal products versus placebo.
After a mean treatment period of 10 weeks, the risk of mortality was 4.5% in the treated patient group versus 2.6% in the placebo group.
Although the causes of death varied in the clinical trials with the atypical antipsychotic drugs, the majority of deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia).
Epidemiological studies suggest that treatment with conventional antipsychotic drugs may increase mortality, as is the case for atypical antipsychotic drugs.
The respective contribution of the antipsychotic drug and patient characteristics to the increase in mortality found in the epidemiological studies is unclear.

Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotic drugs often present acquired risk factors for VTE, any potential risk factors for VTE must be identified before and during treatment with **Solian** and preventive measures should be taken if needed.

Hyperglycemia and Diabetes Mellitus
Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased 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 antipsychotics was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

Seizure
Amisulpride can lower the seizure threshold. Therefore patients with a history of seizures should be closely monitored during treatment with **Solian**.

Special populations
As amisulpride is eliminated by the renal route, the dose should be decreased or an alternative treatment considered in patients with renal insufficiency. There are no data concerning patients with serious renal insufficiency.
Amisulpride, like all antipsychotics, should be used with particular caution in elderly patients due to the potential risk of sedation and hypotension.
Amisulpride, like all antidopaminergic drugs, should be used with caution in patients with Parkinson's disease due to the risk of worsening disease. Amisulpride should be used only if neuroleptic treatment is absolutely necessary.

Withdrawal syndrome
Withdrawal symptoms including nausea, vomiting and insomnia have been described following sudden discontinuation of high doses of antipsychotics. Recurrence of psychotic symptoms may also be observed and involuntary movements disorders (e.g. akathisia, dystonia and dyskinesia) have been reported with amisulpride. It is therefore advisable to discontinue amisulpride treatment gradually.

Hyperprolactinemia
Amisulpride can increase prolactin levels. Patients with a history of hyperprolactinemia and/or potentially prolactin-dependent tumor should be closely monitored during amisulpride treatment.

Benign pituitary tumor
Amisulpride may increase prolactin levels. Cases of benign pituitary tumors, such as prolactinoma, have been observed during amisulpride treatment. In the event of very high prolactin levels or clinical signs of a pituitary tumor (such as visual field disorders and headaches), medical imaging investigations should be performed. If a diagnosis of pituitary tumor is confirmed, amisulpride treatment should be stopped.

Hepatotoxicity
Severe hepatotoxicity has been reported with the use of amisulpride. Patients should be informed that any signs such as asthenia, anorexia, nausea, vomiting, abdominal pain or jaundice must be reported to a doctor immediately. Investigations including a clinical examination and liver function tests must be carried out immediately.

Other
Cases of leukopenia, neutropenia and agranulocytosis have been reported with administration of antipsychotics, including Solian. The occurrence of an infection or fever of unknown etiology may be indicative of leukopenia and require immediate blood tests.
It is inadvisable to use this medicinal product in combination with alcohol, antiparkinsonian dopamine agonists, antiparasitic agents likely to induce torsades de pointes, methadone, levodopa, other neuroleptic agents and medicinal products likely to induce torsades de pointes.

Warning related to excipients
This medicinal product contains lactose. It is not recommended in patients with galactose intolerance, Lapp-lactase deficiency or glucose-galactose malabsorption syndrome (rare hereditary diseases).

Interaction with other medicinal products and other forms of interaction

+ Sedative agents
It must be taken into account that many drugs or substances can have additive depressant effects on the central nervous system and contribute to a decrease in alertness. These drugs include morphine derivatives (analgesics, antitussives, and substitute treaments), neuroleptics, barbiturates, benzodiazepines, non-benzodiazepine anxiolytics (such as meprobamate), hypnotics, sedative antidepressants (amitriptyline, doxepin, mianserine, mirtazapine, trimipramine), sedative H1-antihistamines, centrally acting antihypertensives agents, baclofen and thalidomide.

+ Drugs likely to induce torsades de pointes
This serious arrhythmia can be caused by a number of medicinal products, antiarrhythmic and non-antiarrhythmic. Hypokalemia (see Potassium-depleting agents) is a promoting factor, as is bradycardia (see Bradycardia agents) and pre-existing congenital or acquired QT interval prolongation.
This particularly concerns class IA and III antiarrhythmics as well as some neuroleptics.
For dolasteron, erythromycin, spiramycin, and vincamine, only forms administered intravenously are concerned by this interaction.
In general, using two torsadogenic drugs concomitantly is contraindicated.
Nevertheless, methadone as well as certain sub-classes are exceptions to the rule:

- antiparasitics (chloroquine, halofantrine, lumefantrine, pentamidine) are only inadvisable in combination with other torsadogenic drugs.

- neuroleptics likely to induce torsades de pointes are also inadvisable but not contraindicated in combination with other torsadogenic drugs.

However, citalopram, escitalopram, domperidone, hydroxyzine and piperaquine are not among these exceptions, and are therefore contraindicated when coadministered with all torsadogenic drugs.

Contraindicated combinations

+ Dopamine agonists excluding antiparkinsonians (cabergoline, quinagolide)
Mutual antagonism of effects between dopamine agonists and neuroleptics.

+ **Citalopram, escitalopram, domperidone, hydroxyzine, piperaquine**
There is an increased risk of ventricular arrhythmias, especially torsades de pointes.

Inadvisable combinations

+ Antiparasitics likely to induce torsades de pointes (chloroquine, halofantrine, lumefantrine, pentamidine)
Increased risk of ventricular arrhythmias, particularly torsades de pointes.
If possible, treatment with one of the two drugs should be discontinued.
If the combination cannot be avoided, a preliminary QT should be carried out and ECG monitoring performed.

+ Dopaminergic antiparkinsonian drugs (amantadine, apomorphine, bromocriptine, entacapone, lisuride, pergolide, piribedil, pramipexole, rasagiline, ropinirole, selegiline)
Mutual antagonism of effects between dopamine agonists and neuroleptics.
Dopamine agonists can induce or worsen psychotic disorders. When it is necessary to use a neuroleptic in a patient with Parkinson's disease who is taking dopamine agonists, the dopamine agonists must be gradually reduced and finally discontinued (sudden withdrawal of dopamine agonists exposes the patient to a risk of neuroleptic malignant syndrome).

+ Other drugs likely to induce torsades de pointes: class IA antiarrhythmics (quinidine,hydroquinidine, disopyramide) and class III antiarrhythmics (amiodarone, dronedarone, sotalol, dofetilide, ibutilide), and other drugs such as arsenic compounds, bepridil, cisapride, diphemanil, IV dolasetron, IV erythromycin, levofloxacin, mizolastine, prucalopride, IV vincamine, moxifloxacin, IV spiramycin, toremifene, vandetanib.
Increased risk of ventricular arrhythmias, particularly torsades de pointes.

+ Other neuroleptics likely to induce torsades de pointes (chlorpromazine, cyamemazine, droperidol, flupenthixol, fluphenazine, haloperidol, levomepromazine, pimozide, pipamperone, pipotiazine, sertindole, sulpiride, sultopride, tiapride, zuclopenthixol).
Increased risk of ventricular arrhythmias, particularly torsades de pointes.

+ Alcohol consumption
Alcohol enhances the sedative effects induced by these substances.
Impaired alertness may make it dangerous to drive or to use machines.
Consumption of alcoholic drinks or medicines containing alcohol should be avoided.

+ Levodopa
Mutual antagonism of effects between levodopa and neuroleptics.
In patients with Parkinson's disease, minimum effective doses of each of these drugs should be used.

+ Methadone
Increased risk of ventricular arrhythmias, particularly torsades de pointes.
+ Sodium oxybate
The central nervous depressant effect is potentiated. Impaired alertness may make driving vehicles and using machines dangerous.

+ Hydroxychloroquine
There is an increased risk of ventricular arrhythmias, especially torsades de pointes.

Combinations requiring precautions for use

+ **Anagrelide**
There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.
When coadministering these agents, clinical and ECG monitoring are required

+ **Azithromycin, ciprofloxacin, clarithromycin, levofloxacin, norfloxacin, roxithromycin**
Increased risk of ventricular arrhythmia, particularly torsades de pointes.
When co-administering these agents, clinical and ECG monitoring are required.

+ Beta-blockers in patients with heart failure (bisoprolol, carvedilol, metoprolol, nebivolol)
Increased risk of ventricular arrhythmias, particularly torsades de pointes. In addition, there is a vasodilator effect and risk of hypotension, particularly postural (additive effect). Clinical and ECG monitoring required.

+ Bradycardia agents (particularly class IA antiarrhythmics, beta-blockers, certain class III antiarrhythmics, certain calcium channel blockers, digitalis glycosides, pilocarpine, anticholinesterase agents):
Increased risk of ventricular arrhythmias, particularly torsades de pointes.
Clinical and ECG monitoring required.

+ Potassium-depleting agents (potassium-lowering diuretics, alone or in combination, stimulant laxatives, glucocorticoids, tetracosactides and IV amphotericin B).
Increased risk of ventricular arrhythmias, particularly torsades de pointes.
Any hypokalemia should be corrected before administering amisulpride and clinical, electrolyte and ECG monitoring performed.

+ Lithium
Risk of neuropsychiatric signs suggestive of neuroleptic malignant syndrome or lithium poisoning. Regular clinical monitoring and monitoring of laboratory test results is required, particularly at the start of co-administration.
+ **Ondansetron**
There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.
When coadministering these agents, clinical and ECG monitoring are required.

Combinations to be taken into consideration
+ **Other sedative drugs**
The central nervous depressant effect is potentiated.
Impaired alertness may make driving vehicles and using machines dangerous.

+ **Orlistat**
There is a risk of treatment failure when the drug is coadministered with orlistat.

Fertility, Pregnancy and lactation

Pregnancy
Available data on the use of amisulpride in pregnant women are limited. Therefore, the safety of amisulpride during human pregnancy has not been established.
Amisulpride crosses the placenta.
Animal studies have shown reproductive toxicity.
The use of amisulpride is not recommended during pregnancy and in women of child-bearing potential not using effective contraception, unless the benefits of such treatment outweigh the potential risks to the foetus.

Neonates exposed to antipsychotics drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity and duration; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalisation. Consequently, newborns should be monitored carefully.

Breast-feeding
A significant amount of amisulpride is excreted in breast milk. In some cases the amount exceeds the accepted value of 10% of the mother's weight-adjusted dose, however blood concentrations in breast-fed infants have not been evaluated. There are inadequate data on the effects of amisulpride in neonates/infants.
The benefit of breast-feeding for the infant should be weighed against the benefit of amisulpride treatment when deciding to stop breast-feeding or to not take amisulpride.

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

Effects on ability to drive and use machines

Patients, especially those who drive and use machines, should be warned of the risk of drowsiness or blurred vision associated with the use of this drug.

Undesirable effects

Undesirable effects have been group by frequency using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (frequency cannot be estimated from the available data).

Blood and lymphatic system disorders
Uncommon
Leukopenia, neutropenia.
Rare
Agranulocytosis.

Immune system disorders
Uncommon
Allergic reactions.

Endocrine disorders
Common
Increase in plasma prolactin levels which is reversible on treatment discontinuation. This may result in the following clinical signs and symptoms: galactorrhea, amenorrhea, gynecomastia, breast pain, erectile dysfunction.
Rare
Benign pituitary tumor such as prolactinoma

Metabolism and nutrition disorders
Uncommon
Hyperglycemia, hypertriglyceridemia and hypercholesterolemia.
Rare
Hyponatremia, syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Psychiatric disorders
Common
Insomnia, anxiety, agitation, frigidity.
Uncommon
Confusion.

Nervous system disorders
Very common
Extrapyramidal symptoms (tremor, hypertonia, hypersalivation, akathisia, hypokinesia, dyskinesia) may occur. These symptoms are generally moderate at optimal dosages and partially reversible without discontinuation of **Solian** upon administration of antiparkinsonian medication.
The incidence of extrapyramidal symptoms, which are dose-dependent, is very low in patients being treated for predominantly negative symptoms at doses of 50 mg/day to 300 mg/day.

Common
Acute dystonia (spasmodic torticollis, oculogyric crises, trismus, etc.) may appear. This is reversible without discontinuation of amisulpride but with administration of an anticholinergic antiparkinsonian agent.
Drowsiness.

Uncommon
Tardive dyskinesia, characterized by involuntary movements of the tongue and/or face have been reported, particularly after long-term administration.
Anticholinergic antiparkinsonian agents are ineffective or may induce worsening of the symptoms.
Seizures.

Rare
Potentially fatal neuroleptic malignant syndrome.

Not known
Restless legs syndrome

Eye disorders
Common
Blurred vision

Gastrointestinal disorders
Common
Constipation, nausea, vomiting, dry mouth.

Cardiac disorders
Uncommon
Bradycardia.

Rare
QT interval prolongation, ventricular arrhythmias such as torsades de pointes, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, sudden death

Vascular disorders
Common
Hypotension.

Uncommon
Increase in blood pressure.

Rare
Cases of venous thromboembolism, including cases of pulmonary embolism, sometimes fatal, and deep vein thrombosis, have been reported with antipsychotic drugs.

Respiratory, thoracic and mediastinal disorders
Uncommon
Nasal congestion, inhalation pneumonia (mainly in combination with other antipsychotic agents and drugs with a central nervous depressant effect).

Sleep apnoea*.
*Atypical antipsychotic drugs, such as Amisulpride, have been associated wth cases of sleep apnoea, with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnoea, Solian should be prescribed with caution.

Hepatobiliary disorders
Uncommon
Hepatocellular injury.

Skin and subcutaneous tissue disorders
Rare
Angioedema, urticaria
Not known
Photosensitivity reaction.

Musculoskeletal and systemic disorders
Uncommon
Osteopenia, osteoporosis.

Renal and urinary disorders
Uncommon
Urinary retention.

Pregnancy, puerperium and perinatal conditions
Not known
Neonatal drug withdrawal syndrome.

Investigations
Common
Weight gain.

Uncommon
Elevated liver enzymes, mainly transaminases.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 the national reporting system.

Overdose
To date, data concerning acute overdose with amisulpride are limited. The reported signs and symptoms generally result from increased pharmacological activity manifested clinically by drowsiness, sedation, coma, hypotension and extrapyramidal symptoms. Cases with a fatal outcome have been reported mainly in combination with other antipsychotic drugs.
There is no known specific antidote to amisulpride. In the event of acute overdose, use of concomitant medication must be investigated and appropriate measures taken:

- Close monitoring of vital functions.

- Cardiac monitoring (risk of prolongation of the QT interval) until the patient recovers.
- If severe extrapyramidal symptoms occur, anticholinergic agents must be administered.
- Since amisulpride is poorly dialyzable, hemodialysis is of limited use to eliminate the drug.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

ANTIPSYCHOTIC, ATC code**: N05AL05**

Amisulpride is an antipsychotic drug belonging to the class of substituted benzamides.

Its pharmacodynamic profile is characterized by a selective and predominant affinity for the dopaminergic D_2 and D_3 receptors of the limbic system. Amisulpride is devoid of affinity for serotonin receptors or other neuroreceptors such as histamine, cholinergic and adrenergic receptors.

In animal studies, at high doses, amisulpride preferentially blocks the dopaminergic neurones of the mesolimbic system compared to those in the striatal system. This specific affinity could explain the predominant antipsychotic effects of amisulpride compared with its extrapyramidal effects.

At low doses, amisulpride preferentially blocks the presynaptic D_2 / D_3 dopaminergic receptors, which could explain its effects on negative symptoms.

In a controlled, double-blind study *versus* haloperidol conducted in 191 patients with acute schizophrenia, improvement of secondary negative symptoms was significantly greater with amisulpride in comparison with haloperidol.

Pharmacokinetic properties

In man, amisulpride shows two absorption peaks: the first is attained rapidly, one hour post-dose and the second between 3 and 4 hours after administration.

Corresponding plasma concentrations after administration of a 50mg dose are 39 ± 3 ng/mL (one hour post dose) and 54 ± 4 ng/mL (between 3 and 4 hours post-dose)..

The volume of distribution is 5.8 l/kg; plasma protein binding is low (16%) and no drug interactions related to plasma protein binding are suspected. Absolute bioavailability is 48%.

Amisulpride is poorly metabolized: two inactive metabolites have been identified and account for approximately 4% of the total amount of drug eliminated.

There is no accumulation of amisulpride and its pharmacokinetics remain unchanged after the administration of repeated doses.

The elimination half-life is approximately 12 hours after an oral dose.

Amisulpride is eliminated unchanged in the urine. 50% of an intravenous dose is excreted via the urine, of which 90% is eliminated in the first 24 hours.

Renal clearance is approximately 330 ml/min.

A carbohydrate-rich meal significantly decreases the AUC, Tmax and Cmax of amisulpride but no changes are seen after a high-fat meal. The effect of these findings during treatment with amisulpride is not known.

<u>Hepatic insufficiency</u>

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

<u>Renal insufficiency</u>

The elimination half-life is unchanged in patients with renal insufficiency while total clearance is reduced by a factor of 2.5 to 3.

The AUC of amisulpride in mild kidney failure is increased two-fold and almost ten-fold in moderate kidney failure.

Experience is limited, however, and there are no available data on doses higher than 50 mg.

Amisulpride is poorly dialyzable.

Elderly subjects
The pharmacokinetic data available for subjects aged over 65 years show that a 10-30% increase occurs in Cmax, $T_{1/2}$ and AUC after a single dose of 50 mg.
No data are available after repeated dosing.

Preclinical safety data
The toxicological profile of amisulpride is dominated by the pharmacological effects of the compound.Repeated-dose toxicity studies showed no target organ impairment. In animal studies, amisulpride had an effect on fetal growth and development at doses corresponding to an equivalent human dose of 2 000 mg/day and over in patients weighing 50 kg. There is no evidence that amisulpride has teratogenic potential. No studies have been carried out on the effect of amisulpride on the behavior of the offspring.
Carcinogenesis studies have demonstrated hormone-dependent tumors in rodents. These are not of any clinical relevance in man.
Decreased fertility related to the pharmacological properties of the product (prolactin-mediated effects) was observed in animals.

PHARMACEUTICAL PARTICULARS
List of excipients
Solian 100mg: sodium starch glycolate, lactose monohydrate, microcrystalline cellulose, hypromellose and magnesium stearate

Solian 400mg: sodium starch glycolate, lactose monohydrate, microcrystalline cellulose, hypromellose, magnesium stearate, polyoxyl 40 stearate and titanium dioxide

Shelf life
3 years.

Special precautions for storage
Store below 30°C, away from heat and humidity.

Presentation
30 tablets in blister packs (PVC/aluminium).

Manufactured by
Delpharm Dijon
6, Boulevard de l'Europe
21800 Quétigny
France.

Revision date: October 2019 (CCDS V13 based on FR SmPC Apr19 and MY directive Oct18)