Amisulpride

Core Safety Profile

Formulations: 50, 100, 200 mg tablets; 400 mg film-coated tablet

4.2 Posology and method of administration

- ☐ Elderly:-The safety of amisulpride has been examined in a limited number of elderly patients. Amisulpride should be used with particular caution because of a possible risk of hypotension and sedation. Reduction in dosage may also be required because of renal insufficiency.
- ☐ Children: The efficacy and safety of amisulpride from puberty to the age of 18 years have not been established: There are limited data available on the use of amisulpride in adolescents in schizophrenia. Therefore, the use of amisulpride from puberty to the age of 18 years is not recommended; in children up to puberty amisulpride is contraindicated, as its safety has not yet been established. (see section: 4.3).
- ☐ Renal insufficiency: Amisulpride is eliminated by the renal route. In renal insufficiency, the dose should be reduced to half in patients with creatinin clearance (CRCL) between 30-60 ml/min and to a third in patients with CRCL between 10-30 ml/min. As there is no experience in patients with severe renal impairment (CRCL < 10 ml/min) particular care is recommended in these patients (see section 4.4 Special warnings and precautions for use).
- ☐ Hepatic insufficiency: since the drug is weakly metabolized a dosage reduction should not be necessary.

4.3 Contraindications

- ☐ Hypersensitivity to the active ingredient or to other ingredients of the medicinal product.
- ☐ Concomitant prolactin-dependent tumours (e.g. pituitary gland prolactinomas or breast cancer).
- ☐ Phaeochromocytoma.
- ☐ Children up to puberty.
- ☐ Lactation.
- ☐ Combination with levodopa (see section 4.5. Interactions with other medical products and other forms of interaction).

4.4 Special warnings and precautions for use

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

- ☐ As with other antidopaminergic agents, caution should be also exercised when prescribing amisulpride to patients with Parkinson's disease, since it may cause worsening of the disease. Amisulpride should be used only if neuroleptic treatment cannot be avoided.
- ☐ Prolongation of the QT interval:

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

☐ Stroke:

In 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. Amisulpride 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. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between
1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of 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.

☐ 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 preventative measures undertaken.

- ☐ 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.
- ☐ Amisulpride may lower the seizure threshold. Therefore patients with a history of epilepsy should be closely monitored during amisulpride therapy.
- ☐ Amisulpride is eliminated by the renal route. In cases of renal insufficiency, the dose should be decreased or intermittent treatment could be considered (see section 4.2 Posology and method of administration).
- ☐ In elderly patients, amisulpride, like other neuroleptics, should be used with particular caution because of a possible risk of hypotension and sedation. Reduction in dosage may also be required because of renal insufficiency.
- ☐ Withdrawal symptoms, including nausea, vomiting and insomnia, have been described after abrupt cessation of high therapeutic doses of antipsychotic drugs. . Recurrence of psychotic symptoms may also occur, and tThe 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 [NAME]. 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

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, ropirinol.

Combinations not recommended

- ☐ Amisulpride may enhance the central effects of alcohol.

Combinations to be taken into account

- ☐ CNS depressants including narcotics, analgesics, sedative H1 antihistamines, barbiturates, benzodiazepines and other anxiolytics, clonidine and derivatives.
- ☐ Antihypertensive drugs and other hypotensive medications.
- ☐ Caution is advised when prescribing amisulpride with medicines known to prolong the QT interval, e.g., class IA antiarrhythmics (e.g., quinidine, disopyramide) and class III antiarrhythmics (e.g., amiodarone, sotalol), some antihistaminics, some other antipsychotics and some antimalarials (e.g., mefloquine) (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

In animals, amisulpride did not show 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.

Neonates exposed to antipsychotics, including [NAME], 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.

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, amisulpride 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 reactions 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 trials data 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.

☐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 result in galactorrhoea, amenorrhoea, gynaecomastia, breast pain, and erectile dysfunction.

☐Metabolism and nutrition disorders

Uncommon: Hyperglycemia (see section 4.4 Special warnings and precautions for use).

☐Psychiatric disorders *Common:* Insomnia, anxiety, agitation, orgasmic dysfunction.

☐Nervous system disorders

Very common: Extrapyramidal symptoms may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia, dyskinesia. These symptoms are generally mild at optimal dosages and partially reversible without discontinuation of amisulpride upon administration of antiparkinsonian medication. The incidence of extrapyramidal symptoms which is dose related, remains very low in the treatment of patients with predominantly negative symptoms with doses of 50-300 mg/day.

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

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

☐Cardiac disorders *Common:* Hypotension. *Uncommon:* Bradycardia.

☐Gastrointestinal disorders

Common: Constipation, nausea, vomiting, dry mouth.

☐Investigations *Common:* Weight gain. *Uncommon:* Elevations of hepatic enzymes, mainly transaminases

Post Marketing data In addition, cases of the following adverse reactions have been reported through spontaneous reporting only.

☐Blood and Lymphatic system disorders

Frequency not known: Leukopenia, neutropenia and agranulocytosis (see section 4.4) ☐Nervous system disorders *Frequency not known:* Neuroleptic Malignant Syndrome (see section 4.4 Special warnings and precautions for use), which is a potentially fatal complication. ☐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 precautions for use).

☐Vascular disorders *Frequency not known:* Venous thromboembolism, including pulmonary embolism, sometimes fatal, and deep vein thrombosis

☐Skin and subcutaneous tissue disorders

Frequency not known: Angioedema, urticaria

☐Pregnancy, puerperium and perinatal conditions

Frequency not known: Drug withdrawal syndrome neonatal (see section 4.6)

4.9 Overdose

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

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

Since amisulpride is weakly dialysed, hemodialysis is of no use to eliminate the drug.

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

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