SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amisulpride 100 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
100 mg amisulpride

Excpient:
47.5 mg lactose/Amisulpride 100 mg tablet

For a full list of excipients, see 6.1

3 PHARMACEUTICAL FORM

Tablet.

Amisulpride 100 mg tablets are white and round with break line on one side and embossed with A100 on the other side.

The tablets can be divided into equal halves.

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 Posology 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. No specific titration is required when

initiating the treatment with Amisulpride. 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/d and 300 mg/d are recommended. Doses should be adjusted individually.

Amisulpride can be administered once daily at oral doses up to 300 mg, higher doses should be administered bid.

The minimum effective dose should be used.

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

Children: Amisulpride is contra-indicated in children under 15 years of age 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 4.4 Special warnings and precautions for use).

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

4.3 Contraindications

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

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

Phaeochromocytoma.

Children under 15 years of age.

Lactation.

Combination with the following medications which could induce 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, thioridazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin.

This list is not exhaustive.

Combination with levodopa (see 4.5 Interaction with other medicinal products and other forms of interaction)

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 Amisulpride 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 glycaemic monitoring.

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

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

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

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.

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

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

Prolongation of the QT interval.

Amisulpride induces a dose-dependent 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 patient's clinical status, it is recommended to monitor factors which could favour the occurrence of this rhythm disorder:

-bradycardia less than 55 bpm,

-cardiac disease or family history of sudden death or QT prolongation,

-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, decreased intracardiac conduction, or prolongation of the QT interval (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Baseline ECG is recommended prior to treatment in all patients especially in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination.

During therapy, the need for ECG monitoring (e.g. at dose escalation) should be assessed on an individual patient basis.
The dose of Amisulpride should be reduced if QT is prolonged and discontinued if QTc is >500ms.

Periodic electrolyte monitoring is recommended particularly if the patient is taking diuretics or during inter-current illness.

Concomitant antipsychotics 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.

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

Combinations which are contraindicated

Medications which could induce 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, 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

Amisulpride may enhance the central effects of alcohol.

Combinations which require precautions for use

Medications which enhance the risk of torsades de pointes or could prolong the QT interval:

- bradycardia-inducing medications such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine, guanfacine; digitalis.

- medications which induce hypokalaemia or electrolyte imbalance: hypokalemic diuretics, stimulant laxatives, IV amphotericin B, glucocorticoids, tetracosactides.

- 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.

Dopamine agonists (e.g.: levodopa) since it may attenuate their action.

4.6 Pregnancy and lactation

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.

For women of childbearing potential, effective contraception should be fully discussed with the physician prior to treatment.

Neonates exposed to antipsychotics (including Amisulpride 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. 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 effects have been ranked under headings of frequency using the following convention:

Very common (≥ 1/10)
Common (≥1/100, <1/10)
Uncommon (≥1/1000, <1/100)

Rare (≥ 1/10,000, <1/1,000)
Very rare (<1/10,000)
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.

• 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

• 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 4.4 Special warnings and precautions for use).

• Cardiovascular disorders
Common: Hypotension

Uncommon: Bradycardia

•Investigations:
Common: Weight gain

Uncommon: Elevations of hepatic enzymes, mainly transaminases

• Immune system disorders
Uncommon: Allergic reaction
Post Marketing data

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 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 4.4 Special warnings and precautions for use).

Pregnancy, puerperium and perinatal conditions:
Frequency not known: Drug withdrawal syndrome neonatal (see 4.6) .

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, hemodialysis should not be used to eliminate the drug.

There is no specific antidote to Amisulpride.

Appropriate supportive measures should therefore be instituted with close supervision of vital functions including continuous cardiac monitoring due to the risk of prolongation of the QT interval.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Antipsychotic
ATC-Code: N05A L05

Amisulpride binds selectively with a high affinity to human dopaminergic D_2/D_3 receptor subtypes whereas it is devoid of affinity for D_1, D_4 and D_5 receptor subtypes.

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

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

At low doses it preferentially blocks pre-synaptic D_2/D_3 receptors, producing dopamine release responsible for its disinhibitory effects.

The pharmacological profile explains the clinical efficacy of Amisulpride against both negative and positive symptoms of schizophrenia.

5.2 Pharmacokinetic properties

In man, amisulpride shows two absorption peaks: one which is attained rapidly, one hour postdose and a second between 3 and 4 hours after administration. Corresponding plasma concentrations are 39 ± 3 and 54 ± 4 ng/ml after a 50 mg dose.

The volume of distribution is 5.8 l/kg, plasma protein binding is low (16%) and no drug interactions are suspected.

Absolute bioavailability is 48%. Amisulpride is weakly metabolised: two inactive metabolites, accounting for approximately 4% of the dose, have been identified. There is no accumulation of amisulpride and its pharmacokinetics remain unchanged after the administration of repeated doses. The elimination half-life of amisulpride is approximately 12 hours after an oral dose.

Amisulpride is eliminated unchanged in the urine. Fifty percent of an intravenous dose is excreted via the urine, of which 90% is eliminated in the first 24 hours. Renal clearance is in the order of 20 l/h or 330 ml/min.

A carbohydrate rich meal (containing 68% fluids) significantly decreases the AUCs, Tmax and Cmax of amisulpride but no changes were seen after a high fat meal. However, the significance of these findings in routine clinical use is not known.

Hepatic insufficiency: Since the drug is weakly 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 4.2 Posology and method of administration). 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 persons (> 65 years) show that a 10-30% rise occurs in Cmax, T1/2 and AUC after a single oral dose of 50 mg. No data are available after repeat dosing.

5.3 Preclinical safety data

An overall review of the completed safety studies indicates that 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 rat at up to 1.5 to 4.5 times the expected human AUC.
A mouse carcinogenicity study (120 mg/kg/d) and reproductive studies (160, 300 and 500 mg/kg/d respectively in rat, rabbit and mouse) were performed. The exposure of the animals to amisulpride during these latter studies was not evaluated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Methylcellulose
Sodium starch glycolate (Type A)
Microcrystalline cellulose
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

PVC/aluminium foil blister packs containing 60 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.
Archimedesweg, 2,
2333 CN Leiden,
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PL 27583/0111

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/02/2010

10 DATE OF REVISION OF THE TEXT

05/10/2018