

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Amisulpride 50 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg amisulpride

Excipient with known effect:

Each tablet contains 16.28 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

White round tablet with 'AA 50' on one side and 'G' on the reverse, 6 mm in diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Amisulpride is indicated for the treatment of acute and chronic schizophrenic disorders with:

- positive symptoms (such as delusions, hallucinations, thought disorders, hostility, suspiciousness), and/or
- negative symptoms (deficit syndrome) such as blunted affect, emotional and social withdrawal

This includes patients with predominant negative symptoms.

4.2 Posology and method of administration

Posology

Positive symptoms:

For acute psychotic episodes, a daily dose between 400 mg and 800 mg is recommended.

In individual cases, the daily dose may be increased up to 1200 mg. Doses above 1200 mg/day have not been extensively evaluated for safety and therefore should not be used.

No specific titration is required when initiating treatment. 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.

Predominant negative symptoms (deficit syndrome)

A daily dose between 50 mg and 300 mg is recommended. Doses should be adjusted individually.

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

The minimum effective dose should be used.

*Special populations**Elderly patients over 65 years*

Treatment of elderly patients is not recommended. The safety of amisulpride has been examined in a limited number of elderly patients. If treatment with amisulpride is absolutely necessary, particular caution is required due to a possible risk of hypotension or sedation. Reduction in dosage may also be required because of renal insufficiency.

Paediatric population

The efficacy and safety of amisulpride in children and adolescents under 18 years of age have not been established. There are only limited data available on the use of amisulpride in adolescents in schizophrenia. Therefore, amisulpride should not be used in adolescents from 15 to 18 years of age until further data are available. If absolutely required, treatment of adolescents must be initiated and performed by a physician experienced in treating schizophrenia in this age group. The use of amisulpride is contraindicated in children and adolescents under 15 years of age (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 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), amisulpride should not be used in these patients (see section 4.4).

Hepatic insufficiency

Since amisulpride is weakly metabolised, a dosage reduction should not be necessary.

Duration of treatment

Data from controlled clinical trials covering a period of 1 year is available. The duration of treatment should be determined by the treating physician.

To avoid withdrawal symptoms treatment should be discontinued gradually (see section 4.4).

For doses not practicable with this strength, other strengths of this medicinal product are available.

Method of administration

For oral use.

Tablets should be swallowed whole or halved, with a sufficient amount of liquid.

Amisulpride can be administered independently from meals.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas or breast cancer.
- Pheochromocytoma.
- Children and adolescents under 15 years of age (see section 4.2).
- Lactation (see section 4.6).
- In combination with levodopa (see section 4.5).
- In combination with the following medicinal products which could induce torsade de pointes (see section 4.5):
 - class Ia antiarrhythmics such as quinidine and disopyramide
 - class III antiarrhythmics such as amiodarone and sotalol
 - other medicinal products such as bepridil, cisapride, sultopride, thioridazine, methadone, erythromycin (intravenous application), vincamine (intravenous application), halofantrine, pentamidine, sparfloxacin, azole antifungals

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:

Amisulpride induces a dose-dependent prolongation of the QT interval (see section 4.8). This effect is known to potentiate the risk of serious ventricular arrhythmias such as torsade de pointes. Before any administration, and if possible according to the patient's clinical status, it is recommended to exclude the following 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 medicinal product likely to produce pronounced bradycardia (< 55 bpm), hypokalaemia, decreased intracardiac conduction, or prolongation of the QT interval (see section 4.5).

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 use with antipsychotics should be avoided (see section 4.5).

Stroke:

In randomised clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic drugs, a 3-fold increase of 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 Amisulpride and preventative measures undertaken.

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.

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 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).

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 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 (see section 4.8) and requires immediate haematological investigation.

Benign pituitary tumour:

Amisulpride may increase prolactin levels. Cases of benign pituitary tumours such as prolactinoma have been observed during amisulpride therapy (see section 4.8). 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).

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 (see also section 4.3):

- Medicinal products which could induce torsade de pointes:
 - class Ia antiarrhythmics such as quinidine and disopyramide
 - class III antiarrhythmics such as amiodarone and sotalol
 - other medicinal products such as bepridil, cisapride, sultopride, thioridazine, methadone, erythromycin (intravenous application), vincamine (intravenous application), halofantrine, pentamidine, sparfloxacin, azole antifungals.
- Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics. Amisulpride may oppose the effect of dopamine agonists e.g. bromocriptine, ropinirole.

Combinations not recommended:

- Medicinal products which enhance the risk of torsade de pointes or could prolong the QT interval:
 - bradycardia-inducing medicinal products such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine, guanfacine; and digitalis
 - medicinal products which induce hypokalaemia or electrolyte imbalance: hypokalemic diuretics, stimulant laxatives, amphotericin B (intravenous application), glucocorticoids, and tetracosactides. Hypokalaemia should be corrected.
 - antipsychotics such as pimozide, and haloperidol
 - imipramine antidepressants
 - lithium
 - some antihistamines such as astemizole, and terfenadine

- mefloquine
- Amisulpride may enhance the effects of alcohol. Therefore alcohol should not be consumed during treatment.

Combinations which require precautions for use:

Concomitant use of the following agents can lead to potentiation of the effect:

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

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.

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 (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.

Breast-feeding

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

4.7 Effects on ability to drive and use machines

Even when used as recommended, amisulpride may cause somnolence so that the ability to drive vehicles or operate machinery can be impaired (see section 4.8).

4.8 Undesirable effects

Adverse reactions have been ranked under headings of frequency using the following convention:

Very common ($\geq 1/10$);

Common ($\geq 1/100$ to $< 1/10$);

Uncommon ($\geq 1/1,000$ to $< 1/100$);

Rare ($\geq 1/10,000$ to $< 1/1,000$);

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 could be difficult to differentiate adverse events from symptoms of the underlying disease.

Immune system disorders:

Uncommon: Allergic reactions

Endocrine disorders:

Common: increase in plasma prolactin levels which is reversible after discontinuation of amisulpride. This may result in galactorrhoea, amenorrhoea or menstrual disorders, gynaecomastia, breast pain or enlargement and erectile dysfunction.

Metabolism and nutrition disorders:

Uncommon: Hyperglycaemia (see section 4.4)

Psychiatric disorders:

Common: Insomnia, anxiety, agitation, orgasmic dysfunction

Nervous system disorders:

Very common: Extrapyrarnidal 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 50-300mg/day.

Common: Acute dystonia (spasm torticollis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon administration of antiparkinsonian medication.

Somnolence.

Uncommon: Tardive dyskinesia characterised by rhythmic, involuntary movements primarily of the tongue and/or face has been reported, usually after long-term administration. Antiparkinsonian medication should not be used as it is ineffective and may induce aggravation of the symptoms. Seizures

Cardiac disorders:

Common: Hypotension

Uncommon: Bradycardia

Gastrointestinal disorders:

Common: Constipation, nausea, vomiting, dry mouth.

General disorders and administration site conditions:

Rare: Acute withdrawal symptoms including nausea, vomiting and insomnia after abrupt cessation of high doses, also recurrence of psychotic symptoms, emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) (see section 4.4).

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:

Endocrine disorders:

Not known: Benign pituitary tumour such as prolactinoma (see section 4.3 and section 4.4).

Blood and Lymphatic system disorders

Not known: Leukopenia, neutropenia and agranulocytosis (see section 4.4)

Metabolism and nutrition disorders:

Not known: Hypertriglyceridaemia and hypercholesterolaemia. Hyponatraemia, syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Psychiatric disorders:

Not known: Confusion

Nervous system disorders:

Not known: Neuroleptic malignant syndrome symptom (see section 4.4), which is a potentially fatal complication.

Cardiac disorders:

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).

Vascular disorders:

Not known: Venous thromboembolism, including pulmonary embolism, sometimes fatal, and deep vein thrombosis (see section 4.4).

Skin and subcutaneous tissue disorders

Not known: Angioedema, urticaria

Pregnancy, puerperium and perinatal conditions

Not known: Drug withdrawal syndrome neonatal (see section 4.6)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: + 353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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, haemodialysis is of no use 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 QT interval until the patient recovers.

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

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: antipsychotics: benzamides

ATC code: N05AL05

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

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

In animal studies, at high doses, amisulpride blocks dopamine receptors in the limbic structure in preference to those in the striatum. At low doses it preferentially blocks pre-synaptic D₂/D₃ receptors, producing dopamine release

responsible for its disinhibitory effects.

This pharmacological profile explains the clinical efficacy of amisulpride when used for both negative and positive symptoms of schizophrenia.

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. Absolute bioavailability is 48%.

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

Distribution

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

Biotransformation

Amisulpride is weakly metabolised: two inactive metabolites which account for approximately 4% of the dose have been identified. There is no accumulation of amisulpride and its pharmacokinetics remains unchanged after the administration of repeated doses.

Elimination

The elimination half-life of amisulpride 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 in the order of 20 l/h or 330 ml/min.

Hepatic impairment:

Since amisulpride is weakly metabolised, a dosage reduction should not be necessary in patients with hepatic insufficiency.

Renal impairment:

The elimination half-life is increased 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 section 4.2). Experience is however limited and there is no data with doses greater than 50 mg.

Amisulpride is very weakly dialysed.

Older people

Limited pharmacokinetic data in elderly subjects (> 65 years) show that a 10-30 % rise occurs in C_{\max} , $T_{1/2}$ and AUC after a single oral dose of 50 mg. No data are available after repeat dosing.

5.3 Preclinical safety data

An overall review of the completed safety studies indicates that amisulpride is devoid of any general, organ-specific, teratogenic, mutagenic or carcinogenic risk. Changes observed in rats and dogs at doses below the maximum tolerated dose are either pharmacological effects or are devoid of major toxicological significance under these conditions. Compared with the maximum recommended dosages in man, maximum tolerated doses are 2 and 7 times greater in the rat (200 mg/kg/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
Cellulose microcrystalline

Sodium starch glycolate (Type A)
Hypromellose
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

PVC/Aluminium foil blister packs containing:

12 tablets
20 tablets
30 tablets
50 tablets
60 tablets
90 tablets
100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd t/a Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0577/182/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 19th September 2014

10 DATE OF REVISION OF THE TEXT

November 2016