Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Amisulpride Mylan 200 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg amisulpride.

Excipient with known effect:
Each tablet contains 100 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White to off-white 11.0 mm round, flat tablets with break line on one side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

- Positive symptoms with delusions, hallucinations, thought disorders, hostility and suspicious behavior.
- Primarily negative symptoms (deficit syndrome) with blunted affect, emotional and social withdrawal.

Amisulpride Mylan also controls secondary negative symptoms in productive conditions as well as affective disorders such as depressive mood or retardation.

4.2 Posology and method of administration

Posology:

For acute psychotic episodes the recommended oral dose ranges from 400 to 800 mg/day. In individual cases, the daily dose may be increased up to 1200 mg/day. 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 the treatment with Amisulpride Mylan. Doses should be adjusted according to individual response. Maintenance treatment should be established individually with the minimally effective dose.

For patients with mixed positive and negative symptoms, doses should be adjusted to obtain optimal control of positive symptoms.

For patients characterised by predominant negative symptoms, oral doses between 50 mg/day and 300 mg/day are recommended. Doses should be adjusted individually.
Amisulpride Mylan can be administered once daily orally at a dose up to 400 mg. Higher doses should be divided in two doses.

Elderly
The safety of amisulpride has been examined in a limited number of elderly patients. Amisulpride Mylan should be used with particular caution because of a possible risk of hypotension or sedation (see section 5.2). Reduction in dosage

may also be required because of renal insufficiency.

Paediatric population
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).

Patients with renal impairment
Amisulpride Mylan is eliminated by the renal route. In renal insufficiency, the dose should be reduced to half in patients with creatinine 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 sections 4.4 and 5.2).

Patients with hepatic impairment
Since amisulpride is weakly metabolised, a dosage reduction should not be necessary.

Method of administration:

Amisulpride Mylan tablets can be administered independently from the meals. Tablets should be taken whole or halved with a sufficient amount of liquid.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Concomitant prolactin-dependent tumors (e.g. pituitary gland prolactinomas or breast cancer)
- Phaeochromocytoma.
- Children up to puberty.
- Lactation.
- In combination with levodopa (see section 4.5).

4.4 Special warnings and precautions for use

As with other neuroleptics, Neuroleptic Malignant Syndrome, a potentially fatal complication, characterised by hyperthermia, increased muscle rigidity, autonomic instability, altered consciousness and elevated CPK, may occur. In the event of hyperthermia, particularly with high daily doses, all antipsychotic medicines including Amisulpride Mylan should be discontinued.

Amisulpride Mylan 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).

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

In elderly patients, amisulpride therapy, like other neuroleptics, should be used with particular caution because of a possible risk of hypotension or sedation. Reduction in dosage may also be required in case of renal insufficiency.

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

Prolongation of QT interval
Amisulpride induces prolongation of the QT interval. This effect is known to potentiate the risk of serious ventricular arrhythmias such as torsades de pointes.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.

Particular caution is also advised in the following situations:
- significant bradycardia
- congenital prolongation of the QT interval.
- electrolyte imbalance, in particular, hypokalaemia, hypomagnesaemia,
- concomitant use of medicinal products that cause QT interval prolongation (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 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 Mylan should be used with caution in patients with stroke risk factors.

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 Mylan and preventive measures undertaken.

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.

Breast cancer
Amisulpride causes an increase in plasma 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. Amisulpride is contraindicated in patients with breast cancer (see sections 4.3 and 4.8).

Elderly people with Dementia
Elderly patients with dementia-related psychosis treated with atypical antipsychotics had an increased risk of death compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotics.
The observed risk of death was 1.6 to 1.7 times the risk of death in placebo-treated patients. The rate of death in patient treated with atypical antipsychotic was about 4.5%, compared to a rate of about 2.6% in the placebo group during a typical 10-week controlled trial. There were different causes of death in clinical trials with atypical antipsychotics, but 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.

Amisulpride Mylan is not approved for the treatment of patients with dementia-related behavioural disturbances.

Other
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 Mylan, should get appropriate glycaemic monitoring.

The concomitant prescription of other antipsychotics should be avoided.

Withdrawal symptoms including nausea, vomiting and insomnia have 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) have been reported with amisulpride. Therefore, gradual withdrawal of Amisulpride Mylan is advisable.

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.

Lactose
Patients with rare hereditary problems of galactose intolerance, 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 o dopamine agonists e.g. bromocriptine, ropirinole.

Combinations which are not recommended:
Amisulpride Mylan may enhance the effects of alcohol.

Combinations which must be taken into account:
- CNS depressants including narcotics, anaesthetics, analgesics, sedative H_1-antihistamines, barbiturates benzodiazepines and other anxiolytic medicines, clonidine and derivatives.
- Antihypertensive medicines 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 antihistamines, some other antipsychotics and some antimalarials (e.g., mefloquine) (see section 4.4)

4.6 Fertility, pregnancy and lactation

Pregnancy
Amisulpride did not show reproductive toxicity in animals. Lower fertility associated with pharmacological effect of the product (by means of prolactin) was found. No teratogenic effects of amisulpride were noted.

There is only very limited clinical data on administration of the medicinal product during pregnancy. Therefore the safety of amisulpride during pregnancy in humans has not been established. Use of the medicinal product during pregnancy is not recommended unless the benefit outweighs the possible risk.

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 if amisulpride is excreted in breast milk. Breast-feeding is therefore contraindicated.

4.7 Effects on ability to drive and use machines

Amisulpride Mylan can cause somnolence and blurred vision and therefore also reduce the ability to drive vehicles and operate machines, even when used at recommended doses (see section 4.8).

4.8 Undesirable effects

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

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare

(<1/10000); frequency not known (cannot be determined from available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Clinical 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: Amisulpride causes an increase in plasma prolactin levels, which is reversible after drug discontinuation. This may result in galactorrhoea, amenorrhoea or menstrual disorder, gynaecomastia, breast pain and erectile dysfunction.

Metabolism and nutrition disorders:
Uncommon: Hyperglycemia (see section 4.4)

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 treatment of patients with predominantly negative symptoms with doses of 50-300 mg/day.
Common:
- Acute dystonia (spasmodic 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 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

Postmarketing surveillance:
The following undesirable effects were also reported (spontaneous reports):

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.

Eye disorders:
Not known: Blurred vision

Cardiac disorders:
Not known: prolongation of the QT interval and ventricular arrhythmia such as torsades de pointes, ventricular tachycardia, which could lead to ventricular fibrillation or cardiac arrest, sudden death (see section 4.4).

Vascular disorders:
Not known: Cases of venous thromboembolism, including cases of pulmonary embolism, sometimes fatal and cases of deep vein thrombosis have been reported with antipsychotic drugs (see section 4.4)

Skin and subcutaneous tissue disorders:
Not known: Angioedema, urticaria

Musculoskeletal and connective tissue disorders:
Not known: Osteopenia, osteoporosis

Pregnancy, puerperium and perinatal conditions
Not known: Drug withdrawal syndrome neonatal (see section 4.6)

Respiratory, thoracic and mediastinal disorders
Not known: Nasal congestion

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 overdose is limited. Exaggeration of pharmacological effects of the drug has been reported with symptoms such as drowsiness and sedation, coma, hypotension and extrapyramidal symptoms. Fatal outcomes have been reported mainly in combination with other psychotropic agents.

In cases of acute overdose, the possibility of multiple drug intakes 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 with close supervision of vital functions including continuous cardiac monitoring due to the risk of prolongation of the QT interval, until complete recovery of the patient.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, Antipsychotics, Benzamides
ATC code: N05AL05

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, alpha-adrenergic, H_1-histamine and cholinergic receptors. In addition, amisulpride does not bind to sigma receptors.

In animal studies, at high doses, amisulpride blocks dopamine receptors located in the limbic system in preference to those in the striatum. As opposed to classical neuroleptics, it does not cause catalepsy and hypersensitivity to D_2 dopamine receptors does not develop after repeated treatment. At low doses it preferentially blocks pre-synaptic D_2/D_3 receptors, and causes the secretion of dopamine which is responsible for its disinhibitory effects.

This atypical pharmacological profile can explain amisulpride's antipsychotic effect at higher doses through post-synaptic dopamine receptor blockade and its effect on negative symptoms at lower doses caused by the inhibition of pre-synaptic dopamine receptors. Decreased incidence of undesirable extrapyramidal symptoms can be caused by the preferential activity in the limbic system.

In clinical studies, which monitored patients with acute exacerbation of schizophrenia, amisulpride significantly reduced secondary negative symptoms as well as affective symptoms and psychomotor slow-down.

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, plasma protein binding is low (16%) and no drug interactions are known. Absolute bioavailability is 48%.

Biotransformation
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 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. 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 impairment: since the drug is weakly metabolised, the dosage needs not to be reduced in patients with hepatic insufficiency.

Renal impairment: 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 section 4.2). 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}, $T_{1/2}$ 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), which corresponds to 1.5 – 4.5 higher AUC in rat than in human.

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)
Cellulose, microcrystalline
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

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 blister of 10, 30, 60, 90, 120 or 150 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local 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

PA0577/125/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th August 2009

Date of last renewal: 16th September 2013

10 DATE OF REVISION OF THE TEXT

February 2017