Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Amisulpride Mylan 100 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Amisulpride Mylan contains 100 mg amisulpride per tablet.

Excipient:

50 mg lactose monohydrate per tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White to off-white 8.0 mm round, flat tablets with break line on one side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

- Productive 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

For productive conditions, the recommended oral dose ranges from 400 to 800 mg/day. Doses above 800 mg/day have not been associated with greater efficacy and have induced higher rates of extrapyramidal symptoms. 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 characterized by predominant negative symptoms, oral doses between 50 mg/d and 300 mg/d are recommended. Doses should be adjusted individually.
Amisulpride Mylan may be administered once daily orally at a dose up to 300 mg. Higher doses should be divided in two doses.

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

Elderly
Amisulpride Mylan should be used with particular caution because of a possible risk of hypotension or sedation (see

section 5.2 Pharmacokinetic properties).

Pediatric patients
Amisulpride Mylan is contraindicated in children under 15 years of age as its safety has not yet been established.

Renal insufficiency
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), Amisulpride Mylan is contraindicated in these patients (see section 4.3 Contraindications and section 5.2 Pharmacokinetic properties).

Hepatic insufficiency
Since amisulpride is weakly metabolized, a dosage reduction should not be necessary.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Concomitant prolactin-dependent tumors e.g. pituitary gland prolactinomas and breast cancer.
- Phaeochromocytoma.
- Children up to 15 years of age.
- Lactation.
- In combination with the following medication which could induce torsades de pointes for example:
    - Class Ia antiarrhythmic agents such as quinidine, disopyramide
    - Class III antiarrhythmic agents such as amiodarone, sotalol
    - Other medications such as bepridil, cisapride, sultopride, thioridazine, methadone, intravenous erythromycin, intravenous vincamine, halofantrine, pentamidine, sparfloxacin
- In combination with levodopa.
- Severe renal impaiment (CRCL < 10 ml/min).

4.4 Special warnings and precautions for use

Neuroleptic Malignant Syndrome
As with other neuroleptics, Neuroleptic Malignant Syndrome characterized by hyperthermia, increased muscle rigidity, autonomic instability, 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 Posology and method of administration).
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.
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.

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Prolongation of QT interval
Amisulpride Mylan produces a dose-dependent prolongation of the QT interval. 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 favor the onset of this rhythm disorder, for example:
- Bradycardia less than 55 bpm
- 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_c interval (see section 4.5 Interaction with other medicinal

products and other forms of interaction).

Stroke
In randomized 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.

Increased Mortality in Elderly people with Dementia
Elderly patients with dementia treated with atypical antipsychotics had an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotics, however no study with amisulpride was included.
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 (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for amisulpride.
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 Mylan. 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.

Acute withdrawal symptoms including nausea, vomiting and insomnia have been rarely 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. Therefore, gradual withdrawal is advisable.

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:
Medicinal products that may cause torsades de pointes (see section 4.3 Contraindications):
Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics.

Combinations which are not recommended:
Medicinal products that increase the risk of torsades de pointes or may prolong QT interval:

- Medicines which induce bradycardia, such as bradycardia-inducing calcium channel blockers (diltiazem, verapamil), beta-blockers, clonidine, guanfacine, digitalis.
- Medicines which can cause hypokalaemia: hypokalemic diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactides. Hypokalaemia should be adjusted.
- Neuroleptics such as thioridazine, chlorpromazine, trifluperazine, pimozide, haloperidol, imipramine antidepressants, lithium.

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.
  In combination with other antipsychotics the potentiation of central depressant effects (sedation, somnolence, impaired capacity of reaction) can not be excluded.
- Antihypertensive medicines and other hypotensive medications.
- Amisulpride may oppose the effect of dopamine agonists e.g. bromocriptine, ropinirole.

4.6 Fertility, pregnancy and lactation

Pregnancy
Amisulpride Mylan was devoid of direct effect on reproduction in animals. Lower fertility associated with pharmacological effect of the product (by means of prolactin) was found. No teratogenic effect was noted.
There is only very limited clinical data on administration of the medicinal product during pregnancy. Therefore safety of amisulpride during pregnancy in humans has not been confirmed. Using of the medicinal product during pregnancy is not recommended unless the benefit outweighs the possible risk. If amisulpride is used during pregnancy the newborns may experience related undesirable effects and therefore appropriate monitoring should be considered.

Lactation
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 drowsiness and therefore also reduce the ability to drive vehicles and operate machines, even when used at recommended doses (see section 4.8 Undesirable effects).

4.8 Undesirable effects

Undesirable effects are classified according to their incidence as follows:
Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000); unknown (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.

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

Cardiac disorders:
Common: Hypotension
Uncommon: Bradycardia

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 when administering clinically effective doses to patients with deficit schizophrenia (50-300mg/day).
Common:
- Acute dystonia (spasm torticolis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon administration of antiparkinsonian medication.

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

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 or menstrual disorder, gynaecomastia, breast pain, orgasmic and erectile dysfunction.

Metabolism and nutrition disorders:
Uncommon: Hyperglycemia (see section 4.4 Special warnings and precautions for use)

Immune system disorders:
Uncommon: Allergic reactions

Psychiatric disorders:
Common: Sleeplessness, anxiety, agitation, orgasmic dysfunction

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

Cardiac disorders:
Unknown incidence: 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 Special warnings and precautions for use).

Vascular disorders:
Unknown incidence: Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs

Nervous system disorders:
Unknown incidence: Neuroleptic malignant syndrome symptom (see section 4.4 Special warnings and precautions for use)

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.
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 Mylan. 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: antipsychotics
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, H1-histamine and cholinergic receptors. In addition, amisulpride does not bind to sigma receptors.
In animal studies, at high doses, amisulpride blocks dopamine receptors located primarily outside striatum in the mesolimbic system. As opposed to classical neuroleptics, it does not cause catalepsy. During repeated use, it does not develop hypersensitivity to d2 dopamine receptors. At low doses it preferentially blocks pre-synaptic D2/D3 receptors, producing dopamine release 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

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. 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%. 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. 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 insufficiency: since the drug is weakly metabolized, the dosage needs not to be reduced 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 section 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 subjects (> 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), which corresponds to 1.5 – 4.5 higher AUC in rat than in human. Reproductive studies performed in rats, rabbits and mice did not show any teratogenic potential.

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 or 60 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

PA 577/125/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 August 2009

10 DATE OF REVISION OF THE TEXT

July 2010