Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Amisulpride 200 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg amisulpride

Excipient with known effect:
Each tablet contains 65.12 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White round tablet with 'AMI' breakline '200' on one side and 'G' on the reverse, 10 mm in diameter.

The tablet can be divided into equal doses.

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.
- Phaeochromocytoma.
- Children and adolescents under 15 years of age (see section 4.2).
- 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

Severe liver toxicity has been reported with amisulpride use. Patients should be instructed to immediately report signs such as asthenia, anorexia, nausea, vomiting, abdominal pain or icterus to a physician. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately (see section 4.8).

As with other neuroleptics, neuroleptic malignant syndrome (NMS) may occur. This condition is characterized by hyperthermia, muscle rigidity, autonomic dysfunction, blurred vision, rhabdomyolysis and elevated creatinine phosphokinase (CPK) blood levels, and it is potentially fatal.
If the patient develops signs and symptoms indicative for NMS, or an unexplained hyperthermia is present, particularly with high daily doses, administration of all antipsychotics including amisulpride has to be discontinued.

Rhabdomyolysis has also been observed in patients without neuroleptic malignant syndrome.

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).

Amisulpride contains lactose
Patients with rare hereditary problems of galactose intolerance, total 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:

o class Ia antiarrhythmics such as quinidine and disopyramide

o class III antiarrhythmics such as amiodarone and sotalol

o 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:

o bradycardia-inducing medicinal products such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine, guanfacine; and digitalis

o medicinal products which induce hypokalaemia or electrolyte imbalance: hypokalemic diuretics, stimulant laxatives, amphotericin B (intravenous application), glucocorticoids, and tetracosactides. Hypokalaemia should be corrected.

o antipsychotics such as pimozide, and haloperidol

o imipramine antidepressants

o lithium

o some antihistamines such as astemizole, and terfenadine

o 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 H_1 antihistamines, barbiturates, benzodiazepines and other anxiolytics, clonidine and derivatives.
- Antihypertensive drugs and other hypotensive medications.
- Co-administration of amisulpride and clozapine may lead to an increase in plasma levels of amisulpride

4.6 Fertility, pregnancy and lactation

Pregnancy
There is only limited amount of data from the use of amisulpride in pregnant women. The safety of amisulpride during pregnancy has not been established. The use of amisulpride is not recommended during pregnancy and in women of child bearing potential not using effective contraception unless the benefits justify the potential risks.

Amisulpride crosses the placenta.

Studies in animals have shown reproductive toxicity (see section 5.3).

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
Amisulpride is excreted in breast milk in rather large amounts, above the accepted value of 10% of the maternal weight-adjusted dosage in some cases, but blood concentrations in breastfed infants have not been evaluated. There is insufficient information on the effects of amisulpride in newborns/infants. A decision must be made whether to discontinue breast-feeding or to abstain from amisulpride therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
A decrease in fertility linked to the pharmacological effects of the medicinal product (prolactin-mediated effect) was observed in treated animals.

4.7 Effects on ability to drive and use machines

Even when used as recommended, amisulpride may cause somnolence and blurred vision and, therefore the ability to drive vehicles or operate machinery may 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 (≥1/10);
Common (≥1/100 to <1/10);
Uncommon (≥1/1,000 to <1/100);
Rare (≥1/10,000 to <1/1,000);
Very rare (<1/10,000);
Not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse Drug Reaction
Blood and Lymphatic system disorders	Uncommon	Leukopenia, neutropenia (see section 4.4)
	Rare	Agranulocytosis (see

		section 4.4)
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, • erectile dysfunction.
	Rare	Benign pituitary tumour such as prolactinoma (see sections 4.3 and section 4.4).
Metabolism and nutrition disorders	Uncommon	Hyperglycaemia (see section 4.4). hypertriglyceridaemia and hypercholesterolaemia.
	Rare	Hyponatraemia. Syndrome of inappropriate antidiuretic hormone secretion (SIADH).
Psychiatric disorders	Common	Insomnia. Anxiety. Agitation. Orgasmic dysfunction.
	Uncommon	Confusion
Nervous system disorders	Very common	Extrapyramidal symptoms[1] may occur: • tremor, • rigidity, • hypokinesia, • hypersalivation, • akathisia, • dyskinesia.
	Common	Acute dystonia (spasm torticollis, oculogyric crisis, trismus) may appear.[2] Somnolence.
	Uncommon	Tardive dyskinesia characterised by rhythmic, involuntary movements primarily of the tongue and/or face has been reported, usually after long-term administration.[3] Seizures.
	Rare	Neuroleptic malignant

		syndrome symptom (see section 4.4), which is a potentially fatal complication.
	Not known	Restless leg syndrome
Eye disorders	Common	Blurred vision (see section 4.7)
Cardiac disorders		
	Uncommon	Bradycardia.
	Rare	QT interval prolongation. 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	Common	Hypotension
	Uncommon	Increase in blood pressure
	Rare	Venous thromboembolism, including pulmonary embolism, sometimes fatal, and deep vein thrombosis (see section 4.4).
Respiratory, thoracic and mediastinal disorders	Uncommon	Nasal congestion Aspiration pneumonia (mainly in association with other antipsychotics and CNS depressants)
Gastrointestinal disorders	Common	Constipation. Nausea. Vomiting. Dry mouth.
Hepatobiliary disorders	Uncommon	Hepatocellular injury
Skin and subcutaneous tissue disorders	Rare	Angioedema. Urticaria.
	Not known	Photosensitivity reaction.
Musculoskeletal and connective tissue disorders	Uncommon Not known	Osteopenia. Osteoporosis. Rhabdomyolysis
Renal and urinary disorders	Uncommon	Urinary retention
Pregnancy, puerperium and perinatal conditions	Not known	Drug withdrawal syndrome neonatal (see section 4.6)
Investigations	Common	Weight gain
	Uncommon	Elevations of hepatic enzymes, mainly transaminases
	Not Known	Increased creatine phosphokinase blood level.
Injury, poisoning and procedural complications	Not known	Fall due to adverse reactions disturbing the body's balance

[1] 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.
[2] This is reversible without discontinuation of amisulpride upon administration of antiparkinsonian medication.
[3] Antiparkinsonian medication should not be used as it is ineffective and may induce aggravation ofthe symptoms.

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: Psycholeptics, antipsychotics
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, histamine $H_1$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 D_2/D_3 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.

In animal trials, amisulpride has an effect on feotal growth and development at doses that correspond to Human Equivalent Dose of 2000 mg/day and upwards for a 50 kg patient. No evidence for a teratogenic potential of amisulpride has been observed. Studies on the impact of amisulpride on the behaviour of the offspring have not been conducted.

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:
20 tablets
30 tablets
50 tablets
60 tablets
60 x1 tablets
90 tablets
100 tablets
120 tablets
150 tablets
150 (3 cartons of 50) tablets (200 mg)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23266/064/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 19th September 2014
Date of Last Renewal: 19th February 2019

10 DATE OF REVISION OF THE TEXT

June 2025