SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AMISULPRIDE RATIOPHARM 200 mg, tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg amisulpride.

Excipient: Lactose monohydrate
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White to off white, round tablets with break line.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of psychoses, particularly acute and chronic schizophrenic disorders, in which positive symptoms (such as delusions, hallucinations, thought disorders) and/or negative symptoms (such as blunted affect, emotional and social withdrawal) are prominent, including patients characterised by predominant negative symptoms.

4.2. Posology and method of administration

In general, a daily dose ≤ 400 mg is administered once daily, while doses higher than 400 mg are administered bid. For fine adjustment or doses < 100 mg/day amisulpride ratiopharm is not suitable, as it can be divided only in two equal halves.

**Predominant negative symptoms**
The recommended dosage is 50 to 300 mg/day. Dosages must be adapted individually. The optimal dosage is about 100 mg per day.

**Mixed episodes with positive and negative symptoms**
At the beginning of treatment, doses should be adjusted to obtain optimal control of positive symptoms, i.e. 400 to 800 mg per day. Maintenance treatment should be individually adapted according to the patient's response to obtain the minimally effective dose.

**Acute psychotic episodes**
At the beginning of treatment,
• the IM route can be used for several days at a maximum dose of 400 mg/day, followed by oral treatment,
• the recommended oral dosage is 400 to 800 mg, the maximum dosage must not exceed 1200 mg. Subsequently,
• the dosage is maintained or adapted according to the patient's response.
In each case, the dosage of maintenance treatment should be established individually with the minimally effective dose.

Renal impairment:
As amisulpride is eliminated by the kidneys, the dose in patients with renal impairment should be reduced to one half in patients with creatinine clearance ($\text{Cl}_{\text{cr}}$) between 30-60 ml/min and to one third in patients with $\text{Cl}_{\text{cr}}$ between 10-30 ml/min.

As there is no experience in patients with severe renal impairment ($\text{Cl}_{\text{cr}} < 10 \text{ ml/min}$), amisulpride is contraindicated in these patients (see 4.3. Contraindications)

Hepatic impairment:
As amisulpride is weakly metabolised, dosage reduction is not necessary in patients with hepatic impairment.

4.3. Contraindications

This medicine MUST NOT BE USED in the following cases:
• Known hypersensitivity to amisulpride or to any other ingredients of the product.
• Serious hypertensive crises have been reported in patients with phaeochromocytoma treated with antidopaminergic drugs, including certain benzenamides. This medicine should therefore not be prescribed in patients with known or suspected phaeochromocytoma.
• Children under 15 years of age, in the absence of clinical data in this age-group.
• Lactation.
• Known or suspected prolactin-dependent tumours, e.g. pituitary gland prolactinomas and breast cancer
• Severe renal impairment ($\text{Cl}_{\text{cr}} < 10 \text{ ml/min}$).
• In combination with:
  o dopaminergic agents except in patients with Parkinson’s disease (see Interaction with other medicinal products and other forms of interaction).

4.4. Special warnings and precautions for use

Special warnings

Neuroleptic Malignant Syndrome
As with other neuroleptics, Neuroleptic Malignant Syndrome, characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK, may occur. In the event of hyperthermia, particularly with high daily doses, all antipsychotic drugs should be discontinued.

Prolongation of the QT interval
Amisulpride induces a dose-dependent prolongation of the QT interval. This effect, known to potentiate the risk of serious ventricular arrhythmias such as torsades de pointes, is enhanced by the
pre-existence of bradycardia, hypokalaemia, congenital or acquired long QT interval (combination with a drug prolonging the QTc interval).

Before any administration, and when compatible with the patient’s clinical status, it is recommended to identify any factors that could predispose to the development of this arrhythmia:
• bradycardia less than 55 bpm,
• 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 QTc interval.

It is recommended to perform an ECG as part of the initial assessment of patients requiring long-term neuroleptic therapy.

Combinations with medications which can induce Torsades de pointe are not recommended (see Interaction with other medicinal products and other forms of interaction).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Precautions for use**
As amisulpride is eliminated by the kidneys, the dose should be reduced in patients with renal impairment (see 4.2. Posology and method of administration). No data are available for patients with severe renal impairment (see 4.3. Contra-indications). Neuroleptics are known to lower the seizure threshold. Patients with a history of epilepsy must therefore be closely monitored during treatment. Particular caution is required in the elderly, because of an increased risk of sedation and hypotension. Caution should be also exercised when prescribing amisulpride to patients with Parkinson's disease, amisulpride should be used only if neuroleptic treatment cannot be avoided.

**4.5. Interaction with other medicinal products and other forms of interaction**

**Combinations which are contraindicated**

+ Dopaminergic agents except in patients with Parkinson’s disease Reciprocal antagonism of the effects of the dopaminergic agonist and neuroleptics. In the case of neuroleptic-induced extrapyramidal syndrome, do not treat with a dopaminergic agonist but use an anticholinergic.

**Combinations which are not recommended**

+ Medications which can induce torsades de pointe: Class Ia (quinidine, hydroquinidine, disopyramide), and class III antiarrhythmic agents (amiodarone, sotalol, dofetilide, ibutilide), certain neuroleptics (sulproide, thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, tiapride, pimozide, haloperidol, droperidol), other medications: IV erythromycin, IV spiramycin, halofantrine, pentamidine, sparflxacin, moxifloxacin, gatifloxacin, bepridil, cisapride, diphenamid., mizolastine, IV vincarnine.

Increased risk of ventricular arrhythmias, especially torsades de pointes. If possible, discontinue the medication that can induce torsades de pointes, except for anti-infective agents. If combination therapy cannot be avoided, check the QT interval before starting treatment and monitor ECG.
+ Alcohol
Alcohol may enhance the sedative effect of neuroleptics.
The alteration of the vigilance can make dangerous the driving of vehicles and the use of machines.
Avoid drinking alcohol and taking medicines containing alcohol.

+ Levodopa
Reciprocal antagonism of the effects of levodopa and neuroleptics.
Use minimal effective doses of each of both drugs in patients with Parkinson’s disease.

+ Dopaminergic agonists except levodopa (amantadine, apomorphine, bromocriptine, cabergoline, entacapone, lisuride, pergolide, piribedil, pramipexole, quinagolide, ropinirole, selegiline) in
patients with Parkinson’s disease.
Reciprocal antagonism of the effects of the dopaminergic agonist and neuroleptics.
The dopaminergic agonist can induce or accentuate psychotic disorders.
When neuroleptic therapy cannot be avoided in patients with Parkinson’s disease treated with
dopaminergic agonists, these agents must be tapered off and discontinued (sudden withdrawal of
dopaminergic agonists can induce neuroleptic malignant syndrome).

Combinations which require precautions for use
+ Bradycardia-inducing medications (bradycardia-inducing calcium channel blockers: diltiazem,
verapamil; beta-blockers except for sotalol (see Combinations which are not recommended);
clonidine; guanfacine; mefloquine; cardiac glycosides, cholinesterase inhibitors: donepezil,
rivastigmine, tacrine, ambenonium, galantamine, pyridostigmine, neostigmine)
Increased risk of ventricular arrhythmias, especially torsades de pointes.
Clinical and electrocardiographic monitoring.

+ Potassium-lowering agents (potassium-lowering diuretics, stimulant laxatives, IV amphotericin B, glucocorticoids, cosyntropin)
Increased risk of ventricular arrhythmias, especially torsades de pointes.
Correct any hypokalaemia before starting treatment with amisulpride and ensure clinical, electrolyte and
electrocardiographic monitoring.

Combinations to be taken into account
+ Antihypertensives (all):
Antihypertensive effect and increased risk of orthostatic hypotension (additive effect).

+ Other central nervous system depressants:
Narcotics (analgesics, antitussives and opioid replacement therapy); barbiturates; benzodiazepines;
other non-benzodiazepine anxiolytics; hypnotics; neuroleptics; sedative antidepressants
(amitriptyline, doxepine, mianserin, mirtazapine, trimipramine); sedative H1 antihistamines;
centrally-acting antihypertensives; other drugs: baclofen, thalidomide, pizotifène.
Increase of central depression. Impaired alertness may make the driving of vehicles and the use of
machines dangerous.

+ Beta-blockers in heart failure (bisoprolol, carvedilol, metoprolol):
Vasodilator effect and risk of hypotension, especially orthostatic hypotension (additive effect).

4.6. Pregnancy and lactation

Pregnancy
Maintenance of a good maternal mental state is desirable throughout pregnancy to avoid any risk of decompensation. If drug treatment is necessary to ensure this equilibrium, it must be instituted or continued at effective doses throughout pregnancy.

The analysis of exposed pregnancies has not revealed any particular malformative effect due to amisulpride.

Although no case has been described in neonates, amisulpride, if continued until the end of pregnancy, particularly at high doses, could theoretically cause:
- signs related to its anticholinergic properties, which are enhanced in combination with drugs designed to treat Parkinsonian effects: tachycardia, hyperexcitability, abdominal distension, delayed emission of meconium,
- extrapyramidal signs: rigidity, tremor,
- sedation.

Amisulpride may therefore be used at all stages of pregnancy. Neonatal monitoring will take the above effects into account.

**Lactation**

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

### 4.7. Effects on ability to drive and use machines

Vehicle drivers and machine operators should be advised about the risk of drowsiness related to the use of this drug.

### 4.8. Undesirable effects

**Central nervous system disorders**

**Common:**
- Insomnia, anxiety, agitation,
- Extrapyramidal symptoms (tremor, rigidity, hypersalivation, akathisia, hypokinesia) can occur. These symptoms are generally mild at maintenance dosages and partially reversible without discontinuation of AMISULPRIDE RATIOPHARM, with treatment with an anticholinergic antiparkinsonian agent.

The incidence of extrapyramidal symptoms which are dose-related, remains very low in the treatment of patients with predominantly negative symptoms with doses of 50-300 mg/day

In clinical studies, patients treated with amisulpride presented a lower incidence of extrapyramidal symptoms than patients treated with haloperidol.

**Uncommon:**
- Daytime somnolence.

**Very rarely:**
- Acute dystonia (spastic torticollis, oculogyric crisis, trismus…) may appear. This is reversible without discontinuation of AMISULPRIDE RATIOPHARM, with treatment with an anticholinergic antiparkinsonian agent.
- Tardive dyskinesia characterized by involuntary movements of the tongue and/or face have been reported, especially after long-term.

Anticholinergic antiparkinsonian medication is ineffective or may induce aggravation of the symptoms.

- Cases of seizures.
• Cases of neuroleptic malignant syndrome (see 4.4 Special warnings and precautions for use).

**Endocrine and metabolic disorders**

Common:
• Increase in blood prolactin levels, which is reversible after stopping treatment. This may result in galactorrhoea, amenorrhoea, gynaecomastia, breast pain, impotence and frigidity.
• Weight gain.

**Gastrointestinal disorders**

Uncommon:
• Constipation, nausea, vomiting, dry mouth.

**Cardiac disorders**

Very rarely:
• Cases of hypotension and bradycardia.
• Cases of QT prolongation and very rare cases of torsades de pointes have been reported (see Special warnings).

**Hepatic disorders**

Very rarely:
• Elevations of hepatic enzymes, mainly transaminases, have been reported.

**General disorders**

Very rarely:
• Allergic reactions.

4.9. **Overdose**

For the time being, experience of acute overdose with amisulpride is limited. The symptoms and signs reported are generally due to accentuation of the pharmacological effects of amisulpride, resulting clinically in: drowsiness, sedation, coma, hypotension and extrapyramidal symptoms.

There is no known specific antidote to amisulpride. In the case of acute overdose, the possibility of multiple drug intake should be considered and appropriate measures must be taken:
• Close monitoring of vital functions.
• Cardiac monitoring (risk of prolongation of the QT interval), continued until the patient's recovery.
• If severe extrapyramidal symptoms occur, anticholinergic agents should be administered.
• As amisulpride weakly dialysed, haemodialysis has not an important interest to eliminate the drug.

5. **PHARMACOLOGICAL PROPERTIES**

5.1. **Pharmacodynamic properties**

Pharmacotherapeutic group: ANTIPSYCHOTICS
Amisulpride is an antipsychotic, belonging to the class of substituted benzamides. Its pharmacodynamic profile is characterized by a predominant and selective affinity for D2 and D3 dopaminergic receptors of the limbic system. Amisulpride has no affinity for serotonergic receptors or other histaminic, cholinergic and adrenergic receptors.

In animal studies, at high doses, amisulpride blocks dopamine receptors located in the limbic structures in preference to those in the striatum. This specific affinity could explain the predominant antipsychotic effects of amisulpride compared to its extrapyramidal effects.

At low doses, amisulpride preferentially blocks presynaptic D2/D3 dopaminergic receptors, which could explain its action on negative symptoms.

In a double-blind controlled study versus haloperidol including 191 acute schizophrenic patients, amisulpride was associated with a significantly superior improvement of secondary negative symptoms compared to haloperidol.

5.2. Pharmacokinetic properties

In man, amisulpride shows two absorption peaks: one which is attained rapidly, one hour post-dose and a second between three or four hours after administration.

Corresponding plasma concentrations are 39 ± 3 and 54 ± 4 ng/ml after administration of a 50 mg dose.

The volume of distribution is 5.8 l/kg. Plasma protein binding is low (16%) and no drug interactions are suspected in relation to binding to plasma proteins. Absolute bioavailability is 48%.

Amisulpride is weakly metabolised: two inactive metabolites have been identified, accounting for 4% of the total quantity eliminated.

There is no accumulation of amisulpride and its pharmacokinetics remain unchanged after repeated dosing. The elimination half-life of amisulpride is approximately 12 hours after an oral dose.

Amisulpride is eliminated unchanged in the urine. Fifty percent of an intravenous dose is excreted in the urine, mainly during the first 24 hours (90% of the urinary excretion).

Renal clearance is approximately 330 ml/min.

A carbohydrate rich meal significantly decreases the AUC, 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, a dosage reduction should not be necessary in patients with hepatic impairment.

Renal impairment

The elimination half-life is unchanged in patients with renal impairment while systemic clearance is reduced by a factor of 2.5 to 3.

The AUC of amisulpride is increased twofold in mild renal failure and almost tenfold in moderate renal failure.

However, experience is limited and no data are available at doses greater than 50 mg.

Amisulpride is weakly dialysed.

Elderly
Pharmacokinetic data in elderly subjects over the age of 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 repeated dosing.

5.3. Preclinical safety data

The toxicological profile of amisulpride is dominated by the pharmacological effects of the molecule. No target organ was revealed by repeated dose toxicity studies. Amisulpride is devoid of any genotoxic and teratogenic properties. Carcinogenesis studies have demonstrated hormone-dependent tumours in rodents with no clinical relevance in man. A reduction of fertility related to the pharmacological properties of amisulpride (effects mediated by prolactin) has been observed in animals.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Maize starch, methylcellulose, lactose monohydrate, magnesium stearate, colloidal anhydrous silica.

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 30, 60 or 150 tablets.

6.6. Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

ratiopharm GmbH

To be completed nationally

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT