

 **22 September 2023**

**SUMMARY OF PRODUCT CHARACTERISTICS**

**for**

**Amisulprid "Medochemie Romania", tablets**

**0. D.SP.NO.**

31097

**1. NAME OF THE MEDICINAL PRODUCT**

Amisulprid "Medochemie Romania"

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Amisulprid "Medochemie Romania" 50 mg tablets: Each tablet contains 50 mg of amisulpride.

Amisulprid "Medochemie Romania" 100 mg tablets: Each tablet contains 100 mg of amisulpride.

Amisulprid "Medochemie Romania" 200 mg tablets: Each tablet contains 200 mg of amisulpride.

Amisulprid "Medochemie Romania" 400 mg tablets: Each tablet contains 400 mg of amisulpride.

Excipient with known effect: Lactose monohydrate.

Each 50 mg tablet contains 25.00 mg lactose monohydrate.

Each 100 mg tablet contains 50.00 mg lactose monohydrate.

Each 200 mg tablet contains 100.00 mg lactose monohydrate.

Each 400 mg tablet contains 200.00 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Tablets

Amisulprid "Medochemie Romania" 50 mg tablets: White, round, flat, tablets, with diameter 7 mm

Amisulprid "Medochemie Romania" 100 mg tablets: White, round, flat, tablets, with diameter 9.5 mm, embossed MC on one side

Amisulprid "Medochemie Romania" 200 mg tablets: White, round, flat, scored on one side tablets, with diameter 11.5 mm. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Amisulprid "Medochemie Romania" 400 mg tablets: White, biconvex, capsule shaped tablets, scored on both sides, with dimensions 19 × 10 mm. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Amisulprid "Medochemie Romania" is indicated for the treatment of acute and chronic schizophrenic disorders with:

* positive symptoms (such as delusions, hallucinations, thought disorders, hostility and paranoid delusions);
* negative symptoms (such as blunted affect, emotional and social withdrawal).

Amisulpride also controls secondary negative symptoms and affective disorders such as depression.

**4.2 Posology and method of administration**

Posology

For acute psychotic episodes, oral doses between 400 mg/day and 800 mg/day are recommended. 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. 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 adjusted individually according to the lowest effective dose.

For patients with predominant negative symptoms, oral doses between 50 mg/day and 300 mg/day are recommended. Doses should be adjusted individually.

Amisulprid "Medochemie Romania" may be administered once daily as oral doses up to 400 mg; higher doses should be administered in divided doses.

*Elderly*

The safety of amisulpride has been examined in a limited number of elderly patients. Amisulpride 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.

*Paediatric population*

The efficacy and safety of amisulpride from puberty age to 18 years has 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. Amisulpride is contraindicated in children before puberty, as safety is not yet established (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 (CRCL) between 0.5 and 1.0 ml / s (30 and 60 ml/min) and to one third in patients with CRCL between 0.2 and 0.6 ml / s (10-30 ml/min). As there is no experience in patients with severe renal impairment (CRCL <0.2 ml / s (10 ml/min)) particular care is recommended in these patients group (see section 4.4).

*Hepatic insufficiency*

Since the drug is weakly metabolised a dosage reduction is not required.

Method of administration

For oral administration.

**4.3 Contraindications**

* Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
* Prolactin-dependent tumours e.g. pituitary prolactinomas and breast cancer (see sections 4.4 and 4.8)
* Phaeochromocytoma
* Children before puberty (see section 4.2)
* Congenital prolongation of the QT interval
* Lactation (see section 4.6)
* Concomitant treatment with levodopa (see section 4.5)
* Concomitant treatment with drugs that may prolong the QT interval
* Concomitant treatment with the following drugs that can induce torsades de pointes:
* Antiarrhythmics class Ia, such as quinidine and disopyramide;
* Class III antiarrhythmic drugs such as amiodarone and sotalol;
* Other medicines such as bepridil, cisapride, sultopride, thioridazine, methadone, erythromycin i.v., vincamine i.v., halofantrine, pentamidine, sparfloxacin (see section 4.5).

**4.4 Special warnings and precautions for use**

*Neuroleptic Malignant Syndrome*

As with other antipsychotics, Neuroleptic Malignant Syndrome, a potentially fatal complication, characterized by hyperthermia, muscle rigidity, autonomic nervous system instability, altered consciousness and elevated serum creatine phosphokinase (CPK), may occur. In the event of hyperthermia, particularly with high daily doses, all antipsychotics including amisulpride should be discontinued.

*Parkinson's disease*

As with other antidopaminergic agents, caution should be exercised when prescribing amisulpride to patients with Parkinson's disease since it may cause worsening of the disease. Amisulpride should only be used if antipsychotic 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 increase the risk of serious ventricular arrhythmias such as torsades de pointes.

Prior to administration, and if the patient's clinical condition allows, it is recommended to monitor factors that may increase the risk of occurrence of these rhythm disturbances, e.g.

* Bradycardia below 55 bpm
* Electrolyte imbalance, particularly hypokalemia
* Congenital prolongation of the QT interval.
* Existing medications that may lead to severe bradycardia (< 55 bpm), hypokalaemia, decreased intracardiac conduction, or prolongation of the QT interval (see section 4.5).

*Stroke*

In randomized clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotics, a 3-fold increase in the risk of cerebrovascular events was observed. The mechanism of this risk increase is not known. An increase in the risk with other antipsychotics, or other patient populations 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 antipsychotics are at an increased risk of death. Analyses of seventeen placebo-controlled trials (usually for 10 weeks), mainly in patients taking atypical antipsychotics, revealed a risk of death in the group treated with antipsychotics of 1.6 to 1.7 times compared to that of the placebo-group. During a typical 10-week controlled trial, the incidence of death in the group treated with antipsychotics was about 4.5%, compared with about 2.6% in the placebo group. Although the cause of death in clinical trials with atypical antipsychotics were varied, most of the deaths appeared to be either cardiovascular (e.g. hearth 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 treatment as opposed to some characteristic(s) of the patients is not clear.

*Venous thromboembolism*

Cases of venous thromboembolism (VTE) have been reported in patients treated with antipsychotics. Patients treated with antipsychotics often present with acquired risk factors for VTE. Therefore, all possible risk factors for VTE should be identified before and during treatment with amisulpride and preventive measures should be undertaken.

*Breast cancer*

Amisulpride may increase prolactin levels. Caution should therefore be exercised and patients with history of breast cancer or cases of breast cancer in the family should be carefully monitored during treatment with amisulpride.

*Tumours of the pituitary gland*

Amisulpride may increase prolactin levels. Cases of benign pituitary tumors, such as prolactinomas, have been observed during amisulpride treatment (see section 4.8). In case of very high prolactin levels or clinical signs of pituitary gland tumors (such as altered visual field and headache), pituitary imaging should be performed. If the diagnosis of pituitary tumour is confirmed, the treatment with amisulpride must be discontinued (see section 4.3).

*Hyperglycaemia*

Hyperglycaemia has been reported in patients treated with some atypical antipsychotics, including amisulpride. Therefore, patients with an established diagnosis of diabetes mellitus or with risk factors for diabetes who have started treatment with amisulpride, should get appropriate glycaemic monitoring.

*Epilepsy*

Amisulpride may lower the seizure threshold. Therefore, patients with a history of epilepsy should be closely monitored during amisulpride treatment.

*Renal insufficiency*

Amisulpride is eliminated by the renal route. In cases of renal insufficiency, the dose should be decreased or intermittent treatment prescribed (see section 4.2).

*Elderly*

Like with other antipsychotics, in elderly patients amisulpride 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*

Acute withdrawal symptoms including nausea, vomiting and insomnia have been reported following sudden discontinuation of high dose antipsychotics. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal of amisulpride is advisable.

*Hepatotoxicity*

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

*Leukopenia, neutropenia and agranulocytosis*

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.

*Lactose*

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

*Sodium*

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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

*Contraindicated combinations*

Medicines which may induce torsades de pointes or prolong the QT interval (see sections 4.3 and 4.4):

* Class Ia antiarrhythmics such as quinidine and disopyramide.
* Class III antiarrhythmics such as amiodarone and sotalol.
* Other medicines such as bepridil, cisapride, sultopride, thioridazine, methadone, erythromycin i.v., vincamine i.v., halofantrine, pentamidine, sparfloxacin (see section 4.3).

Levodopa due to the mutual antagonism of effects between levodopa and antipsychotics.

Amisulpride may block the effect of dopamine agonists e.g. bromocriptine, ropinirole.

*Combinations not recommended*

Amisulpride may enhance the effect of alcohol on the central nervous system.

Medicines that increase the risk of torsades de pointes or may prolong the QT interval:

* Medicines that may cause bradycardia, including beta-blockers. Bradycardia inducing calcium antagonists such as diltiazem, verapamil, clonidine, guanfacine and digoxin.
* Medicines that induce electrolyte imbalance: hypokalaemic diuretics, stimulant laxatives, i.v. amphotericin B, glucocorticoids and tetracosactides. Hypokalemia should be corrected.
* Antipsychotic drugs as pimozide and haloperidol, imipramine antidepressants, lithium.

*Combinations to be taken into account*

* CNS depressants including narcotics, anaesthetics, analgesics, sedative H1 antihistamines, barbiturates, benzodiazepines and other anxiolytics, clonidine and derivatives.
* Antihypertensive drugs and other hypotensive medications
* Co-administration of clozapine may lead to increased plasma concentrations of amisulpride.

**4.6 Fertility, pregnancy and lactation**

Pregnancy

Very limited clinical data on amisulpride use in pregnant woman are available. Therefore, the safety of amisulpride in human pregnancy has not been established.

Amisulpride crosses the placenta.

Animal studies have shown reproductive toxicity (see section 5.3).

The use of amisulpride is not recommended during pregnancy and in women of childbearing potential not using effective contraception, unless the benefits outweigh the potential risks.

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, dyspnoea, or eating disorders. Consequently, newborns should be carefully monitored.

Breastfeeding

Amisulpride is excreted in some cases in breast milk in rather large amounts above the accepted value of 10% of the mother's weight-adjusted dose, but blood concentrations in breast-fed infants have not been assessed. There is insufficient information on the effects of amisulpride in neonates / infants. A decision must be made to discontinue breast-feeding or to refrain from amisulpride treatment, taking into account the benefits of breast-feeding for the child and the benefits of treatment for the woman.

Fertility

Decreased fertility related to the pharmacological effects of the drug (prolactin mediated effect) was observed in treated animals.

**4.7 Effects on ability to drive and use machines**

No traffic warning.

Even 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**

The following side effects are listed by frequency according to the following categories: 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). Within each frequency grouping, adverse reactions are presented according to their severity. The most serious adverse reactions are listed first.

| **System Organ Class** | **Frequency** | **Adverse reactions** |
| --- | --- | --- |
| **Blood and lymphatic system disorders** | Uncommon | Leucopenia, neutropenia |
| Rare | Agranulocytosis |
| **Immune system disorders** | Uncommon | Allergic reactions |
| **Endocrine disorders** | Common | Hyperprolactinemia, galactorrhea, amenorrhea, gynaecomastia, mastodynia and erectile dysfunction |
| Rare | Benign pituitary tumors, such as prolactinomas |
| **Metabolism and nutrition disorders** | Uncommon | Hyperglycaemia, hypertriglyceridemia, hypercholesterolemia |
| Rare | Hyponatraemia and SIADH (syndrome of inappropriate antidiuretic hormone secretion) |
| **Psychiatric disorders** | Common | Insomnia, anxiety, agitation, orgasm dysfunction |
| Uncommon | Confusion |
| **Nervous system disorders** | Very common | Extrapyramidal symptoms (tremor, rigidity, hypokinesia, hypersalivation, akathisia, dyskinesia). |
| Common | Acute dystonia (spasmodic torticollis, oculogyric crisis, trismus), somnolence |
| Uncommon | Tardive dyskinesia (characterized by rhythmic, involuntary movements primarily of the tongue and/or face have been reported, usually after long term administration or withdrawal). Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms. Seizures |
| Rare | Malignant neuroleptic syndrome, which is a potentially lethal complication |
| Not known  | Restless legs syndrome |
| **Eye disorders** | Common | Blurred vision  |
| **Cardiac disorders** | Uncommon | Bradycardia |
| Rare | QT interval prolongation, ventricular arrhythmias such as torsades de pointes, ventricular tachycardia, ventricular fibrillation, cardiac arrest, sudden death (see section 4.4) |
| **Vascular disorders** | Common | Hypotension |
| Uncommon | Hypertension |
| Rare | Cases of venous thromboembolism, including cases of pulmonary embolism, and cases of deep vein thrombosis, sometimes fatal |
| **Respiratory, thoracic and mediastinal disorders** | Uncommon | Nasal congestion, aspiration pneumonia (mainly associated with other CNS depressants) |
| **Gastrointestinal disorders** | Common | Constipation, nausea, vomiting, dry mouth |
| **Hepatobiliary disorders** | Uncommon | Hepatocellular damage |
| **Skin and subcutaneous tissue disorders** | Rare | Angioedema, urticaria |
| Not known | Photosensibility |
| **Musculoskeletal and connective tissue disorders** | Uncommon | Osteopenia, Osteoporosis |
| **Renal and urinary disorders** | Uncommon | Urinary retention |
| **Pregnancy, puerperium and perinatal conditions** | Not known | Neonatal withdrawal syndrome  |
| **Investigations** | Common | Weight gain |
| Uncommon | Elevations of hepatic enzymes, mainly transaminases |

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:

Lægemiddelstyrelsen

Axel Heides Gade 1

DK-2300 København S

Website: www.meldenbivirkning.dk

**4.9 Overdose**

There are limited data regarding amisulpride overdosage.

Symptoms

Exaggeration of the known pharmacological effects of the active substance such as drowsiness and sedation, coma, hypotension and extrapyramidal symptoms. Fatal outcomes have been reported mainly in combination with other psychotropic agents.

Management

In cases of acute overdosage, the possibility of multiple drug intake should be considered. Amisulpride is poorly dialysed, haemodialysis is of no use to eliminate the drug. There is no specific antidote for amisulpride. Appropriate supportive measures should therefore be instituted: close supervision of vital functions and continuous cardiac monitoring (risk of prolongation of QT interval) until the patient recovers.

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

Patients where overdose is suspected should be ECG monitored.

**4.10 Legal status**

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**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 D2/D3 receptor subtypes whereas it is devoid of affinity for D1, D4 and D5 receptor subtypes.

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

In animal studies, at high doses, amisulpride blocks post-synaptic D2 receptors located in the limbic structures in preference to those in the striatum. Unlike classical antipsychoticss it does not induce catalepsy and hypersensitivity of D2 dopamine receptors does not develop after repeated treatment.

At low doses it preferentially blocks pre-synaptic D2/D3 receptors, producing dopamine release responsible for its disinhibitory effects.

This atypical pharmacological profile may explain amilsulpride's antipsychotic effect at higher doses through post-synaptic dopamine receptor blockade and its efficacy against negative symptoms at lower doses, through pre-synaptic dopamine receptor blockade.

Furthermore, the decreased tendency of amisulpride to provoke extrapyramidal symptoms can probably be attributed to its predominant effect in the limbic system.

**5.2 Pharmacokinetic properties**

In humans, 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 suspected.

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 remain 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.

The kinetic profile of amisulpride is not affected by food intake.

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 metabolised a dosage reduction should not be necessary 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). Experience is however limited and there is no data with doses greater than 50 mg.

Amisulpride is very weakly dialysed.

*Elderly patients:*

Limited pharmacokinetic data in elderly subjects (> 65 years) show that a 10-30% rise occurs in Cmax, T½ 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/day) and dog (120 mg/kg/day) respectively in terms of AUC. No carcinogenic risk, relevant to humans was identified in mice (up to 120 mg/kg/day) and rats (up to 240 mg/kg/day), considering that the dosage administered in the rat corresponds to 1.5 to 4.5 times the expected human AUC. Reproductive studies performed in rats, rabbits and mice did not show any teratogenic potential.

In animal studies, amisulpride produced an effect on fetal growth and development at doses equivalent to a human equivalent dose of 2000 mg/day and above for a 50 kg patient. There was no evidence of teratogenic potential of amisulpride. Studies on the effect of amisulpride on offspring behavior have not been performed.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Lactose monohydrate,

Sodium starch glycolate type A,

Hypromellose 2910 E5,

Cellulose Microcrystalline PH-101,

Magnesium stearate

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

36 months.

For bottles: 18 months

**6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

**6.5 Nature and contents of container**

Amisulprid "Medochemie Romania" 50 mg tablets: PVC/PE/PVDC-Alu blisters or PVC/PVDC-Alu blisters packs containing 12, 30, 90 and 100 tablets.

Amisulprid "Medochemie Romania" 100 mg, 200 mg and 400 mg tablets: PVC/PE/PVDC-Alu blisters or PVC/PVDC-Alu blisters packs containing 30, 90 and 100 tablets.

Amisulprid "Medochemie Romania" 100 mg and 400 mg tablets: Bottles containing 200 tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

No special requirements.

**7. MARKETING AUTHORISATION HOLDER**

Medochemie Romania Srl.

Str. Prof. Dr. Ioan Cantacuzino nr. 5, sector 1

011437 Bucharest

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**8. MARKETING AUTHORISATION NUMBER(S)**

50 mg: 60851

100 mg: 60852

200 mg: 60853

400 mg: 60854

**9. DATE OF FIRST AUTHORISATION**

 18 July 2019

**10. DATE OF REVISION OF THE TEXT**

22 September 2023