

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

AMISULPRIDE 200mg TABLETS

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200.000mg Amisulpride.

Excipient with known effect: Lactose monohydrate
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

White to off-white, round tablets with a break line, diameter 12.5mm and impressed "C" and "AM" on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Amisulpride is indicated for the treatment of 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

Posology

For acute psychotic episodes, oral doses between 400 mg per day and 800 mg per day are recommended. In individual cases, the daily dose may be increased up to 1200 mg per day. Doses above 1200 mg per 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 established individually with the minimally effective dose.

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

Amisulpride can be administered once daily at oral doses up to 300 mg, higher doses should be administered twice daily.

Elderly

Amisulpride should be used with particular caution because of a possible risk of hypotension or sedation.

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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, amisulpride should not be used from puberty to the age of 18 years; amisulpride is contraindicated in children up to puberty (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 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 4.4 Special warnings and precautions for use)

Hepatic insufficiency

Since Amisulpride is weakly metabolised a dosage reduction should not be necessary.

Method of administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to amisulpride or to any of the excipients listed in section 6.1.
- Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer
- Pheochromocytoma
- Children till puberty
- Lactation
- Combination with levodopa

(see 4.5 Interactions with other medical products and other forms of interaction)

4.4 Special warnings and precautions for use

As with other neuroleptics, Neuroleptic Malignant Syndrome, a potentially fatal complication, characterised 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 medicines including Amisulpride should be discontinued.

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 is eliminated by the renal route. In cases of renal insufficiency, the dose should be decreased and intermittent treatment should be considered (see 4.2 Posology and method of administration).

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

Concomitant neuroleptics should be avoided (see section 4.5)

Elderly patients

In elderly patients, Amisulpride, 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 because of renal insufficiency.

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. Amisulpride is not licensed for the treatment of dementia-related behavioural disturbances.

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.

Patients with cardiovascular disease

Prolongation of the QT interval

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

Caution should be used in patients with cardiovascular disease or a family history of QT prolongation.

Stroke

In randomized 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.

Lactose

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

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.

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).

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.

Acute withdrawal symptoms including nausea, vomiting and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotic drugs. Withdrawal symptoms have been described after abrupt cessation of high therapeutic doses of antipsychotic drugs. The emergence of involuntary movement disorders (such as akathisia, dystonia, and dyskinesia) has been reported with amisulpride. Therefore, gradual withdrawal of amisulpride is advisable.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations contra-indicated

Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics. Amisulpride may oppose the effect of dopamine agonists e.g. bromocriptine, ropinirole.

Combinations not recommended

Amisulpride may enhance the central effects of alcohol.

Combinations to be considered

CNS depressants including narcotics, anaesthetics, analgesics, sedative H1 antihistamines, barbiturates, benzodiazepines and other anxiolytic drugs, clonidine and derivatives.

Antihypertensive drugs and other hypotensive medicines.

Co-administration of amisulpride and clozapine may lead to an increase in plasma levels of amisulpride.

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 antihistaminics, 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. A decrease in fertility linked to the pharmacological effects of the medicine (prolactin mediated effect) was observed. No teratogenic effects were noted.

Very limited clinical data on exposed pregnancies are available. Therefore, the safety of Amisulpride during human pregnancy has not been established. Use of the drug is not recommended during pregnancy unless the benefits justify the potential risks. If amisulpride is used during pregnancy, neonates may show adverse effects of amisulpride and thus appropriate monitoring should be considered.

Breast-feeding

It is not known whether Amisulpride is excreted in breast milk, breast-feeding is therefore contra-indicated.

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. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

4.7 Effects on ability to drive and use machines

Even used as recommended, Amisulpride may cause somnolence and blurred vision so that the ability to drive vehicles or operate machinery can 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 ($\geq 1/10$); common ($\geq 1/100$; $< 1/10$); uncommon ($\geq 1/1,000$; $< 1/100$); rare ($\geq 1/10,000$; $< 1/1,000$); very rare

(<1/10,000); frequency not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:

Uncommon: Leukopenia, neutropenia (see section 4.4)

Rare: Agranulocytosis (see section 4.4)

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 the treatment of patients with predominantly negative symptoms with doses of 50-300 mg/day.

Common: Acute dystonia (spasm torticollis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon treatment with an antiparkinsonian agent. Somnolence.

Uncommon: Tardive dyskinesia characterized by rhythmic, involuntary movements primarily of the tongue and/or face have been reported, usually after long term administration.

Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms. Seizures.

Rare: Neuroleptic Malignant Syndrome (see section 4.4), which is a potentially fatal complication.

Psychiatric disorders:

Common: Insomnia, anxiety, agitation, orgasmic dysfunction.

Uncommon: confusion.

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, gynaecomastia, breast pain, and erectile dysfunction.

Rare: Benign pituitary tumour such as prolactinoma (see Section 4.3 and 4.4)

Metabolism and nutrition disorders:

Uncommon: Hyperglycemia (see section 4.4) hypertriglyceridemia and hypercholesterolaemia

Rare: Hyponatraemia, syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Eye disorders:

Common: Blurred vision (see Section 4.7)

Cardiovascular disorders:

Common: QT interval prolongation (see section 4.4).

Uncommon: Bradycardia.

Rare: Ventricular arrhythmias such as torsade de pointes, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, sudden death (see section 4.4).

Investigations:

Common: Weight gain.

Uncommon: Elevations of hepatic enzymes, mainly transaminases.

Immune system disorders:

Uncommon: Allergic reactions.

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, pneumonia aspiration (mainly in association with other antipsychotics and CNS depressants).

Skin and subcutaneous tissue disorders:

Frequency not known: Angioedema, urticaria

Musculoskeletal and connective tissue disorders:

Uncommon: osteopenia, osteoporosis

Renal and urinary disorders:

Uncommon: urinary retention

Pregnancy, puerperium and perinatal conditions:

Frequency not known: Drug withdrawal syndrome neonatal (see section 4.6)

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 the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Experience with Amisulpride in overdosage is limited. Exaggeration of the known pharmacological effects of the drug have been reported. These include drowsiness and sedation, coma, hypotension and extrapyramidal symptoms.

In cases of acute overdosage, the possibility of multiple drug intake 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.

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzamide antipsychotic

ATC code: N05A L05

Mechanism of action

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, α -adrenergic, histamine H₁ and cholinergic receptors. In addition, amisulpride does not bind to sigma sites.

Pharmacodynamic effects

In animal studies, at high doses, amisulpride blocks dopamine receptors located in the limbic structures in preference to those in the striatum. Unlike classical neuroleptics 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 amisulpride'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. In addition, the reduced tendency of amisulpride to produce extrapyramidal side effects may be related to its preferential limbic activity.

Clinical efficacy and safety

In clinical studies including schizophrenic patients with acute exacerbations, amisulpride significantly alleviated secondary negative symptoms as well as affective symptoms such as depressed mood.

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 suspected.

Biotransformation & Elimination

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. Fifty percent 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. Kinetic profile of amisulpride is not influenced by diet.

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.

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 chapter 4.2). Experience is however limited and there is no data with doses greater than 50 mg.

Amisulpride is very weakly dialysed.

Elderly

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch,
Lactose monohydrate,
Methylcellulose
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Blisters comprising of 25µm Al foil and 250µm PVC contained within a printed carton box.

Pack sizes: 10, 20, 28, 30, 50, 56, 60, 84, 90,100 or 150.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 00142/0586

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 November 2004
Date of latest renewal: 01 November 2009

10 DATE OF REVISION OF THE TEXT

09/01/2019