

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Amisulpride Teva 400 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg amisulpride.

Excipients

Each tablet contains 240.9 mg lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White to almost white, capsule-shaped tablet, debossed “MS 400” and scoreline on one side and plain on the other. The tablet can be divided into equal halves.

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
- primary negative symptoms (deficit syndrome) such as blunted affect, emotional and social withdrawal.

4.2 Posology and method of administration

Positive symptoms

The recommended dose is 400-800 mg amisulpride daily.

In individual cases, the daily dose may be increased to 1,200 mg amisulpride. Doses above 1,200 mg/day have not been sufficiently evaluated for safety and therefore should not be used.

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

No specific titration is required when initiating treatment with amisulpride.

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.

As higher doses are generally required for the treatment of positive symptoms, higher strength tablets should be used.

Primary negative symptoms (deficit syndrome)

The recommended dose is 50-300 mg amisulpride daily.

Doses should be adjusted individually.

Amisulpride may be administered as a single dose up to 300 mg.

Special populations

Renal insufficiency

The daily dose should be reduced to half in patients with creatinine clearance between 30 and 60 ml/min and to a third in patients with creatinine clearance between 10 and 30 ml/min. As there is no experience in patients with severe renal insufficiency (creatinine clearance less than 10 ml/min), amisulpride is contraindicated in these patients (see section 4.3).

Hepatic insufficiency

Since amisulpride is weakly metabolised dose reduction should not be necessary in patients with hepatic insufficiency.

Elderly

Treatment of elderly patients (> 65 years) is not recommended as there is insufficient clinical experience. Treatment with amisulpride bears a possible risk of hypotension or sedation (see also section 5.2).

Paediatric patients

Amisulpride is contraindicated in children and adolescents under 18 years of age (see section 4.3).

Method of administration

Amisulpride may be taken without regard to meals. The tablets should be taken unchewed, with a sufficient amount of fluid.

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.

For doses not realisable/practicable with this strength, other strengths of this medicinal product are available.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer
- Pheochromocytoma
- Combination with levodopa (see section 4.5)
- Children till puberty
- Lactation.

4.4 Special warnings and precautions for use

Neuroleptic malignant syndrome, characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated creatine phosphokinase (CPK), may occur. In the event of hyperthermia, particularly with high daily doses, all antipsychotics including amisulpride should be discontinued.

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 *torsades 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:

- prior cardiac disorders,
- bradycardia less than 55 beats per minute (bpm),
- electrolyte disorders, especially hypokalaemia, hypomagnesaemia, hypocalcaemia,
- congenital prolongation of the QT interval,
- on-going treatment with agents likely to produce pronounced bradycardia (< 55 bpm), hypokalaemia, decreased intracardiac conduction, or prolongation of the QT interval (see section 4.5).

Cerebrovascular accident (CVA)

In randomised, placebo-controlled clinical trials in elderly patients with dementia treated with atypical antipsychotics, a three-fold increase was observed in the risk of cerebrovascular adverse events. The mechanism leading to this increase in risk is unknown. It cannot be excluded that this effect might occur with other antipsychotics or in other patient populations. Amisulpride should therefore be used with caution in patients at risk for CVA.

Venous thromboembolism (VTE)

Cases of venous thromboembolism (VTE) have been reported with antipsychotic agents. 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 preventive measures undertaken.

Hyperglycaemia has been reported during treatment with some atypical antipsychotics including amisulpride. Patients on amisulpride with or at risk of diabetes should monitor their glucose levels regularly.

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

Amisulpride is eliminated by the renal route. In cases of mild-to-moderate renal insufficiency (creatinine clearance greater than 10 ml/min), the daily dose should be decreased (see section 4.2).

Amisulpride is not recommended for use in patients over 65 years of age, owing to a lack of experience. It may lead to sedation and hypotension in this patient population (see section 5.2).

Acute withdrawal symptoms including nausea, vomiting and insomnia have been rarely described after abrupt cessation of high doses of antipsychotic agents. 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 is advisable.

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

4.5 Interaction with other medicinal products and other forms of interaction

Combinations which are contraindicated

Amisulpride should not be administered concomitantly with agents which could induce serious cardiac arrhythmias (*torsade de pointes*):

- Class I and III antiarrhythmics (quinidine, disopyramide, procainamide, mexiletine, flecainide, propafenone, amiodarone, sotalol),
- Thioridazine, sultopride (neuroleptics),
- Some antibiotics (pentamidine), antimalarials (halofantrine), gyrase inhibitors (sparfloxacin), imidazole antifungals and macrolides (IV erythromycin)

- Cisapride (gastro-intestinal agent)
- Bepiridil
- Methadone
- IV vincamine (vasodilator)
- Amisulpride should not be administered concomitantly with dopamine agonists (e.g. levodopa for Parkinson's disease) due to reciprocal antagonism (see section 4.3).

Combinations which are not recommended

Amisulpride is not recommended in combination with the following agents which increase the risk of serious cardiac arrhythmias (*torsade de pointes*) or which may affect cardiac conduction (QT prolongation):

- Bradycardia-inducing agents such as beta-blockers, some calcium channel blockers such as diltiazem or verapamil, clonidine, guanfacine, digitalis glycosides
- Hypokalaemic agents such as diuretics, stimulant laxatives, IV amphotericin B, glucocorticoids, tetracosactide. Hypokalaemia must be treated.
- Neuroleptics such as pimozide, haloperidol
- Tricyclic antidepressants
- Lithium
- Some antihistamines (astemizole, terfenadine).

Amisulpride may potentiate the central effects of alcohol, which should therefore not be consumed during treatment.

Combinations requiring precautions for use

Caution is required when using the following agents concomitantly (due to potentiation of effect):

- Centrally-acting agents such as narcotics, anaesthetics, sedative H₁ antihistamines, barbiturates, benzodiazepines and other anxiolytics, clonidine and its derivatives
- Antihypertensives and other blood-pressure-lowering agents.

There is no data on interactions with H₂ antagonists such as cimetidine.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is only very limited clinical data on the use of amisulpride during pregnancy. Animal studies indicate that amisulpride exerts an influence on embryofetal development and growth without having teratogenic potential. The safety of amisulpride during human pregnancy has not been established. Therefore, use is not recommended during pregnancy unless the benefits justify the potential risks.

Neonates exposed to amisulpride during pregnancy may exhibit adverse events and should therefore be monitored. A decrease in female fertility linked to the pharmacological effects of the substance (prolactin-mediated effect) was observed.

Lactation

It is not known whether amisulpride is excreted in breast milk, breast-feeding is therefore contra-indicated and must be discontinued before initiation of therapy (see section 4.3).

4.7 Effects on ability to drive and use machines

Amisulpride has moderate influence on the ability to drive and use machines. Even used as recommended, it may affect reaction time (e.g. through somnolence) so that the ability to drive vehicles or operate machinery can be impaired (see section 4.8). This is especially true when used concomitantly with alcohol.

4.8 Undesirable effects

The adverse events/reactions are described according to the following frequency convention:

Very common	$\geq 1/10$
Common	$\geq 1/100$ to $< 1/10$
Uncommon	$\geq 1/1,000$ to $< 1/100$
Rare	$\geq 1/10,000$ to $< 1/1,000$
Very rare	$< 1/10,000$
Not known	(cannot be estimated from the available data)

Clinical trials data

The following adverse reactions have been observed in controlled clinical trials. It should be noted that in some instances it can be difficult to differentiate adverse events from symptoms of the underlying disease.

Investigations

Common:	Weight gain
Uncommon:	Increased hepatic enzyme levels, mainly transaminases

Cardiac disorders

Uncommon:	Bradycardia
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Nervous system disorders

Very common:	Extrapyramidal disorders such as 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 agents. The incidence of extrapyramidal symptoms, which is dose-related, remains very low in the treatment of patients with doses of 50-300 mg/day.
Common:	Acute dystonia such as spasm torticollis, oculogyric crisis, trismus. This is reversible without discontinuation of amisulpride upon treatment with an antiparkinsonian agent. Somnolence, dizziness
Uncommon:	Tardive dyskinesia characterised by rhythmic, involuntary movements primarily of the tongue and/or face, usually after long term administration. Antiparkinsonian treatment should not be used as it is ineffective or may induce aggravation of the symptoms. Seizures

Gastrointestinal disorders

Common:	Gastrointestinal disorders such as constipation, nausea, vomiting, mouth dryness
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Endocrine disorders

Common:	Amisulpride causes an increase in plasma prolactin levels, reversible after drug discontinuation. This may result in galactorrhoea, amenorrhoea or menstrual disorders, gynaecomastia, breast pain or enlargement, prolactinoma and erectile dysfunction.
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Metabolism and nutrition disorders

Uncommon:	Hyperglycaemia (see section 4.4)
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Vascular disorders

Common:	Hypotension
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Immune system disorders

Uncommon:	Allergic reactions
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Psychiatric disorders

Common:	Insomnia, anxiety, agitation, orgasmic dysfunction
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Post marketing data

In addition, cases of the following adverse events/reactions were spontaneously reported after market launch:

Cardiac disorders

Not known: QT prolongation, ventricular arrhythmias such as torsade de pointes and ventricular tachycardia, which can lead to fibrillation or cardiac arrest and sudden death (see section 4.4).

Nervous system disorders

Not known: Neuroleptic malignant syndrome (see section 4.4)

Vascular disorders

Not known: Venous thromboembolism, including pulmonary embolism, sometimes fatal, and deep vein thrombosis

Skin and subcutaneous tissue disorders

Not known: Angioedema, urticaria

Pregnancy, puerperium and perinatal conditions

Not known: Drug withdrawal syndrome neonatal (see section 4.6)

General disorders

Rare: Acute withdrawal symptoms including nausea, vomiting and insomnia after abrupt cessation of high doses, also recurrence of psychotic symptoms, emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) (see section 4.4).

4.9 OverdoseSymptoms

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

Treatment

In cases of acute overdose, the possibility of multiple agent intake should be considered. Since amisulpride is weakly dialysable, haemodialysis should not be used to eliminate it. There is no known specific antidote to amisulpride. Appropriate supportive measures should therefore be instituted in hospital, close supervision of vital functions and cardiac (ECG) monitoring is recommended (risk of prolongation of QT interval).

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

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antipsychotics, benzamides

ATC code: N05A L05

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 other atypical neuroleptics, amisulpride has no affinity for serotonin, α -adrenergic, histamine H₁ and cholinergic receptors. In addition, it does not bind to sigma sites.

At high doses amisulpride blocks post-synaptic D₂ 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 clinical efficacy against both the positive and negative symptoms of schizophrenic psychotic disorders and its reduced tendency to produce extrapyramidal adverse effects.

5.2 Pharmacokinetic properties

In humans, amisulpride shows two absorption peaks after oral administration: 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. As plasma protein binding is low (16%), interactions are unlikely.

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.

A carbohydrate-rich meal (containing 68% fluids) significantly decreases the AUC, 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 amisulpride is weakly metabolised, dose reduction should not be necessary in patients with hepatic insufficiency.

Renal insufficiency

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 area under the curve (AUC) of amisulpride in mild renal failure increased two-fold and almost ten-fold in moderate renal failure.

Amisulpride is very weakly dialysable.

Elderly patients

In elderly patients (>65 years), slight changes were observed in the kinetic profile (10% increase in AUC) which are probably due to age-related changes in renal function.

5.3 Preclinical safety data

No specific organ toxicity was identified in chronic toxicity studies in rats receiving 200 mg/kg/day amisulpride and dogs receiving at most 120 mg/kg/day. Apathy, lethargy and tremor were observed. Increases in cholesterol and lipid values and transient tachycardia occurred only in dogs.

Animal studies indicate an influence on embryofetal growth and development, but no teratogenic potential. Adequate studies on the effect on the offspring have not been performed.

Carcinogenicity studies in mice and rats revealed an increased incidence of mammary, pituitary, adrenal and endocrine pancreatic tumours. The no-effect level dose could not be established. An increased incidence of tumours was observed in the lowest dose group (30 mg/kg) in both species.

The induction of tumours can be explained by the antidopaminergic and hyperprolactinaemic effects of amisulpride, and the particular sensitivity of rodents to these hormonal changes. The induction mechanism in rodents is known.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Potato starch
Hypromellose
Sodium starch glycolate (type A)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Transparent PVC/PVdC – aluminium blisters
1, 10, 20, 30, 50, 5 x 50, 60, 90, 100 & 120 tablets. Hospital pack with 500 (10 x 50) tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA749/75/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th April 2009

10 DATE OF REVISION OF THE TEXT

April 2012