

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Amisulpride 400 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Amisulpride 400mg per tablet.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-Coated Tablet

White to off-white scored film-coated tablets.

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

For acute psychotic episodes, oral doses between 400 mg/day and 800 mg/day are recommended. Doses above 800 mg/day have not been associated with greater efficacy and have induced higher rates of extrapyramidal symptoms. 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/day and 300 mg/day are recommended. Doses should be adjusted individually.

Amisulpride should be administered b.i.d. for doses above 400mg.

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 or sedation. Reduction in dosage may also be required because of renal insufficiency.

Children:

Amisulpride is contra-indicated in children up to puberty as its safety has not yet been established.

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) particular care is recommended in these patients.

Hepatic insufficiency:

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

4.3 Contraindications

Hypersensitivity to the active ingredient or to other ingredients of the product.

Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer.

Phaeochromocytoma.

Children up to puberty.

Lactation.

4.4 Special warnings and precautions for use

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

Amisulpride is eliminated by the renal route. In cases of severe renal insufficiency or renal dialysis, the dose should be decreased and intermittent treatment should be considered (see Section 4.2).

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

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.

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.

Amisulpride should be prescribed with caution in patients with these factors and patients with cardiovascular disorders which may predispose to prolongation of the QT interval.

Avoid concomitant prescription of other antipsychotics.

Acute withdrawal symptoms including nausea, vomiting and insomnia have been rarely described after abrupt cessation of high doses of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) have been reported. Therefore, gradual withdrawal is advisable.

4.5 Interaction with other medicinal products and other forms of interaction

Amisulpride may enhance the central effects of alcohol.

Caution should be exercised with the concomitant administration of drugs such as:

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

Antihypertensive drugs and other hypotensive medications.

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

Dopamine agonists (e.g. levodopa) since it may attenuate their action.

4.6 Pregnancy and lactation

Pregnancy

In animals, amisulpride did not show direct reproductive toxicity. A decrease in fertility linked to the pharmacological effects of the drug (prolactin mediated effect) was observed. No teratogenic effects of amisulpride were noted. The safety of amisulpride during human pregnancy has not been established. Therefore, use of the drug is not recommended during pregnancy unless the benefits justify the potential risks.

Lactation

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

4.7 Effects on ability to drive and use machines

Even used as recommended, Amisulpride may affect reaction time so that the ability to drive vehicles or operate machinery can be impaired.

4.8 Undesirable effects

The following adverse effects 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.

Common adverse effects (5-10%): insomnia, anxiety, agitation.

Less common adverse effects (0.1-5%): somnolence, gastrointestinal disorders such as constipation, nausea, vomiting, dry mouth.

In common with other neuroleptics:

Amisulpride causes an increase in plasma prolactin levels which is reversible after drug discontinuation. This may result in galactorrhoea, amenorrhoea, gynaecomastia, breast pain, orgasmic dysfunction and impotence.

Weight gain may occur under therapy with Amisulpride.

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

Extrapyramidal symptoms may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia. 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.

Tardive dyskinesia characterised 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.

Cardiovascular disorders

Hypotension and bradycardia have been reported occasionally.

Very rare cases of QT prolongation and of ventricular arrhythmias such as of torsade de pointes, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, have been reported. Very rare cases of sudden death have been reported.

Allergic reactions and cases of seizures have been reported occasionally.

Rare cases of Neuroleptic Malignant Syndrome have been reported (see special warnings and special precautions for use).

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, haemodialysis should not be used to eliminate the drug. There is no specific antidote to amisulpride. Appropriate supportive measures should therefore be instituted, close supervision of vital functions and cardiac monitoring is recommended until the patient recovers.

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

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antipsychotics

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

In animals, at high doses it 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 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.

In clinical studies including schizophrenic patients with acute exacerbations, amisulpride significantly alleviated secondary negative symptoms.

5.2 Pharmacokinetic properties

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

50mg dose.

The volume of distribution is 5.8 l/kg. As plasma protein binding is low (16%) drug 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 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 for dosing recommendations). Experience is however limited and there is no data with doses greater than 50 mg.

Amisulpride is very weakly dialysed.

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/day) and dog (120 mg/kg/day) respectively in terms of AUC. No carcinogenic risk, relevant to man, was identified in the mouse (up to 120 mg/kg/day) and in the rat (up to 240 mg/kg/day), corresponding for the rat to 1.5 to 4.5 times the expected human AUC.

Reproductive studies performed in the rat, rabbit and mouse did not show any teratogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium starch glycolate
Lactose monohydrate
Microcrystalline cellulose
Hypromellose
Magnesium stearate
Polyoxyl 40 stearate
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

No special precautions.

6.5 Nature and contents of container

PVC/aluminium foil blister packs containing 30, 60 or 90 tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Winthrop Pharmaceuticals UK Limited
One Onslow Street
Guildford
Surrey
GU1 4YS
United Kingdom

Trading as:
Winthrop Pharmaceuticals
PO Box 611
Guildford
Surrey
GU1 4YS
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1046/13/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 August 2003

10 DATE OF REVISION OF THE TEXT

October 2005