Public Assessment Report

Amisulpride Tablets

Strengths: 50mg, 100mg, 200mg, 400mg

PL 20046/0013
PL 20046/0014
PL 20046/0015
PL 20046/0016

Focus Pharmaceuticals Limited

Table of Contents

Lay Summary

The MHRA granted Focus Pharmaceuticals Limited Marketing Authorisations (licenses) for the medicinal products Amisulpride 50mg, 100mg, 200mg and 400mg Tablets on 21st April 2006. Amisulpride is a bezamide neuroleptic agent and is structurally related to Sulpride. These drugs are dopamine receptor antagonists. Amisulpride is indicated for the treatment of acute and chronic schizophrenic disorders. The claimed indications are consistent with those licensed in the cross-referral product.

This application has been made under 2001/83/EC Article 10.1 as amended, claiming essential similarity to Solian tablets Sanofi-Synthelabo PL 11723/0308(50mg), PL 11723/0355 (100mg), PL 11723/0309 (200mg) PL 11723/0356 (400mg).

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Amisulpride 50mg, 100mg, 200mg and 400mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

SCIENTIFIC DISCUSSION

Introduction

This Public Assessment Report is based on the National Assessment Report for the submissions PL 20046/0013, PL 20046/0014, PL 20046/0015, and PL 20046/0016 for Amisulpride 50mg, 100mg, 200mg and 400mg Tablets respectively. These applications are submitted under Article 10.1 of EC Directives 2001/83/EC as amended, claiming essential similarity to Solian tablets Sanofi-Synthelabo PL 11723/0308(50mg), PL 11723/0355 (100mg), PL 11723/0309 (200mg) PL 11723/0356 (400mg). The original product is stated as being Solian 200mg Tablets first Authorised 1986 in France (original licence number 556 654.5). The 10 year rule for registration in the EU of *"essentially similar"* products has been fulfilled.

Amisulpride is a bezamide neuroleptic agent and is structurally related to Sulpride. These drugs are dopamine receptor antagonists. The claimed indications are consistent with those licensed in the cross-referral product.

PHARMACEUTICAL ASSESSMENT

Drug Substance

The active ingredient, amisulpride, is covered by an up-to-date European DMF and a letter of access was provided. The final Drug Substance Specification was satisfactory. The description of the manufacturing process, process validation and batch data were acceptable. Stability data supported the shelf-life of the drugs substance of three years.

The source of the drug substance was found to be acceptable for these products.

Drug Product

The manufacture has provided an appropriate licence from the relevant authority, appropriate licenses were also provided for packaging and batch release sites. All excipients for the tablet cores are pharmacopoeial (Ph.Eur), analytical control is as described in the monographs. Satisfactory certificates of analysis are supplied by the excipient supplier and finished product manufacturers. TSE issues are addressed in a satisfactory manner.

The qualitative composition of the drug products is given in the tables below.

Amisulpride
Lactose monohydrate
Maize Starch
Methyl cellulose
Water purified
Silica, Colloidal hydrated
Magnesium stearate

Table 1. 50mg 100mg and 200mg Tablets

Amisulpride
Lactose monohydrate
Cellulose microcrystalline
Hypromellose
Water purified
Magnesium stearate

Table 2. 400mg Tablets

There is a Ph.Eur monograph for amisulpride and the specification proposed by applicant/AIM is consistent with Ph.Eur requirements. Tests for appearance, solubility, identification and detection of impurities are carried out by both active substance manufacturer and finished product manufacturer and are in compliance with requirements of the European Pharmacopoeia.

Data for dissolution, comparative impurity profiles and bioequivalency of Amisulpride 50mg, 100mg, 200mg and 400mg Tablets were supplied and these products were found to be essentially similar to the innovator product Solian tablets.

Packaging consists of hard tempered aluminium foil which has an outer lacquer of nitrocellulose and an inner layer consisting of a blend of poly butyl methacrylate and poly vinyl chloride copolymer. The shelf-life for the finished product is 3 years and is supported by satisfactory data.

The Patient Information Leaflet and packaging material were found to be pharmaceutically acceptable.

Conclusion
A marketing authorisation was granted.

CLINICAL ASSESSMENT

1. INDICATIONS

The applicant has submitted the following:

> *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.*

The above is identical to the SPC text for the reference product Solian approved in the UK and is therefore satisfactory.

2. DOSE & DOSE SCHEDULE

The submitted text for section 4.2 of the SPC is identical to that of the reference product Solian approved in the UK and is therefore satisfactory.

3. CLINICAL PHARMACOLOGY

Amisulpride binds selectively with a high affinity to human dopaminergic D_2/D_3 receptor subtypes. It no affinity for D_1, D_4 and D_5 receptor subtypes or serotonin, ∝-adrenergic, histamine H_1 and cholinergic receptors.

BIOEQUIVALENCE

Two bioequivalence studies are presented. The clinical expert justifies the applicability of the bioequivalence studies performed on the 200mg and 400mg

strengths to the 50mg and 100mg products. In particular Fig 2 illustrates linearity of kinetics up to 1200mg daily and the 50mg, 100mg and 200mg products are pharmaceutical scale ups. Differences for the 400mg dosage form necessitate an additional study for this strength.

STUDY V.21-4

In this comparative, randomised, two-way, two-period, single dose crossover study, 36 healthy fasted male volunteers received a single 400mg tablet orally of either the applicant's test product or the reference product Solian. Serum drug levels of amisulpride were followed for 72 hours following dosing and the schedule was appropriate for accurate determination of AUCinf and Cmax. The washout period of 14 days between phases was sufficiently long. The randomisation scheme was balanced for sequence and appears random.

Log-transformed data for AUCt, AUCinf and Cmax were analysed by ANOVA.

RESULTS

There was one major protocol violator – a subject who withdrew after the first period due to an oculogyric crisis. This individual was excluded from the analysis. There were no sequence or period effects. Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

AUCt	**1.00 (0.94 – 1.06)**
AUCinf	**0.99 (0.93 – 1.05)**
Cmax	**1.10 (0.95 – 1.28)**

Tmax was 3.5 hrs for both products

ASSESSOR'S COMMENT

Bioequivalence for the 400mg product has been satisfactorily demonstrated in accordance with CPMP criteria. A wider acceptance range than the standard 80-125% (which is only just missed) is acceptable for Cmax. The slightly higher estimated Cmax is not considered clinically relevant.

STUDY V.21-3

In this comparative, randomised, two-way, two-period, single dose crossover study, 36 healthy fasted male volunteers received a single 200mg tablet orally of either the applicant's test product or the reference product Solian. Serum drug levels of amisulpride were followed for 72 hours following dosing and the schedule was appropriate for accurate determination of AUCinf and Cmax. The washout period of 14 days between phases was sufficiently long. The randomisation scheme was balanced for sequence and appears random.
Log-transformed data for AUCt, AUCinf and Cmax were analysed by ANOVA.

RESULTS

There no major protocol violators and no sequence or period effects. Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

AUCt	**1.10 (1.05 – 1.15)**
AUCinf	**1.10 (1.05 – 1.15)**
Cmax	**1.20 (1.09 – 1.32)**

Tmax was 4.5 hrs for test product, 3.5 hrs reference

The individual patient data are generally reassuring, showing mostly good superimposability of the plots. It is notable that in a number of cases the peaks for Solian are significantly attenuated relative to the test product but after 6 hours little difference is apparent.

ASSESSOR'S COMMENT

Bioequivalence has been satisfactorily demonstrated in accordance with CPMP criteria despite the demonstrated slight superavailbility of the test product. The wider acceptance range for Cmax (75-133%) was pre-defined in the protocol. It is acceptable for this drug and the slightly higher estimated Cmax is not considered clinically relevant.

4. EFFICACY

No new data on the efficacy of amisulpride are submitted and none are required for this type of application.

5. SAFETY

No new data on the safety of amisulpride are submitted and none are required for this type of application. The single significant AE in the biostudies (an oculogyric crisis) is well known.

6. EXPERT REPORTS

A satisfactory expert report is provided. It includes a review of the bioequivalence studies

7. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is mostly identical to the SPC for the reference product Solian approved in the UK. Additionally it includes a warning on withdrawal reactions.

> *Acute withdrawal symptoms including nausea, vomiting and insomnia have very rarely been 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 akathisa, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.*

This is satisfactory.

8. PATIENT INFORMATION LEAFLET (PIL)

A full colour mock-up is provided. The PIL is well written and is satisfactory.

9. LABELLING

The labelling is medically satisfactory.

10. APPLICATION FORM (MAA)

The MAA is medically satisfactory.

11. DISCUSSION

Bioequivalence to the claimed essentially similar product has been demonstrated.

The SPC is mostly identical to the SPC for the reference product Solian approved in the UK except for an additional warning on withdrawal reactions. It is satisfactory. The rest of the product literature including PIL and labelling are satisfactory.

12. MEDICAL CONCLUSION

Marketing authorisations may be granted for these products.

OVERALL CONCLUSION AND RISK/BENEFIT ANALYSIS

Quality
The quality characteristics of Amisuldpride are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch and the product was found to be essentially similar to the reference product. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

Preclinical
No new preclinical data were submitted and none are required for applications of this type.

Efficacy
No new efficacy data for Amisulpride were submitted and none are required for this type of application. Bioequivalency with the reference product Solian was established.

Risk Benefit Assessment
The quality of the product is acceptable and the product is essentially similar to the reference product. Amisulpride 50mg, 100mg, 200 mg and 400mg Tablets have a positive risk/benefit assessment.

STEPS TAKEN DURING ASSESSMENT

1	The MHRA received the application on 3rd October 2003..
2	Following initial assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 11th February2004, 20th December 2004.
3	The applicant provided further information in regard to the quality assessment on 7th February 2006.
4	The application was determined on 21st April 2006.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Amisulpride 50mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Amisulpride 50 mg per tablet

3. PHARMACEUTICAL FORM

Tablet

White round shaped tablet embossed “AS 50” on one side and a score-line on the reverse.

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/d and 800 mg/d are recommended. In individual cases, the daily dose may be increased up to 1200 mg/d. Doses above 1200 mg/d 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/d and 300 mg/d 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 bid.

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

Children : Amisulpride is contra-indicated in children under 15 years of age 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 (see 4.4 Special warning and precautions for use).

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 drug
Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer
Phaeochromocytoma
Children under 15 years of age
Pregnancy or lactation
Women of childbearing potential unless using adequate contraception
Combination with the following medications which could induce torsades de pointes:
- Class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide
- Class III antiarrhythmic agents such as amiodarone, sotalol.
- Others medications such as bepridil, cisapride, sultopride, thioridazine, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin.

This list is not exhaustive.
Combination with levodopa
(see 4.5 Interactions with other medical products and other forms of interaction)

4.4. Special warnings and special precautions for use

As with other neuroleptics, Neuroleptic Malignant Syndrome, 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 drugs including Amisulpride should be discontinued.

Amisulpride is eliminated by the renal route. In cases of severe 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 Amisulpride therapy.

In elderly patients, Amisulpride, like other neuroleptics, should be used with particular caution because of a possible risk of hypotension or sedation.

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.

Acute withdrawal symptoms including nausea, vomiting and insomnia have very rarely been 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 akathisa, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

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.
Hypokalaemia should be corrected.
Before any administration, and if possible according to the patient's clinical status, it is recommended to monitor factors which could favour the occurrence of this rhythm disorder: - 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 (see 4.5 Interaction with other medicinal products and other forms of interaction).

4.5. Interactions with other medicinal products and other forms of interaction

COMBINATIONS WHICH ARE CONTRAINDICATED

Medications which could induce torsades de pointes:
- Class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide.
- Class III antiarrhythmic agents such as amiodarone, sotalol.
- Others medications such as bepridil, cisapride, sultopride, thioridazine, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin.

This list is not exhaustive.
Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics.

COMBINATIONS WHICH ARE NOT RECOMMENDED

Amisulpride may enhance the central effects of alcohol.

COMBINATIONS WHICH REQUIRE PRECAUTIONS FOR USE
Medications which enhance the risk of torsades de pointes:
- Bradycardia-inducing medications such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine, guanfacine; digitalis.
- Medications which induce hypokalaemia: hypokalemic diuretics, stimulant laxatives, IV amphotericin B , glucocorticoids, tetracosactides.
- Neuroleptics such as pimozide, haloperidol; imipramine antidepressants; lithium

COMBINATIONS TO BE TAKEN INTO ACCOUNT

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

Antihypertensive drugs and other hypotensive medications

Dopamine agonists (eg: levodopa) since it may attenuate their action

4.6. Pregnancy and lactation

Pregnancy

In animals, Amisulpride did not show 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 contraindicated during pregnancy and in women of child bearing potential unless using adequate contraception.

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.

As 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 torticolis, 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 50-300mg/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.

Hypotension and bradycardia have been reported occasionally. Cases of QT prolongation and very rare cases of torsades de pointes have been reported.

Acute withdrawal reactions have very rarely been reported (see Section 4.4).

Allergic reactions, elevations of hepatic enzymes, mainly transaminases and cases of seizures have been very rarely reported.

Very rare cases of Neuroleptic Malignant Syndrome have been reported (see 4.4 Special warnings and 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, 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 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
ATC Code: NO5A LO5

Amisulpride binds selectively with a high affinity to human dopaminergic D_2/D_3 receptor subtypes whereas it is devoid of affinity for D_1, D_4 and D_5 receptor subtypes.

Unlike classical and atypical neuroleptics, amisulpride has no affinity for serotonin,

∝-adrenergic, histamine H_1 and cholinergic receptors. In addition, amisulpride does not bind to sigma sites.

In animal studies, at high doses, amisulpride blocks dopamine receptors located in the limbic structures in preference to those in the striatum. At low doses it preferentially blocks pre-synaptic D_2/D_3 receptors, producing dopamine release responsible for its disinhibitory effects.

This pharmacological profile explains the clinical efficacy of Amisulpride against both negative and positive symptoms of schizophrenia.

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 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. 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, 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 chapter 4.2). 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 Cmax, T1/2 and AUC after a single oral dose of 50mg. No data 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, Silica colloidal hydrated, magnesium stearate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

No special precautions for storage.

6.5. Nature and content of container

250µmPVC/20µm hard temper aluminium foil blister packs containing 30, 60 and 150 tablets

Not all pack sizes may be marketed.

6.6. Instructions for use, handling (,and disposal)

No special precautions

7. MARKETING AUTHORISATION HOLDER

Focus Pharmaceuticals Limited
Unit 5, Faraday Court
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Centrum 100
Burton upon Trent
Staffs, DE14 2WX
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 20046/0013

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/04/2006

10 DATE OF REVISION OF THE TEXT

21/04/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Amisulpride 100mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Amisulpride 100 mg per tablet

3. PHARMACEUTICAL FORM

Tablet

White round shaped tablet embossed “AS 100” on one side and a break-line on the reverse.

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/d and 800 mg/d are recommended. In individual cases, the daily dose may be increased up to 1200 mg/d. Doses above 1200 mg/d 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/d and 300 mg/d 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 bid.

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

Children : Amisulpride is contra-indicated in children under 15 years of age 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 (see 4.4 Special warnings and special precautions for use)

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 drug

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

Phaeochromocytoma

Children under 15 years of age

Pregnancy and lactation

Women of childbearing potential unless using adequate contraception.

Combination with the following medications which could induce torsades de pointes:
- Class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide.
- Class III antiarrhythmic agents such as amiodarone, sotalol.
- Others medications such as bepridil, cisapride, sultopride, thioridazine, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin.

This list is not exhaustive.
Combination with levodopa
(see 4.5 Interactions with other medical products and other forms of interaction)

4.4. Special warnings and special precautions for use

As with other neuroleptics, Neuroleptic Malignant Syndrome, 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 drugs including Amisulpride should be discontinued.

Amisulpride is eliminated by the renal route. In cases of severe 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 Amisulpride therapy.
In elderly patients, Amisulpride, like other neuroleptics, should be used with particular caution because of a possible risk of hypotension or sedation.

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.

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.
Hypokalaemia should be corrected.
Before any administration, and if possible according to the patient's clinical status, it is recommended to monitor factors which could favour the occurrence of this rhythm disorder:

- 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 (see 4.5 Interaction with other medicinal products and other forms of interaction).

4.5. Interactions with other medicinal products and other forms of interaction

COMBINATIONS WHICH ARE CONTRAINDICATED

Medications which could induce torsades de pointes:
- Class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide.
- Class III antiarrhythmic agents such as amiodarone, sotalol.
- Others medications such as bepridil, cisapride, sultopride, thioridazine, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin.

This list is not exhaustive.
Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics.

COMBINATIONS WHICH ARE NOT RECOMMENDED

Amisulpride may enhance the central effects of alcohol.

COMBINATIONS WHICH REQUIRE PRECAUTIONS FOR USE
Medications which enhance the risk of torsades de pointes:
- Bradycardia-inducing medications such as beta-blockers, bradycardia--inducing calcium channel blockers such as diltiazem and verapamil, clonidine, guanfacine ; digitalis.
- Medications which induce hypokalaemia : hypokalemic diuretics, stimulant laxatives, IV amphotericin B , glucocorticoids, tetracosactides.
- Neuroleptics such as pimozide, haloperidol; impipramine antidepressants; lithium

COMBINATIONS TO BE TAKEN INTO ACCOUNT

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

antihypertensive drugs and other hypotensive medications

dopamine agonists (eg : levodopa) since it may attenuate their action.

4.6. Pregnancy and lactation

Pregnancy

In animals, Amisulpride did not show 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 contraindicated during pregnancy and in women of child bearing potential unless using adequate contraception.

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.

As 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 torticolis, 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 50-300mg/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.

Hypotension and bradycardia have been reported occasionally. Cases of QT prolongation and very rare cases of torsades de point have been reported.

Allergic reactions, elevations of hepatic enzymes, mainly transaminases and cases of seizures have been very rarely reported.

Very rare cases of Neuroleptic Malignant Syndrome have been reported (see 4.4 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 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. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics
ATC Code: NO5A LO5

Amisulpride binds selectively with a high affinity to human dopaminergic D_2/D_3 receptor subtypes whereas it is devoid of affinity for D_1, D_4 and D_5 receptor subtypes.

Unlike classical and atypical neuroleptics, amisulpride has no affinity for serotonin,
$\propto$-adrenergic, histamine H_1 and cholinergic receptors. In addition, amisulpride does not bind to sigma sites.

In animal studies, at high doses, amisulpride blocks dopamine receptors located in the limbic structures in preference to those in the striatum.

At low doses it preferentially blocks pre-synaptic D_2/D_3 receptors, producing dopamine release responsible for its disinhibitory effects.

This pharmacological profile explains the clinical efficacy of Amisulpride against both negative and positive symptoms of schizophrenia.

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 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. 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, 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 chapter 4.2). 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 Cmax, T1/2 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, Silica ,colloidal hydrated, magnesium stearate.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years

6.4. Special precautions for storage

No special precautions for storage.

6.5. Nature and content of container

250µmPVC/20µm hard temper aluminium foil blister packs containing 30, 60 or 150 tablets

Not all pack sizes may be marketed.

6.6. Instructions for use, handling (,and disposal)

No special precautions

7. MARKETING AUTHORISATION HOLDER

Focus Pharmaceuticals Limited
Unit 5, Faraday Court
First Avenue
Centrum 100
Burton upon Trent
Staffs, DE14 2WX
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 20046/0014

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/04/2006

10 DATE OF REVISION OF THE TEXT

21/04/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Amisulpride 200mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Amisulpride 200mg per tablet

3. PHARMACEUTICAL FORM

Tablet

White round shaped tablet embossed “AS 200” on one side and a break-line on the reverse.

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/d and 800 mg/d are recommended. In individual cases, the daily dose may be increased up to 1200 mg/d. Doses above 1200 mg/d 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/d and 300 mg/d 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 bid.

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

Children : Amisulpride is contra-indicated in children under 15 years of age 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. (see 4.4 Special warning and special precautions for use)

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 drug
Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer
Phaeochromocytoma
Children under 15 years of age
Pregnancy or lactation
Women of childbearing potential unless using adequate contraception
Combination with the following medications which could induce torsades de pointes:
- Class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide
- Class III antiarrhythmic agents such as amiodarone, sotalol.
- Others medications such as bepridil, cisapride, sultopride, thioridazine, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin.

This list is not exhaustive.
Combination with levodopa
(see 4.5 Interactions with other medical products and other forms of interaction)

4.4. Special warnings and special precautions for use

As with other neuroleptics, Neuroleptic Malignant Syndrome, 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 drugs including Amisulpride should be discontinued.

Amisulpride is eliminated by the renal route. In cases of severe 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 Amisulpride therapy.

In elderly patients, Amisulpride, like other neuroleptics, should be used with particular caution because of a possible risk of hypotension or sedation.

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.
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.
Hypokalaemia should be corrected.
Before any administration, and if possible according to the patient's clinical status, it is recommended to monitor factors which could favour the occurrence of this rhythm disorder:

- 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 (see 4.5 Interaction with other medicinal products and other forms of interaction).

4.5. Interactions with other medicinal products and other forms of interaction

COMBINATIONS WHICH ARE CONTRAINDICATED

Medications which could induce torsades de pointes:
- Class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide.
- Class III antiarrhythmic agents such as amiodarone, sotalol.

- Others medications such as bepridil, cisapride, sultopride, thioridazine, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin.

This list is not exhaustive.
Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics.

COMBINATIONS WHICH ARE NOT RECOMMENDED

Amisulpride may enhance the central effects of alcohol.

COMBINATIONS WHICH REQUIRE PRECAUTIONS FOR USE
Medications which enhance the risk of torsades de pointes:
- Bradycardia-inducing medications such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine, guanfacine; digitalis.
- Medications which induce hypokalaemia: hypokalemic diuretics, stimulant laxatives, IV amphotericin B , glucocorticoids, tetracosactides.
- Neuroleptics such as pimozide, haloperidol; imipramine antidepressants; lithium

COMBINATIONS TO BE TAKEN INTO ACCOUNT

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

Antihypertensive drugs and other hypotensive medications

Dopamine agonists (eg: levodopa) since it may attenuate their action

4.6. Pregnancy and lactation

Pregnancy

In animals, Amisulpride did not show 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 contraindicated during pregnancy and in women of child bearing potential unless using adequate contraception.

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.

As 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 torticolis, 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 50-300mg/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.

Hypotension and bradycardia have been reported occasionally. Cases of QT prolongation and very rare cases of torsades de pointes have been reported.

Allergic reactions, elevations of hepatic enzymes, mainly transaminases and cases of seizures have been very rarely reported.

Very rare cases of Neuroleptic Malignant Syndrome have been reported (see 4.4 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, 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. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics
ATC Code: NO5A LO5

Amisulpride binds selectively with a high affinity to human dopaminergic D_2/D_3 receptor subtypes whereas it is devoid of affinity for D_1, D_4 and D_5 receptor subtypes.

Unlike classical and atypical neuroleptics, amisulpride has no affinity for serotonin,
$\propto$-adrenergic, histamine H_1 and cholinergic receptors. In addition, amisulpride does not bind to sigma sites.

In animal studies, at high doses, amisulpride blocks dopamine receptors located in the limbic structures in preference to those in the striatum.
At low doses it preferentially blocks pre-synaptic D_2/D_3 receptors, producing dopamine release responsible for its disinhibitory effects.

This pharmacological profile explains the clinical efficacy of Amisulpride against both negative and positive symptoms of schizophrenia.

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 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. 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). 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 Cmax, $T_{½}$ 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, Silica colloidal hydrated, magnesium stearate.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years

6.4. Special precautions for storage

No special precautions for storage.

6.5. Nature and content of container

250µmPVC/20µm hard temper aluminium foil blister packs containing 60 or 150 tablets.

Not all pack sizes may be marketed.

6.6. Instructions for use, handling (,and disposal)

No special precautions

7. MARKETING AUTHORISATION HOLDER

Focus Pharmaceuticals Limited
Unit 5, Faraday Court
First Avenue
Centrum 100
Burton upon Trent
Staffs, DE14 2WX
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 20046/0015

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/04/2006

10 DATE OF REVISION OF THE TEXT

21/04/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Amisulpride 400mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Amisulpride 400 mg per tablet

3. PHARMACEUTICAL FORM

Film Coated Tablet

White film coated capsule shaped tablet embossed “AS 400”on one side and a break-line on the reverse.

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/d and 800 mg/d are recommended. In individual cases, the daily dose may be increased up to 1200 mg/d. Doses above 1200 mg/d 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/d and 300 mg/d 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 bid.

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

Children : Amisulpride is contra-indicated in children under 15 years of age 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 (see 4.4 Special warning and precautions for use).

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 drug
Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer
Phaeochromocytoma
Children under 15 years of age
Pregnancy or lactation
Women of childbearing potential unless using adequate contraception
Combination with the following medications which could induce torsades de pointes:
- Class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide
- Class III antiarrhythmic agents such as amiodarone, sotalol.
- Others medications such as bepridil, cisapride, sultopride, thioridazine, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin.

This list is not exhaustive.
Combination with levodopa
(see 4.5 Interactions with other medical products and other forms of interaction)

4.4. Special warnings and special precautions for use

As with other neuroleptics, Neuroleptic Malignant Syndrome, 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 drugs including Amisulpride should be discontinued.

Amisulpride is eliminated by the renal route. In cases of severe 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 Amisulpride therapy.
In elderly patients, Amisulpride, like other neuroleptics, should be used with particular caution because of a possible risk of hypotension or sedation.

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.

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.

Hypokalaemia should be corrected.
Before any administration, and if possible according to the patient's clinical

status, it is recommended to monitor factors which could favour the

occurrence of this rhythm disorder:

- 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 (see 4.5 Interaction with other medicinal products and other forms of interaction).

4.5. Interactions with other medicinal products and other forms of interaction

COMBINATIONS WHICH ARE CONTRAINDICATED

Medications which could induce torsades de pointes:

- Class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide.
- Class III antiarrhythmic agents such as amiodarone, sotalol.
- Others medications such as bepridil, cisapride, sultopride, thioridazine, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin.

This list is not exhaustive.
Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics.

COMBINATIONS WHICH ARE NOT RECOMMENDED

Amisulpride may enhance the central effects of alcohol.

COMBINATIONS WHICH REQUIRE PRECAUTIONS FOR USE
Medications which enhance the risk of torsades de pointes:
- Bradycardia-inducing medications such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine, guanfacine; digitalis.
- Medications which induce hypokalaemia: hypokalemic diuretics, stimulant laxatives, IV amphotericin B , glucocorticoids, tetracosactides.
- Neuroleptics such as pimozide, haloperidol; imipramine antidepressants; lithium

COMBINATIONS TO BE TAKEN INTO ACCOUNT

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

Antihypertensive drugs and other hypotensive medications

Dopamine agonists (eg: levodopa) since it may attenuate their action

4.6. Pregnancy and lactation

Pregnancy

In animals, Amisulpride did not show 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 contraindicated during pregnancy and in women of child bearing potential unless using adequate contraception.

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.

As 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 torticolis, 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 50-300mg/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.

Hypotension and bradycardia have been reported occasionally. Case of QT prolongation and very rare cases of torsades de pointes have been reported.

Allergic reactions, elevations of hepatic enzymes, mainly transaminases and cases of seizures have been very rarely reported occasionally.

Very rare cases of Neuroleptic Malignant Syndrome have been reported (see 4.4 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, 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. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics
ATC Code: NO5A LO5

Amisulpride binds selectively with a high affinity to human dopaminergic D_2/D_3 receptor subtypes whereas it is devoid of affinity for D_1, D_4 and D_5 receptor subtypes.

Unlike classical and atypical neuroleptics, amisulpride has no affinity for serotonin,
$\propto$-adrenergic, histamine H_1 and cholinergic receptors. In addition, amisulpride does not bind to sigma sites.

In animal studies, at high doses, amisulpride blocks dopamine receptors located in the limbic structures in preference to those in the striatum.

At low doses it preferentially blocks pre-synaptic D_2/D_3 receptors, producing dopamine release responsible for its disinhibitory effects.

This pharmacological profile explains the clinical efficacy of Amisulpride against both negative and positive symptoms of schizophrenia.

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 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. 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, 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 chapter 4.2). 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 Cmax, T1/2 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

Lactose Monohydrate
Cellulose microcrystalline
Sodium Starch Glycolate (Type A)
Hypromellose
Magnesium Stearate

Film Coating:

Titanium Dioxide (E171)
Hypromellose 5cP (E464)
Polyethylene glycol 400

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years

6.4. Special precautions for storage

No special precautions.

6.5. Nature and content of container

250µmPVC/20µm hard temper aluminium foil blister packs containing 30, 60 or 150 tablets

Not all pack sizes may be marketed.

6.6. Instructions for use, handling (,and disposal)

No special precautions

7. MARKETING AUTHORISATION HOLDER

Focus Pharmaceuticals Limited
Unit 5, Faraday Court
First Avenue
Centrum 100
Burton upon Trent
Staffs, DE14 2WX
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 20046/0016

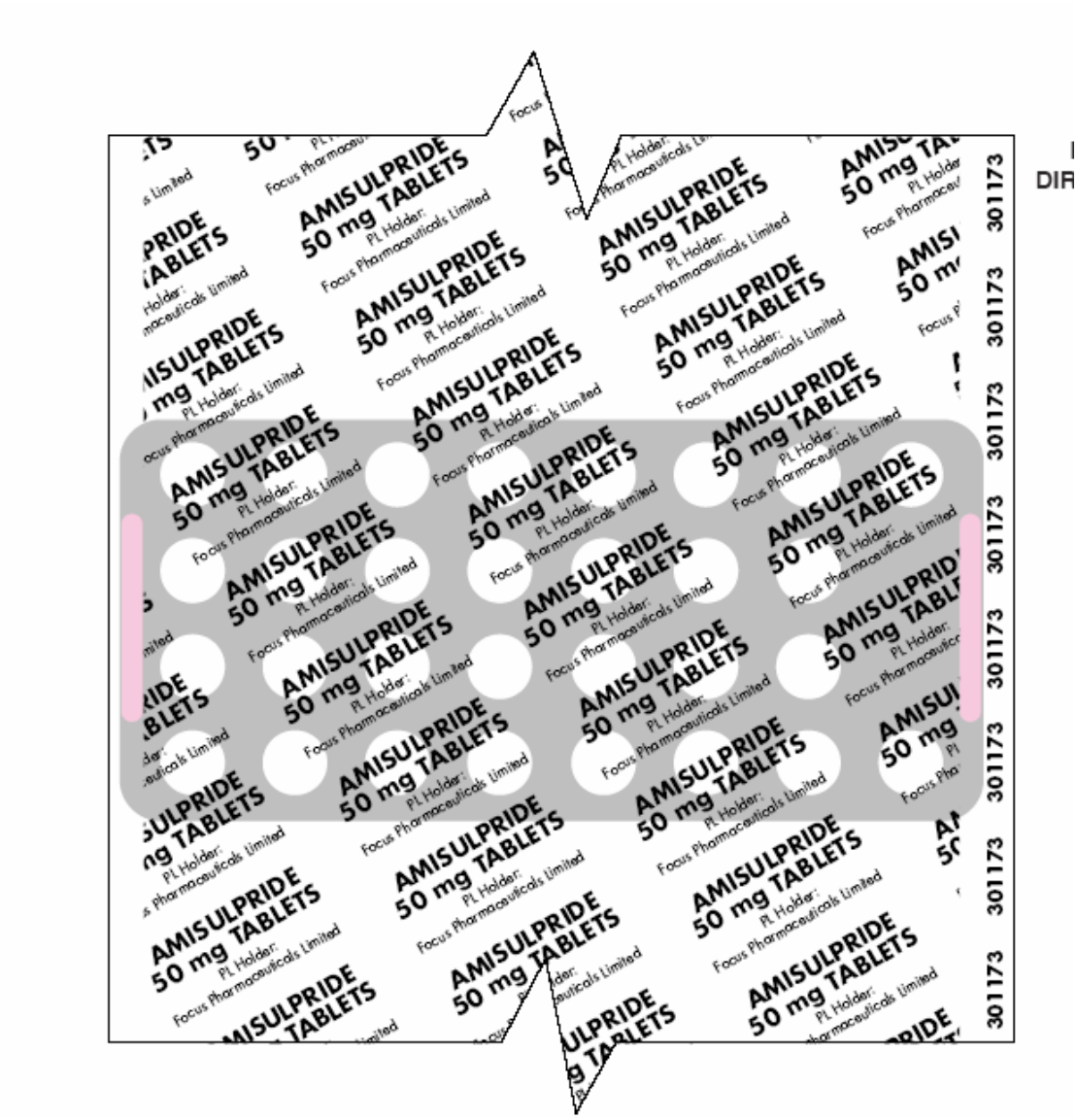
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

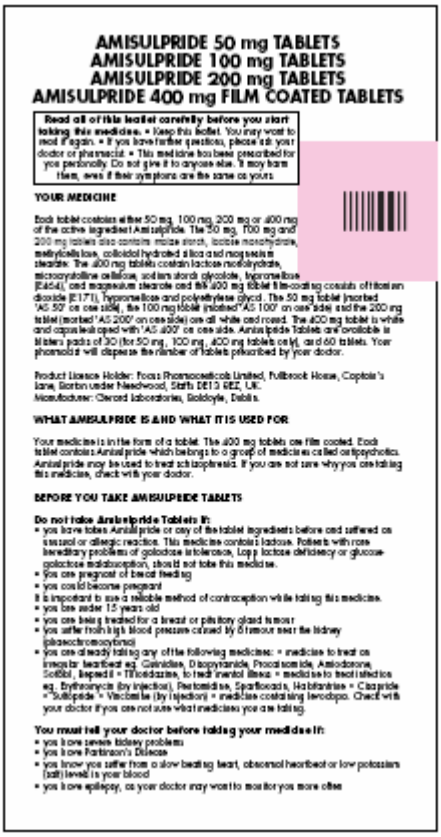
21/04/2006

10 DATE OF REVISION OF THE TEXT

21/04/2006

LABELS AND LEAFLETS


AMISULPRIDE
50 mg TABLETS
PL Holder:
Focus Pharmaceuticals Limited
301173



AMISULPRIDE 50 mg TABLETS
AMISULPRIDE 100 mg TABLETS
AMISULPRIDE 200 mg TABLETS
AMISULPRIDE 400 mg FILM COATED TABLETS

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Product Licence Holder: Focus Pharmaceuticals Limited, Fullbrook House, Copthale's lane, Borrton under Needwood, Staffs DE13 8EZ, UK.
Manufacturer: Clerard Laboratories, Baldoyle, Dublin.

WHAT AMISULPRIDE IS AND WHAT IT IS USED FOR

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- You are pregnant or breast feeding
- you could become pregnant
It is important to use a reliable method of contraception while taking this medicine.
- you are under 15 years old
- you are being treated for a breast or pituitary gland tumour
- you suffer from high blood pressure caused by a tumour near the kidney (phaeochromocytoma)
- you are already taking any of the following medicines: • medicine to treat an irregular heartbeat eg. Quinidine, Disopyramide, Procainamide, Amiodarone, Sotalol, Bepridil • Thioridazine, to treat mental illness • medicine to treat infection eg. Erythromycin (by injection), Pentamidine, Sparfloxacin, Mefloquine • Cisapride • Sultopride • Vincamine (by injection) • medicine containing levodopa. Check with your doctor if you are not sure what medicines you are taking.

You must tell your doctor before taking your medicine if:
- you have severe kidney problems
- you have Parkinson's Disease
- you know you suffer from a slow beating heart, abnormal heartbeat or low potassium (salt) level in your blood
- you have epilepsy, as your doctor may want to monitor you more often
- you are already taking any of the following medicines: • medicine to treat a heart condition or lower blood pressure eg. Atenolol, Diltiazem, Verapamil, Clonidine, Digoxin, Clearfadine • diuretics ("water" tablets) eg. Furosemide • laxatives eg. Senna • steroids such as Prednisolone • Tetracosactide • Amphotericin B (by injection), to treat infection • other medicine to treat mental illness eg. Pimozide, Haloperidol, Lithium • antidepressants eg. Imipramine • strong painkillers • sedative medicine eg. Benzodiazepines, antihistamines(eg • medicine to treat Parkinson's Disease
- you are going to have surgery and will need a general anaesthetic

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HOW TO TAKE AMISULPRIDE TABLETS

The dose of Amisulpride your doctor gives you will depend on the type of symptoms you are having. Patients can suffer from a mixture of "positive symptoms" (eg. hallucinations, delusions, thought disorder) and "negative symptoms" (eg. depression, lethargy, poor speech).

ADULTS - The usual dose is between 400 mg and 800 mg of Amisulpride a day, divided into two doses. Your doctor may increase this dose to help improve your symptoms, up to 1200 mg of Amisulpride in some cases. If you are mostly suffering from "negative symptoms" your doctor will give you a lower dose of between 50 mg and 300 mg of Amisulpride a day, taken as a single dose. He/she will adjust your dose to best treat the symptoms.

ELDERLY - Elderly patients are more sensitive to the effects of Amisulpride and will be given lower doses.

Patients with kidney disease will be given lower or less frequent doses depending on the severity of the disease.

CHILDREN - Amisulpride Tablets should not be given to children under 15 years.

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POSSIBLE SIDE EFFECTS

Amisulpride Tablets are usually well tolerated and side effects from taking these tablets are uncommon. Common side effects, occurring in 5-10% of patients, include difficulty sleeping, feeling anxious and agitated. Less common side effects, occurring in 0.1-5% of patients, include sleepiness, constipation, feeling or being sick, weight gain and a dry mouth. Other effects include swelling or leaking of milk from the breasts, breast pain, upset of menstrual cycle, impotence, loss of sexual function and uncontrollable movements. These effects go away on stopping treatment. Sometimes patients have suffered from low blood pressure or a slow beating heart, and rarely, allergic reactions, raised liver enzymes (shown in a blood test) and fits.

Tell your doctor if any of the following effects happen to you: • a racing heart beat, sweating, stiffening muscles and in some cases loss of consciousness • feeling anxious, tremor, dribbling and loss of muscle control • abnormal movements of the face and body (more likely in patients on long-term treatment). These effects are rare. You may need medical attention.

If you should suffer from any undesired effect please tell your pharmacist or doctor.

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Date of leaflet preparation: May 2003 301175


Amisulpride 100 mg Tablets
60 Tablets in blisters of 20
Generics [UK] Limited, Potters Bar, Herts.
100 mg
Amisulpride
100 mg Tablets
60 Tablets in blisters of 20
Generics [UK] Limited, Potters Bar, Herts.
Amisulpride 100 mg Tablets
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Generics [UK] Limited, Potters Bar, Herts.
Amisulpride 100 mg Tablets
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Each tablet contains: 100 mg of the active ingredient Amisulpride.
Dosage: For oral use as directed by the doctor. For further information see leaflet enclosed.
Keep out of the reach and sight of children.
There are no special storage instructions.
PL 20046/0014 POM 301325
Product licence holder: Focus Pharmaceuticals Ltd., Staffs DE13 8EZ, United Kingdom.
Distributed by: Generics [UK] Limited, Potters Bar, Herts.
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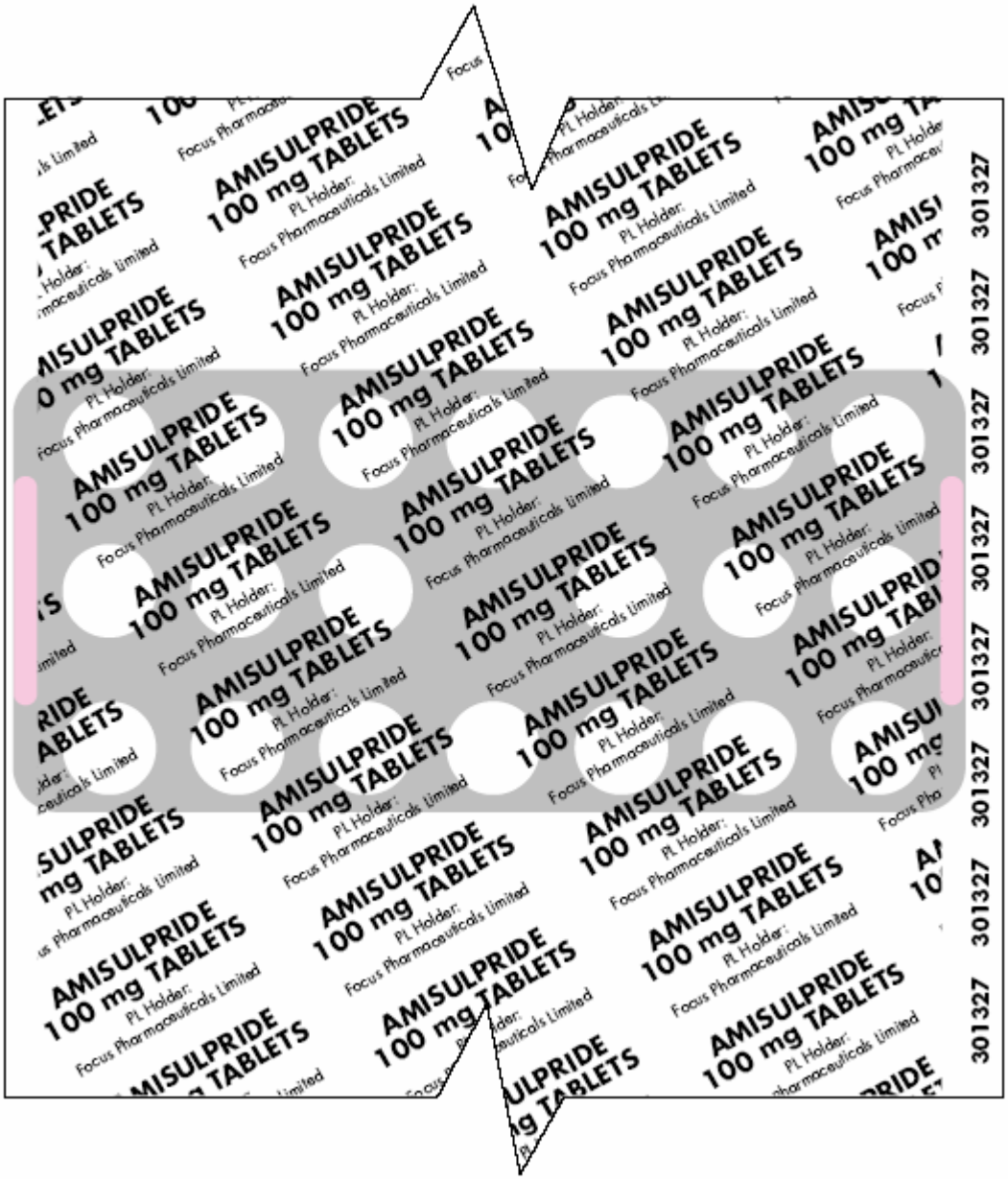
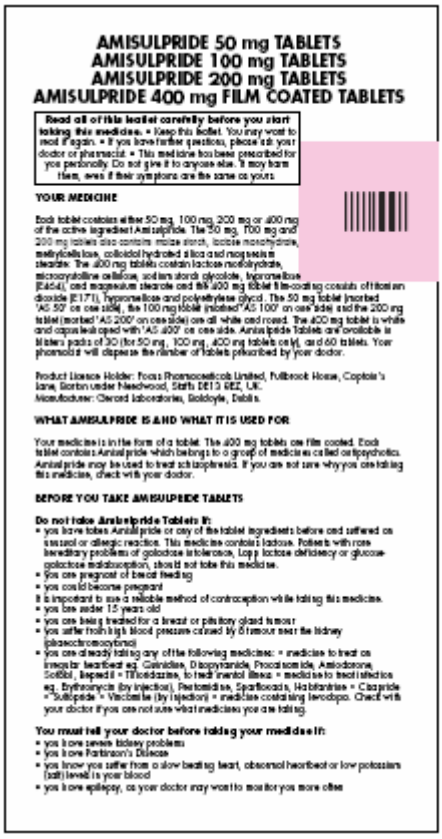
MERCK generics
Affix Dispensing Label Here
60 Tablets in blisters of 20
100 mg
Amisulpride 100 mg Tablets


AMISULPRIDE
100 mg TABLETS
PL Holder:
Focus Pharmaceuticals Limited
301327



AMISULPRIDE 50 mg TABLETS
AMISULPRIDE 100 mg TABLETS
AMISULPRIDE 200 mg TABLETS
AMISULPRIDE 400 mg FILM COATED TABLETS

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200 mg
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Keep out of the reach and sight of children.
There are no special storage instructions.
PL 20046/0015 PCM 301172
Product licence holder: Focus Pharmaceuticals Ltd, Staffs DE13 0RZ, United Kingdom.
Distributed by: Generics [UK] Limited, Potters Bar, Herts.
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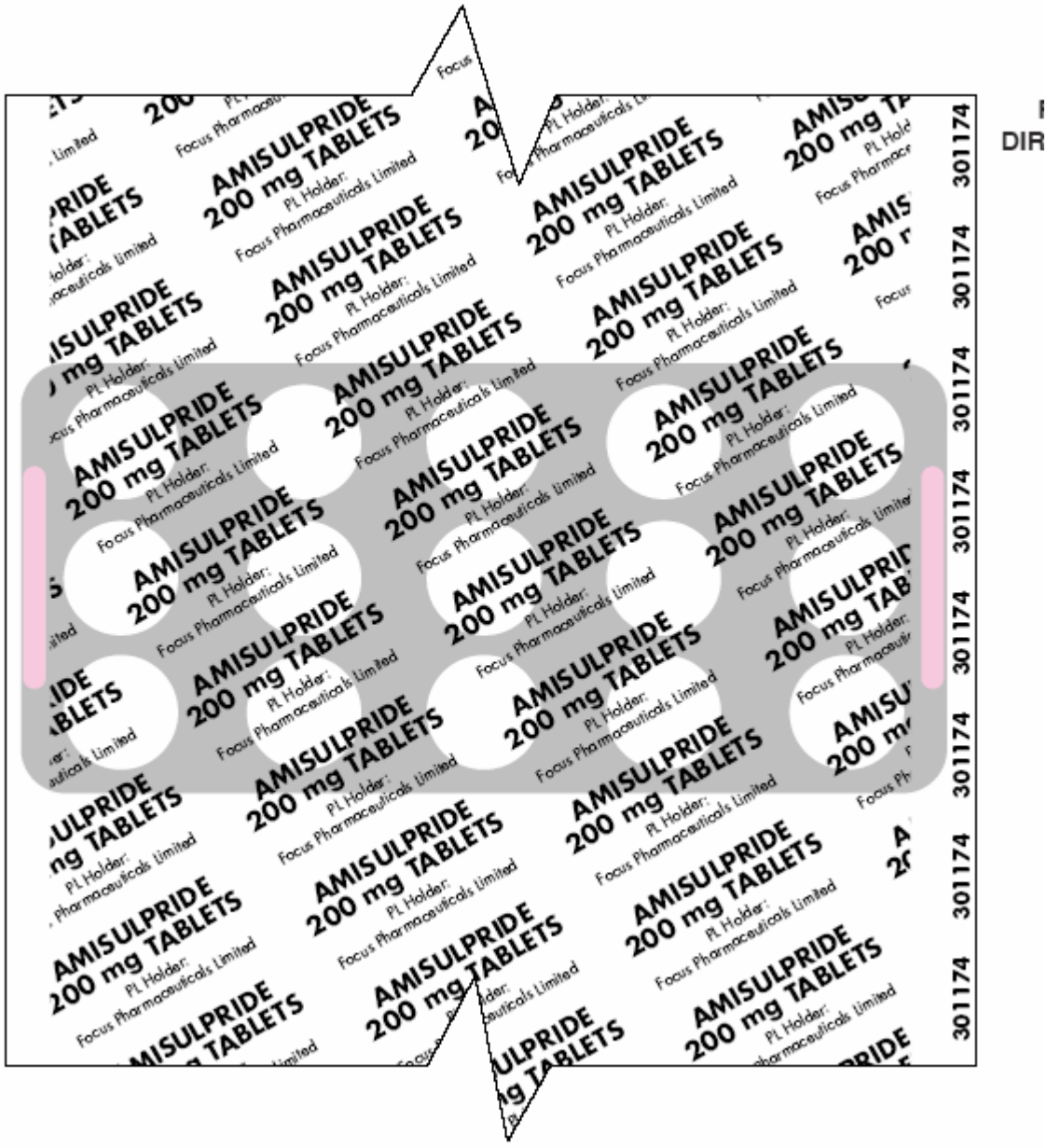
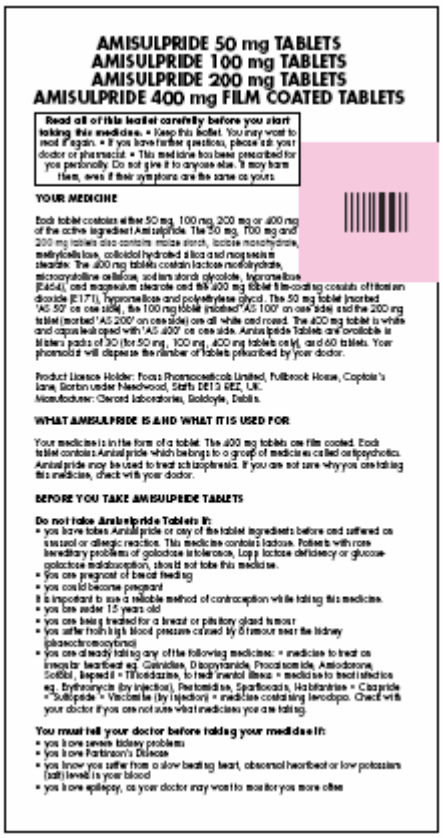
Affix Dispensing Label Here
60 Tablets in blisters of 15
Amisulpride
200 mg Tablets
200 mg


AMISULPRIDE
200 mg TABLETS
PL Holder:
Focus Pharmaceuticals Limited
301174



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AMISULPRIDE 200 mg TABLETS
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POSSIBLE SIDE EFFECTS

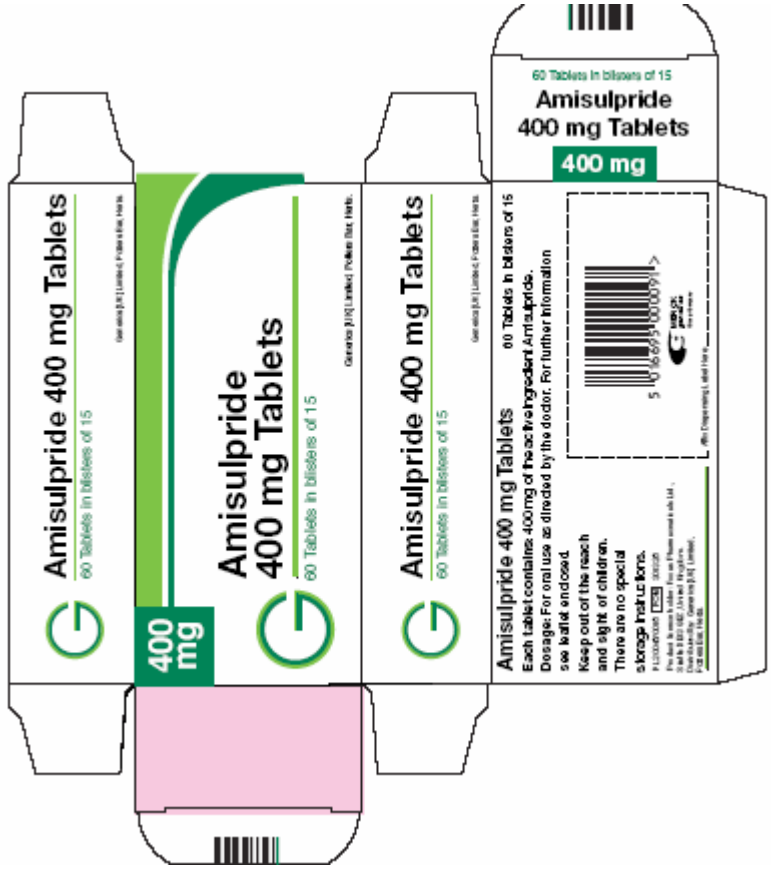
Amisulpride Tablets are usually well tolerated and side effects from taking these tablets are uncommon. Common side effects, occurring in 5-10% of patients, include difficulty sleeping, feeling anxious and agitated. Less common side effects, occurring in 0.1-5% of patients, include sleepiness, constipation, feeling or being sick, weight gain and a dry mouth. Other effects include swelling or leaking of milk from the breasts, breast pain, upset of menstrual cycle, impotence, loss of sexual function and uncontrollable movements. These effects go away on stopping treatment. Sometimes patients have suffered from low blood pressure or a slow beating heart, and rarely, allergic reactions, raised liver enzymes (shown in a blood test) and fits.

Tell your doctor if any of the following effects happen to you: • a racing heartbeat, sweating, stiffening muscles and in some cases loss of consciousness • feeling anxious, tremor, dribbling and loss of muscle control • abnormal movements of the face and body (more likely in patients on long-term treatment). These effects are rare. You may need medical attention.

If you should suffer from any undesired effect please tell your pharmacist or doctor.

DO NOT TAKE THIS MEDICINE AFTER THE EXPIRY DATE SHOWN ON THE CARTON. REMEMBER this medicine was prescribed by your doctor for you. **DO NOT** give it to others. It may harm them.

Date of leaflet preparation: May 2003 301175


Amisulpride 400 mg Tablets
60 Tablets in blisters of 15
400 mg
Amisulpride
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60 Tablets in blisters of 15
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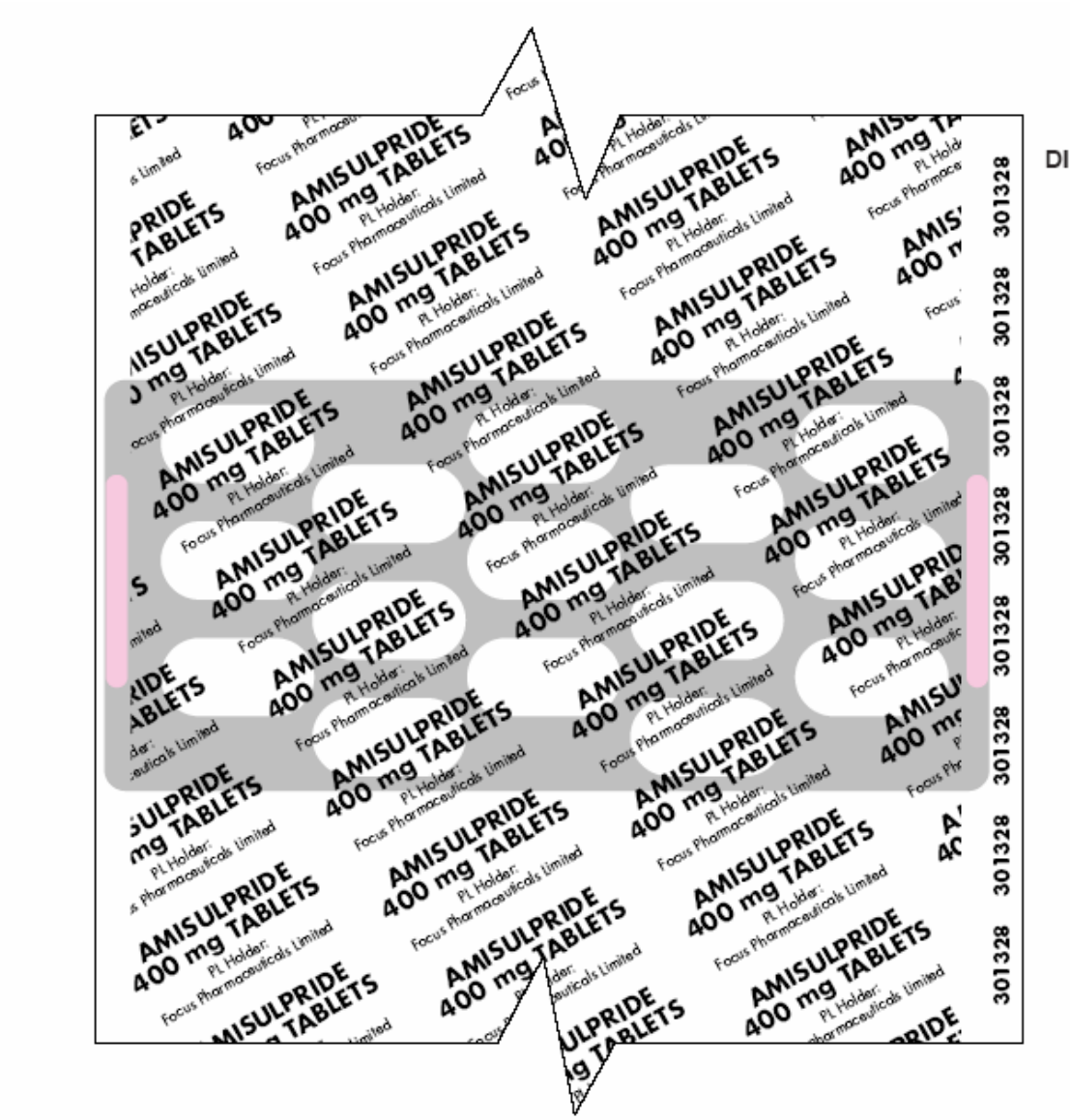
Amisulpride
400 mg Tablets
400 mg
Amisulpride 400 mg Tablets
60 Tablets in blisters of 15
Each tablet contains 400mg of the active ingredient Amisulpride.
Dosage: For oral use as directed by the doctor. For further information
see leaflet enclosed.
Keep out of the reach
and sight of children.
There are no special
storage instructions.


AMISULPRIDE
400 mg TABLETS
PL Holder:
Focus Pharmaceuticals Limited
301328

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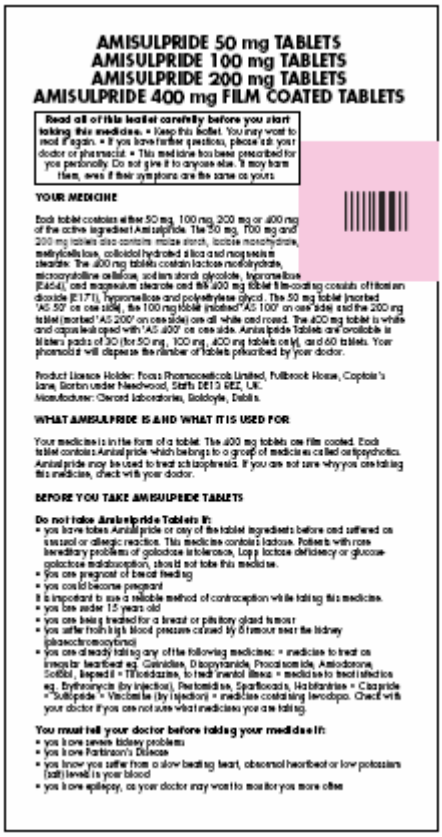


AMISULPRIDE 50 mg TABLETS
AMISULPRIDE 100 mg TABLETS
AMISULPRIDE 200 mg TABLETS
AMISULPRIDE 400 mg FILM COATED TABLETS

Read all of this leaflet carefully before you start taking this medicine. • Keep this leaflet. You may want to read it again. • If you have further questions, please ask your doctor or pharmacist. • This medicine has been prescribed for you personally. Do not give it to anyone else. It may harm them, even if their symptoms are the same as yours.

YOUR MEDICINE

Each tablet contains either 50 mg, 100 mg, 200 mg or 400 mg of the active ingredient Amisulpride. The 50 mg, 100 mg and 200 mg tablets also contain maize starch, sodium monohydrate, methylcellulose, colloidal hydrated silica and magnesium stearate. The 400 mg tablets contain lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, hypromellose (E464), and magnesium stearate and the 400 mg tablet film-coating consists of titanium dioxide (E171), hypromellose and polyethylene glycol. The 50 mg tablet (marked 'AS 50' on one side), the 100 mg tablet (marked 'AS 100' on one side) and the 200 mg tablet (marked 'AS 200' on one side) are all white and round. The 400 mg tablet is white and capsule-shaped with 'AS 400' on one side. Amisulpride Tablets are available in blister packs of 30 (for 50 mg, 100 mg, 400 mg tablets only), and 60 tablets. Your pharmacist will dispense the number of tablets prescribed by your doctor.

Product Licence Holder: Focus Pharmaceuticals Limited, Fullbrook House, Copthall's lane, Barton-under-Needwood, Staffs DE13 8BZ, UK.
Manufacturer: Clonard Laboratories, Baldoyle, Dublin.

WHAT AMISULPRIDE IS AND WHAT IT IS USED FOR

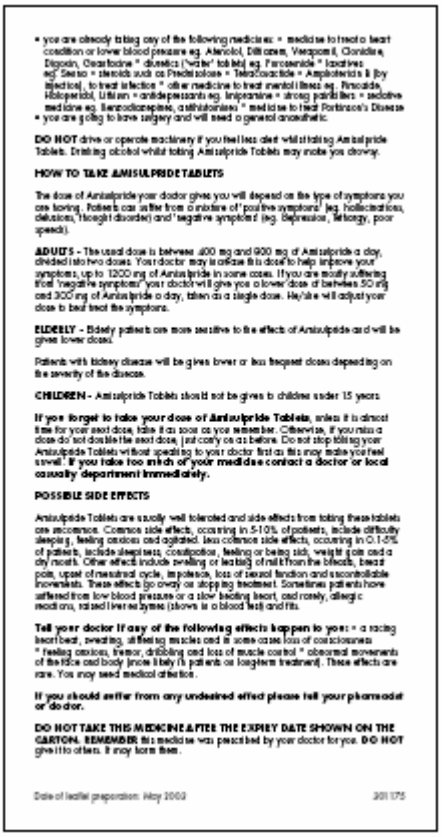
Your medicine is in the form of a tablet. The 400 mg tablets are film coated. Each tablet contains Amisulpride which belongs to a group of medicines called antipsychotics. Amisulpride may be used to treat schizophrenia. If you are not sure why you are taking this medicine, check with your doctor.

BEFORE YOU TAKE AMISULPRIDE TABLETS

Do not take Amisulpride Tablets if:
- you have taken Amisulpride or any of the tablet ingredients before and suffered an unusual or allergic reaction. This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption, should not take this medicine.
- You are pregnant or breast feeding
- you could become pregnant

It is important to use a reliable method of contraception while taking this medicine.
- you are under 15 years old
- you are being treated for a breast or pituitary gland tumour
- you suffer from high blood pressure caused by a tumour near the kidney (phaeochromocytoma)
- you are already taking any of the following medicines: • medicine to treat an irregular heartbeat eg. Cisapride, Disopyramide, Procainamide, Amiodarone, Sotalol, Bepridil • Thioridazine, to treat mental illness • medicine to treat infection eg. Erythromycin (by injection), Pentamidine, Sparfloxacin, Halofantrine • Cisapride • Sultopride • Vincamine (by injection) • medicines containing levodopa. Check with your doctor if you are not sure what medicines you are taking.

You must tell your doctor before taking your medicine if:
- you have severe kidney problems
- you have Parkinson's Disease
- you know you suffer from a slow beating heart, abnormal heartbeat or low potassium (salt) levels in your blood
- you have epilepsy, as your doctor may want to monitor you more often



- you are already taking any of the following medicines: • medicine to treat a heart condition or lower blood pressure eg. Atenolol, Diltiazem, Verapamil, Clonidine, Digoxin, Guanfacine • diuretics ("water" tablets) eg. Furosemide • laxatives eg. Senna • steroids such as Prednisolone • Tetracosactide • Amphotericin B (by injection), to treat infection • other medicine to treat mental illness eg. Pimozide, Haloperidol, Lithium • antidepressants eg. Imipramine • strong painkillers • sedative medicine eg. Benzodiazepines, antihistamines • medicine to treat Parkinson's Disease
- you are going to have surgery and will need a general anaesthetic.

DO NOT drive or operate machinery if you feel less alert whilst taking Amisulpride Tablets. Drinking alcohol whilst taking Amisulpride Tablets may make you drowsy.

HOW TO TAKE AMISULPRIDE TABLETS

The dose of Amisulpride your doctor gives you will depend on the type of symptoms you are having. Patients can suffer from a mixture of "positive symptoms" (eg. hallucinations, delusions, thought disorder) and "negative symptoms" (eg. depression, lethargy, poor speech).

ADULTS - The usual dose is between 400 mg and 800 mg of Amisulpride a day, divided into two doses. Your doctor may increase this dose to help improve your symptoms, up to 1200 mg of Amisulpride in some cases. If you are mostly suffering from "negative symptoms" your doctor will give you a lower dose of between 50 mg and 300 mg of Amisulpride a day, taken as a single dose. He/she will adjust your dose to best treat the symptoms.

ELDERLY - Elderly patients are more sensitive to the effects of Amisulpride and will be given lower doses.

Patients with kidney disease will be given lower or less frequent doses depending on the severity of the disease.

CHILDREN - Amisulpride Tablets should not be given to children under 15 years.

If you forget to take your dose of Amisulpride Tablets, unless it is almost time for your next dose, take it as soon as you remember. Otherwise, if you miss a dose do not double the next dose, just carry on as before. Do not stop taking your Amisulpride Tablets without speaking to your doctor first as this may make you feel unwell. **If you take too much of your medicine contact a doctor or local casualty department immediately.**

POSSIBLE SIDE EFFECTS

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