AMISULPRIDE 50MG TABLETS
PL 10880/0036 and PL 10880/0040

AMISULPRIDE 100MG TABLETS
PL 10880/0037 and PL 10880/0041

AMISULPRIDE 200MG TABLETS
PL 10880/0038 and PL 10880/0042

AMISULPRIDE 400MG TABLETS
PL 10880/0039 and PL 10880/0043

UKPAR

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LAY SUMMARY

The MHRA today granted Hexal AG Marketing Authorisations (licences) for the medicinal products Amisulpride 50mg Tablets (PL 10880/0036 and 0040), Amisulpride 100mg Tablets (PL 10880/0037 and 0041), Amisulpride 200mg Tablets (PL 10880/0038 and 0042) and Amisulpride 400mg Tablets (PL 10880/0039 and 0043). These are prescription-only medicines (POM) for the treatment of schizophrenia.

Amisulpride Tablets contain the active ingredient amisulpride, which acts as an antipsychotic and improves feelings, thoughts and/or behaviour when any of these is affected by schizophrenia.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Amisulpride Tablets outweigh the risks, hence Marketing Authorisations have been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Amisulpride 50, 100, 200 and 400mg Tablets to Hexal AG (PL 10880/0036-43) on 5th January 2007. The products are prescription-only medicines.

These are two sets of parallel applications for four strengths of Amisulpride Tablets, submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming essential similarity to the original products Solian 50mg, 100mg, 200mg and 400mg Tablets (Sanofi-Synthelabo Ltd, UK).

The products contain the active ingredient amisulpride, a bezamide neuroleptic agent structurally related to sulpiride that acts as a dopamine receptor antagonist. 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.

These applications for Amisulpride 50mg, 100mg, 200mg and 400mg Tablets were submitted at the same time and depend on the bioequivalence studies comparing the applicant's 200mg and 400mg tablets against Solian Tablets of the same strength. Consequently, sections of this Scientific Discussion refer to all products.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Amisulpride

INN: Amisulpride
Chemical name: 4 amino-N-[[(2RS)-1-ethylpyrrolidin-2-yl]methyl]-5-(ethylsulphonyl)-2-methoxybenzamide (as stated in Ph.Eur)
4-amino-N-[(1ethyl-2-pirrolidinyl)methyl]-5-(ethylsulfonyl)-o-anisamide

Physical form: White or almost white, crystalline powder, bitter taste
Molecular formula: $C_{17}H_{27}N_30_4S$
Molecular weight: 369.5
Stereoisomerism/chirality: One chiral centre (Racemic Mixture)

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance amisulpride.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification.

An adequate retest period has been defined based on conducted stability studies.

DRUG PRODUCT

Other ingredients

50, 100, 200 mg tablets:
Other ingredients consist of pharmaceutical excipients, namely maize starch, lactose monohydrate, methylcellulose, colloidal anhydrous silica and magnesium stearate. All excipients used comply with their respective Ph Eur monograph. Satisfactory certificates of analysis have been provided for all excipients.

400 mg film-coated tablets:
Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, magnesium stearate, methylcellulose, microcrystalline cellulose, sodium starch glycolate (type A) for the tablet cores and macrogol 6000, magnesium stearate, talc, titanium dioxide (E 171) and polymethacrylate for the film-coating. All excipients comply with their respective Ph Eur monograph or a suitable in-house monograph (polymethacrylate). Satisfactory certificates of analysis have been provided for all excipients.

With the exception of lactose and magnesium stearate, none of the excipients used contain materials of animal or human origin. The manufacturer of lactose monohydrate has confirmed that this is sourced from healthy animals under the same conditions as milk for human consumption. The manufacturer of magnesium stearate has provided a TSE

certificate of suitability. A commitment has also been provided that for future production magnesium stearate will be sourced from vegetable origins.

Dissolution
Dissolution profiles were found to be similar to those of the reference product Solian Tablets. The data demonstrate that the dissolution specification is acceptable.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of each strength of product. The results appear satisfactory.

Finished product specification
The finished product specification is satisfactory. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
Specifications and Certificates of Analysis for all packaging have been provided. These are satisfactory. The primary packaging has been shown to comply with relevant regulations regarding the contact of materials with foodstuff.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 36 months has been set for all strengths. The 400 mg tablets should not be stored above 25°C.

Bioequivalence
Two studies were performed comparing test amisulpride 200mg and 400mg tablets versus Solian® 200mg and 400mg Tablets (Sanofi-Synthelabo, France). Both studies were carried out in accordance with current Good Clinical Practice.

The applicant has justified the choice of the reference product as, although licensed in France, it is manufactured in the same place as the UK product. As there is proportionally the same formulation used between the 50, 100 and 200mg strengths, and their dissolution profiles are similar, it was not considered necessary for the 50 and 100mg strengths to be tested for bioequivalence.

Satisfactory certificates of analysis have been provided for batches of test and reference product used.

The analytical method employed for analysis of samples is HPLC with UV detection and with metoclopramide as the internal standard. This method has been appropriately validated. The stability of the analyte in the biological matrix has been demonstrated.

Summary of pharmacokinetic parameters 200mg (arithmetic means)

Parameter	Reference	Test	90% CI
C_{max} (ng/ml)	409 ± 151	424 ± 200	86.6-114.0
$AUC_{0-\infty}$ (ng.h/ml)	3581 ± 929	3549 ± 959	93.5-104.0

Summary of pharmacokinetic parameters 400mg (arithmetic means)

Parameter	Reference	Test	90% CI
C_{max} (ng/ml)	1391 ± 602	1269 ± 512	81.8-103.0
$AUC_{0-\infty}$ (ng.h/ml)	8891 ± 2096	8808 ± 1962	94.7-104.0

As the AUC-ratio the 90% confidence interval of relative bioavailability lies within an acceptance range of 0.80-1.25, it is concluded that both the 200mg and 400mg tablets are bioequivalent to the French reference products. The French reference product is the same as the UK brand leader Solian®, thus bioequivalence with the UK brand leader is proven.

ADMINISTRATIVE

Expert Report

A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics

These are consistent with those for the reference products and are satisfactory.

Labelling

These are satisfactory

Patient Information Leaflet

This is consistent with that for the reference products and is satisfactory.

MAA Forms

These are satisfactory.

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance. In addition, similar dissolution profiles have been demonstrated for the proposed and reference products.

PRECLINICAL ASSESSMENT

These applications for generic products claims essential similarity to Solian 50mg, 100mg, 200mg and 400mg Tablets (Sanofi-Synthelabo Ltd, UK), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for applications of this type.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

The applicant commissioned two blinded, randomised, single-dose comparative bioavailability studies, one for 200mg test product versus 200mg Solian Tablets and one for 400mg test product versus 400mg Solian Tablets.

Results are presented in the pharmaceutical assessment. Bioequivalence was shown between the test and reference products.

EFFICACY

No new data has been provided.

SAFETY

No new data has been provided.

EXPERT REPORTS

A clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

This is consistent with that for the reference product and is satisfactory.

LABELLING

These are satisfactory

APPLICATION FORMS (MAA)

These are satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

These are consistent with those for the reference products and are satisfactory.

DISCUSSION

The applicant has satisfactorily demonstrated comparable bioavailability to the originator cross-reference product, with ratios for AUC and C_{max} lying within the 90% confidence interval range of 80-125%.

MEDICAL CONCLUSION

Marketing authorisations are recommended for these applications.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Amisulpride 50, 100, 200 and 400mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. 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

Bioequivalence has been demonstrated between the applicant's Amisulpride 200mg and 400mg Tablets and the reference products Solian 200mg and 400mg Tablets (Sanofi-Synthelabo, France). Given that linear kinetics apply between the 50, 100 and 200mg strength tablets, that proportional formulae for the tablets have been used and that similar dissolution results have been shown, separate bioequivalence studies for the 50 and 100mg tablets are not considered necessary.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Solian Tablets.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the reference products are interchangeable. Extensive clinical experience with amisulpride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 17th July 2003
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 1st September 2003
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 1st December 2003, and further information relating to the quality dossiers on 30th October 2003 and 5th October 2004.
4	The applicant responded to the MHRA's requests, providing further information on 25th February 2004 for the clinical sections, and again on 25th February 2004, 16th September 2004 and 10th January 2005 for the quality sections.
5	The applications were determined on 5th January 2007

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

1 NAME OF THE MEDICINAL PRODUCT

Amisulpride 50mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 50 mg amisulpride.
For excipients, see 6.1 "List of excipients"

3 PHARMACEUTICAL FORM

White to off white, round tablets (approx. diameter 7.0 mm) with break line on one side and embossed with "50" on the other side.

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 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.
- other 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 “Interaction with other medicinal products and other forms of interaction”)

4.4 Special warnings and precautions for use

As with other neuroleptics, Neuroleptic Malignant Syndrome, characterized 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 prescribed (see 4.2 Posology and method of administration).

Amisulpride can 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 intervals (see 4.5 Interaction with other medicinal products and other forms of interaction)

The tablets contain lactose. Patient with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations which are contraindicated

Medications which could induce torsades de pointes:
- class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide.
- class III antiarrhythmic agents such as amiodarone, sotalol.
- other 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 (e.g.: levodopa) since it may attenuate their action

4.6 Pregnancy and lactation

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 contraindicated during pregnancy and in women of child bearing potential unless using adequate contraception.

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

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 events (0.1-5 %):

Somnolence; gastrointestinal disorders such as constipation, nausea, vomiting, dry mouth

In common with other neuroleptics:
Amilsulpride 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 50-300 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.

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 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 should not be used 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

Antipsychotic
ATC-Code: N05A L05

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, alpha-adrenergic, histamine H1 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 presynaptic 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 4.2 “Posology and method of administration”). Experience is however limited and there is no data with doses greater than 50 mg.

Amisulpride is very weakly dialised.

Limited pharmacokinetic data in elderly persons (>65 years) show that a 10-30% rise occurs in C_{max}, $T_{1/2}$ and AUC after a single oral dose of 50 mg. No data are available after repeat dosing.

5.3 Preclinical safety data

An overall review of the completed safety studies indicates that amisulpride is devoid of any general, organ-specific, teratogenic, mutagenic or carcinogenic risk. Changes observed in rats and dogs at doses below the maximum tolerated dose are either pharmacological effects or are devoid of major toxicological significance under these conditions. Compared with the maximum recommended dosages in man, maximum tolerated doses are 2 and 7 times greater in the rat (200 mg/kg/d) and dog (120 mg/kg/d) respectively in terms of AUC. No carcinogenic risk, relevant to man, was identified in the rat at up to 1.5 to 4.5 times the expected human AUC.

A mouse carcinogenicity study (120 mg/kg/d) and reproductive studies (160, 300 and 500 mg/kg/d respectively in rat, rabbit and mouse) were performed. The exposure of the animals to amisulpride during these latter studies was not evaluated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica
Lactose monohydrate
Magnesium stearate
Maize starch
Methylcellulose

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

No special precautions for storage

6.5 Nature and contents of container

The tablets are packed in PVC/aluminium blisters and inserted into a carton.

Pack sizes:
20, 30, 50, 60, 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

HEXAL AG
Industriestraße 25
D-83607 Holzkirchen
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 10880/0036

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/01/2007

10 DATE OF REVISION OF THE TEXT

05/01/2007

1 NAME OF THE MEDICINAL PRODUCT

Amisulpride 100mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 100 mg amisulpride.
For excipients, see 6.1 "List of excipients"

3 PHARMACEUTICAL FORM

White to off white, round tablets (approx. diameter 9.5 mm) with break line on one side and embossed with "100" on the other side.

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 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.
- other 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 “Interaction with other medicinal products and other forms of interaction”)

4.4 Special warnings and precautions for use

As with other neuroleptics, Neuroleptic Malignant Syndrome, characterized 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 prescribed (see 4.2 Posology and method of administration).

Amisulpride can 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 intervals (see 4.5 Interaction with other medicinal products and other forms of interaction)

The tablets contain lactose. Patient with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations which are contraindicated

Medications which could induce torsades de pointes:
- class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide.
- class III antiarrhythmic agents such as amiodarone, sotalol.
- other 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 (e.g.: levodopa) since it may attenuate their action

4.6 Pregnancy and lactation

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 contraindicated during pregnancy and in women of child bearing potential unless using adequate contraception.

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

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 events (0.1-5 %):

Somnolence; gastrointestinal disorders such as constipation, nausea, vomiting, dry mouth

In common with other neuroleptics:
Amilsulpride 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 50-300 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.

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 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 should not be used 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

Antipsychotic
ATC-Code: N05A L05

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, alpha-adrenergic, histamine H1 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 presynaptic 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 4.2 “Posology and method of administration”). Experience is however limited and there is no data with doses greater than 50 mg.

Amisulpride is very weakly dialised.

Limited pharmacokinetic data in elderly persons (>65 years) show that a 10-30% rise occurs in C_{max}, $T_{1/2}$ and AUC after a single oral dose of 50 mg. No data are available after repeat dosing.

5.3 Preclinical safety data

An overall review of the completed safety studies indicates that amisulpride is devoid of any general, organ-specific, teratogenic, mutagenic or carcinogenic risk. Changes observed in rats and dogs at doses below the maximum tolerated dose are either pharmacological effects or are devoid of major toxicological significance under these conditions. Compared with the maximum recommended dosages in man, maximum tolerated doses are 2 and 7 times greater in the rat (200 mg/kg/d) and dog (120 mg/kg/d) respectively in terms of AUC. No carcinogenic risk, relevant to man, was identified in the rat at up to 1.5 to 4.5 times the expected human AUC.

A mouse carcinogenicity study (120 mg/kg/d) and reproductive studies (160, 300 and 500 mg/kg/d respectively in rat, rabbit and mouse) were performed. The exposure of the animals to amisulpride during these latter studies was not evaluated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica
Lactose monohydrate
Magnesium stearate
Maize starch
Methylcellulose

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

No special precautions for storage

6.5 Nature and contents of container

The tablets are packed in PVC/aluminium blisters and inserted into a carton.

Pack sizes:
20, 30, 50, 60, 100, 120 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

HEXAL AG
Industriestraße 25
D-83607 Holzkirchen
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 10880/0037

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/01/2007

10 DATE OF REVISION OF THE TEXT

05/01/2007

1 NAME OF THE MEDICINAL PRODUCT

Amisulpride 200mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 200 mg amisulpride.
For excipients, see 6.1 "List of excipients"

3 PHARMACEUTICAL FORM

White to off white, round tablets (approx. diameter 12.5 mm) with break line on one side and embossed with "200" on the other side.

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 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.
- other 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 “Interaction with other medicinal products and other forms of interaction”)

4.4 Special warnings and precautions for use

As with other neuroleptics, Neuroleptic Malignant Syndrome, characterized 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 prescribed (see 4.2 Posology and method of administration).

Amisulpride can 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 intervals (see 4.5 Interaction with other medicinal products and other forms of interaction)

The tablets contain lactose. Patient with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations which are contraindicated

Medications which could induce torsades de pointes:
- class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide.
- class III antiarrhythmic agents such as amiodarone, sotalol.
- other 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 (e.g.: levodopa) since it may attenuate their action

4.6 Pregnancy and lactation

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 contraindicated during pregnancy and in women of child bearing potential unless using adequate contraception.

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

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 events (0.1-5 %):

Somnolence; gastrointestinal disorders such as constipation, nausea, vomiting, dry mouth

In common with other neuroleptics:
Amilsulpride 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 50-300 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.

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 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 should not be used 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

Antipsychotic
ATC-Code: N05A L05

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, alpha-adrenergic, histamine H1 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 presynaptic 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 4.2 “Posology and method of administration”). Experience is however limited and there is no data with doses greater than 50 mg.

Amisulpride is very weakly dialised.

Limited pharmacokinetic data in elderly persons (>65 years) show that a 10-30% rise occurs in C_{max}, $T_{1/2}$ and AUC after a single oral dose of 50 mg. No data are available after repeat dosing.

5.3 Preclinical safety data

An overall review of the completed safety studies indicates that amisulpride is devoid of any general, organ-specific, teratogenic, mutagenic or carcinogenic risk. Changes observed in rats and dogs at doses below the maximum tolerated dose are either pharmacological effects or are devoid of major toxicological significance under these conditions. Compared with the maximum recommended dosages in man, maximum tolerated doses are 2 and 7 times greater in the rat (200 mg/kg/d) and dog (120 mg/kg/d) respectively in terms of AUC. No carcinogenic risk, relevant to man, was identified in the rat at up to 1.5 to 4.5 times the expected human AUC.

A mouse carcinogenicity study (120 mg/kg/d) and reproductive studies (160, 300 and 500 mg/kg/d respectively in rat, rabbit and mouse) were performed. The exposure of the animals to amisulpride during these latter studies was not evaluated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica
Lactose monohydrate
Magnesium stearate
Maize starch
Methylcellulose

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

No special precautions for storage

6.5 Nature and contents of container

The tablets are packed in PVC/aluminium blisters and inserted into a carton.

Pack sizes:
20, 30, 50, 60, 100, 120, 160 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

HEXAL AG
Industriestraße 25
D-83607 Holzkirchen
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 10880/0038

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/01/2007

10 DATE OF REVISION OF THE TEXT

05/01/2007

1 NAME OF THE MEDICINAL PRODUCT

Amisulpride 400mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 400 mg amisulpride.
For excipients, see 6.1 "List of excipients"

3 PHARMACEUTICAL FORM

White to off white, ovoidal shaped, film-coated, biconvex tablets with break line. The dimension is approximately 18 mm long and 8 mm wide.

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 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.
- other 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 “Interaction with other medicinal products and other forms of interaction”)

4.4 Special warnings and precautions for use

As with other neuroleptics, Neuroleptic Malignant Syndrome, characterized 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 prescribed (see 4.2 Posology and method of administration).

Amisulpride can 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 intervals (see 4.5 Interaction with other medicinal products and other forms of interaction)

The tablets contain lactose. Patient with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations which are contraindicated

Medications which could induce torsades de pointes:
- class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide.
- class III antiarrhythmic agents such as amiodarone, sotalol.
- other 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 (e.g.: levodopa) since it may attenuate their action

4.6 Pregnancy and lactation

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 contraindicated during pregnancy and in women of child bearing potential unless using adequate contraception.

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

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 events (0.1-5 %):

Somnolence; gastrointestinal disorders such as constipation, nausea, vomiting, dry mouth

In common with other neuroleptics:

Amilsulpride 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 50-300 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.

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 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 should not be used 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

Antipsychotic
ATC-Code: N05A L05

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, alpha-adrenergic, histamine H1 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 presynaptic 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 4.2 “Posology and method of administration”). Experience is however limited and there is no data with doses greater than 50 mg.

Amisulpride is very weakly dialised.

Limited pharmacokinetic data in elderly persons (>65 years) show that a 10-30% rise occurs in C_{max}, $T_{1/2}$ and AUC after a single oral dose of 50 mg. No data are available after repeat dosing.

5.3 Preclinical safety data

An overall review of the completed safety studies indicates that amisulpride is devoid of any general, organ-specific, teratogenic, mutagenic or carcinogenic risk. Changes observed in rats and dogs at doses below the maximum tolerated dose are either pharmacological effects or are devoid of major toxicological significance under these conditions. Compared with the maximum recommended dosages in man, maximum tolerated doses are 2 and 7 times greater in the rat (200 mg/kg/d) and dog (120 mg/kg/d) respectively in terms of AUC. No carcinogenic risk, relevant to man, was identified in the rat at up to 1.5 to 4.5 times the expected human AUC.

A mouse carcinogenicity study (120 mg/kg/d) and reproductive studies (160, 300 and 500 mg/kg/d respectively in rat, rabbit and mouse) were performed. The exposure of the animals to amisulpride during these latter studies was not evaluated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate
Magnesium stearate
Methylcellulose
Microcrystalline cellulose
Sodium starch glycolate (type A)

Coating:
Macrogol 6000
Magnesium stearate
Polymethacrylate
Talc
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

The tablets are packed in PVC/aluminium blisters and inserted into a carton.

Pack sizes:
20, 30, 50, 60, 100, 120 tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

HEXAL AG
Industriestraße 25
D-83607 Holzkirchen
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 10880/0039

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/01/2007

10 DATE OF REVISION OF THE TEXT

05/01/2007

PATIENT INFORMATION LEAFLET

Amisulpride 50mg, 100mg, 200mg and 400mg Tablets

Please read this entire leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

The name of this medicine is Amisulpride Tablets. There are 4 strengths available: 50mg, 100mg, 200mg or 400mg Tablets.

- The active substance is amisulpride.
- Other ingredients are colloidal anhydrous silica, lactose monohydrate, magnesium stearate, maize starch and methylcellulose
- For the 400mg tablets only, the other ingredients are lactose monohydrate, magnesium stearate, methylcellulose, microcrystalline cellulose and sodium starch glycollate. The coating contains macrogol 6000, magnesium stearate, polymethacrylate, talc, and titanium dioxide (E171).

Marketing Authorisation Holder:
HEXAL AG
Industriestrasse 25
D-83607, Holzkirchen
Germany

Manufacturer:
Salutas Pharma GmbH,
Otto-Von-Guericke-Allee 1,
39179 Barleben, Germany

1. What Amisulpride is and what it is used for.

Amisulpride 50mg, 100mg and 200mg Tablets are white to off-white, round tablets with a break line on one side and are embossed with "50", "100" and "200" on the other side, respectively.
Amisulpride 400mg Tablets are white to off-white, oval shaped, film-coated tablets with a break line.
Each tablet contains 50mg, 100mg, 200mg or 400mg of the active ingredient amisulpride.

Amisulpride Tablets are available in blister packs of 60 tablets.

Amisulpride belongs to a group of medicines known as antipsychotic drugs. These improve feelings, thought and/or behaviour when either of these is affected in certain medical conditions.

Amisulpride Tablets are used to treat schizophrenia. This condition causes symptoms such as sensing, seeing or hearing things which do not exist, mistaken beliefs or suspicions (known as positive symptoms). Sometimes people may feel tense, or depressed (known as negative symptoms).

2. Before you take Amisulpride Tablets

Do not take Amisulpride Tablets if any of the following apply to you.

- If you have breast cancer or other tumours
- If you are under the age of 15 years old
- If you are pregnant, planning to become pregnant or breast-feeding.
- If you are taking certain medicines (please see final section of part 2 entitled "Taking other medicines")
- If you are sensitive or allergic to amisulpride or any other of the ingredients.

Take special care with Amisulpride Tablets if:

- you have been on the medication and suffer from muscle stiffness or hyperthermia (an increased body temperature). Consult your doctor immediately.
- you suffer from kidney problems, your doctor may decide to reduce your dose.
- you suffer from epilepsy, since amisulpride can increase the chances of a seizure occurring.
- you are elderly, since amisulpride can cause low blood pressure.
- you suffer from Parkinson's disease, since taking amisulpride could worsen the disease.
- you have suffered from certain heart conditions or low potassium levels, since amisulpride could cause disruption of your heart rate.

If your doctor has told you that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Pregnancy and breast-feeding
Do not take Amisulpride if you are pregnant, think you may be pregnant, or are breast-feeding.

Driving or using machines
Amisulpride can affect your reaction time, so you should you not drive or operate machinery whilst taking amisulpride.

Taking other medicines
Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines, even those not prescribed but bought without a prescription.

DO NOT take any of the following medicines while taking Amisulpride Tablets:

- Class Ia antiarrythmic medicines (medicines used to treat disturbed heart rhythms) such as quinidine, disopyramide and procainamide.
- Class III antiarrythmic agents such as amiodarone and sotalol
- Bepridil (used to treat angina/chest pain and disruptions in heart rhythm)
- Cisapride (used to treat acid reflux)
- Sultopride (used to treat schizophrenia)
- Thioridazine (used to treat schizophrenia in adults)
- IV Erythromycin (used to skin disorders and acne)
- IV Vincamine (used in various disorders of the brain)
- Halofantrine (used to prevent malaria)
- Pentamidine (used to treat infections in HIV infected patients)
- Sparfloxacin (an anti-bacterial used to treat pneumonia)
- Levodopa (used to treat Parkinson's disease)

It is **NOT RECOMMENDED** to drink alcohol while you are taking amisulpride.

You should inform your doctor or pharmacist if you are taking any of the following since some medicines may influence the effect of or be influenced by Amisulpride Tablets:

- Medicines used to treat high blood pressure (which result in a lower heart rate) such as beta-blockers and calcium channel blockers e.g. diltiazem and verapamil, clonidine, guanfacine and digitalis.
- Medicines which cause low potassium levels such as diuretics (water tablets), laxatives, amphoteracin B, and glucocorticoids such as prednisolone (used to treat allergies)
- Pimozide or Haloperidol (used to treat schizophrenia)
- Antidepressants (medicines used to treat depression, such as imipramine)

- Lithium (used to treat depression or mental disorders)
- Anaesthetics
- Pain-killers (such as paracetamol)
- Antihistamines (such as chlorpheniramine), used to treat allergies
- Barbiturates (such as phenobarbitone), used to treat epilepsy
- Drugs used to treat anxiety such as diazepam
- Medicines used to treat high blood pressure (such as clonidine)
- Any medicines that interact with dopamine (such as levodopa).

3. How to take Amisulpride Tablets

You should always take this medicine as prescribed by your doctor. Do not take more than the doctor told you to. Read and follow the instructions on the pharmacist's label. If you are not sure about anything please ask your doctor or pharmacist.

Adults: The usual oral dose is between 400mg a day and 800mg a day. In certain cases your doctor may increase your dose up to 1200mg a day.

For patients who suffer from both positive and negative symptoms (please see the end of part 1 for description of this), your doctor will adjust your dose so that there is adequate control of the positive symptoms, this will be different in different individuals.

To maintain treatment, your doctor will use the lowest possible dose that is effective for you.

In patients who suffer mainly from the negative symptoms, oral doses between 50mg and 300mg are recommended.

Oral doses of up to 300mg can be administered once a day, however higher doses must be given twice a day.

Elderly: Care should be taken when using amisulpride in elderly people since there is a risk or low blood pressure or drowsiness.

Children: Amisulpride should not be used in children under 15 years old.

Patients with kidney problems: Your doctor will advise of the correct dose to take, this may be reduced by half the normal dose.

There is unlikely to be any need to alter the dose if you suffer from liver problems.

It is important that you keep taking Amisulpride Tablets until the prescribed course is finished. Do not stop taking the tablets just because you feel better.

If you forget to take Amisulpride Tablets at the right time, take them as soon as you remember. Do not take a double dose to make up for forgotten individual doses.

If you have taken more Amisulpride Tablets than you should, drink plenty of water and consult your doctor or the nearest hospital casualty department immediately. Take this leaflet or some tablets with you so that people will know what you have taken.

4. Possible side effects

Like all medicines, Amisulpride Tablets can have side effects.

Common side effects include:

- an inability to sleep
- anxiety
- feeling agitated
- drowsiness
- constipation
- feeling sick or being sick
- dry mouth
- production of milk from the breasts without childbirth or being a nursing mother.
- absence of menstruation
- enlargement of one or both breasts in men
- breast pain
- lack of orgasm and impotence
- weight gain
- problems with your muscles
- shakiness or stiffness
- reduced movement
- increased production of saliva
- feeling restless

Rare side effects include:

- regular, involuntary movements of the tongue and face
- low blood pressure and a slow heart rate
- longer heart intervals and a rare condition in which there is an increased heart rate (torsades de pointes)

Allergic reactions such as rashes, epileptic fits and a rare condition called Neuroleptic Malignant Syndrome (in which you suffer from increased body temperature and muscle stiffness, have also been reported in very rare cases.

If you suffer from any of these or notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. Storing Amisulpride Tablets

Keep out of reach and sight of children.
Store in the original package.
Do not take after the expiry date on the labelling.

There are no special storage instructions for Amisulpride 50mg, 100mg and 200mg Tablets, however, as with all medicines do not store these Amisulpride Tablets anywhere too hot or damp.
Do not store Amisulpride 400mg Tablets above 25°C.

If you notice any visible signs of deterioration in the tablets, such as chipped, broken or discoloured tablets, take them to your pharmacist for advice before taking them.

If your doctor tells you to stop taking your medicine you should return any remaining tablets to the pharmacist, unless your doctor tells you to keep them at home. Do not use Amisulpride Tablets after the expiry date on the package.

REMEMBER

This medicine is only for YOU. Only a doctor can prescribe it, so never offer it to anybody else,. It may harm them, even if their symptoms seem to be the same as yours.

Product Licence Number:
PL 10880/0036: Amisulpride 50mg Tablets
PL 10880/0037: Amisulpride 100mg Tablets
PL 10880/0038: Amisulpride 200mg Tablets
PL 10880/0039: Amisulpride 400mg Tablets

Leaflet prepared: 30th March 2006

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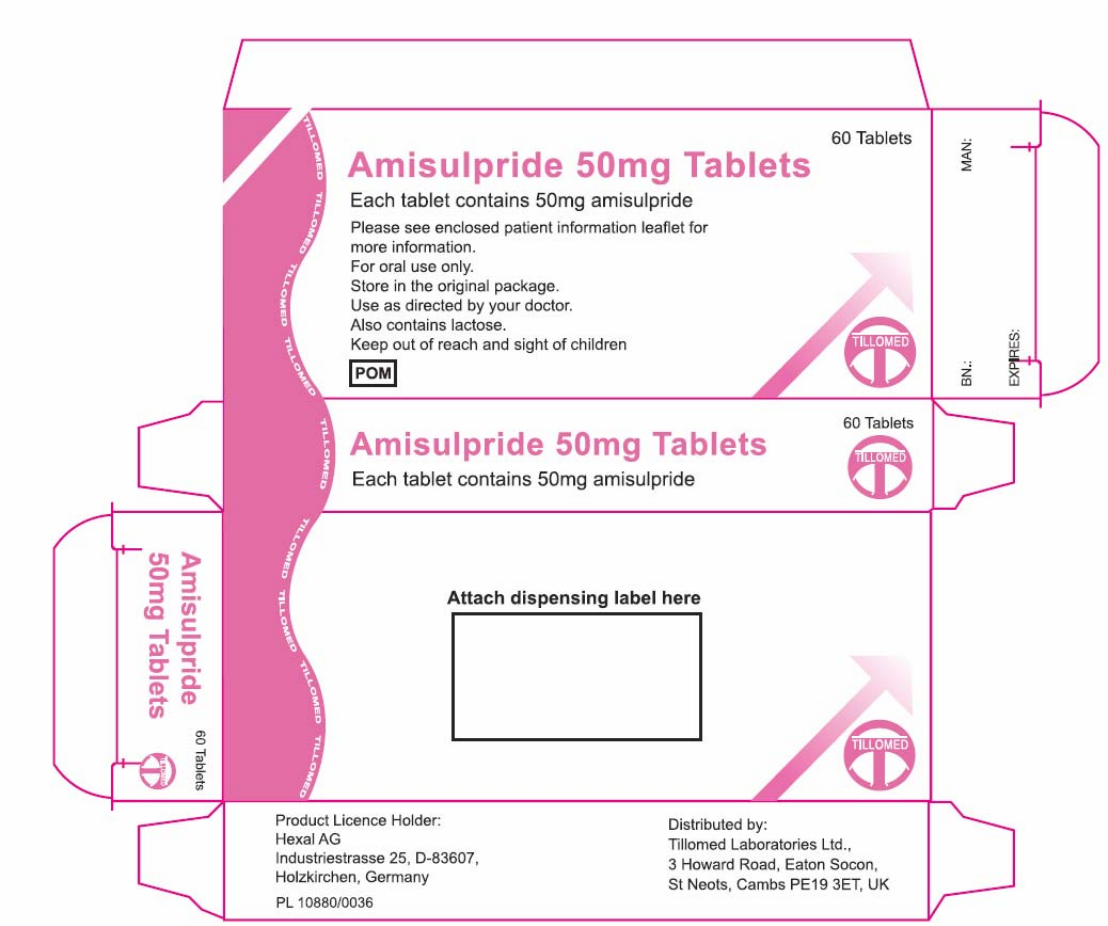
Amisulpride 50mg Tablets
60 Tablets
Each tablet contains 50mg amisulpride
Please see enclosed patient information leaflet for more information.
For oral use only.
Store in the original package.
Use as directed by your doctor.
Also contains lactose.
Keep out of reach and sight of children
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BN.:
EXPIRES:
Amisulpride 50mg Tablets
60 Tablets
Each tablet contains 50mg amisulpride
Attach dispensing label here
Amisulpride 50mg Tablets
60 Tablets
Product Licence Holder:
Hexal AG
Industriestrasse 25, D-83607,
Holzkirchen, Germany
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Amisulpride
50mg Tablets
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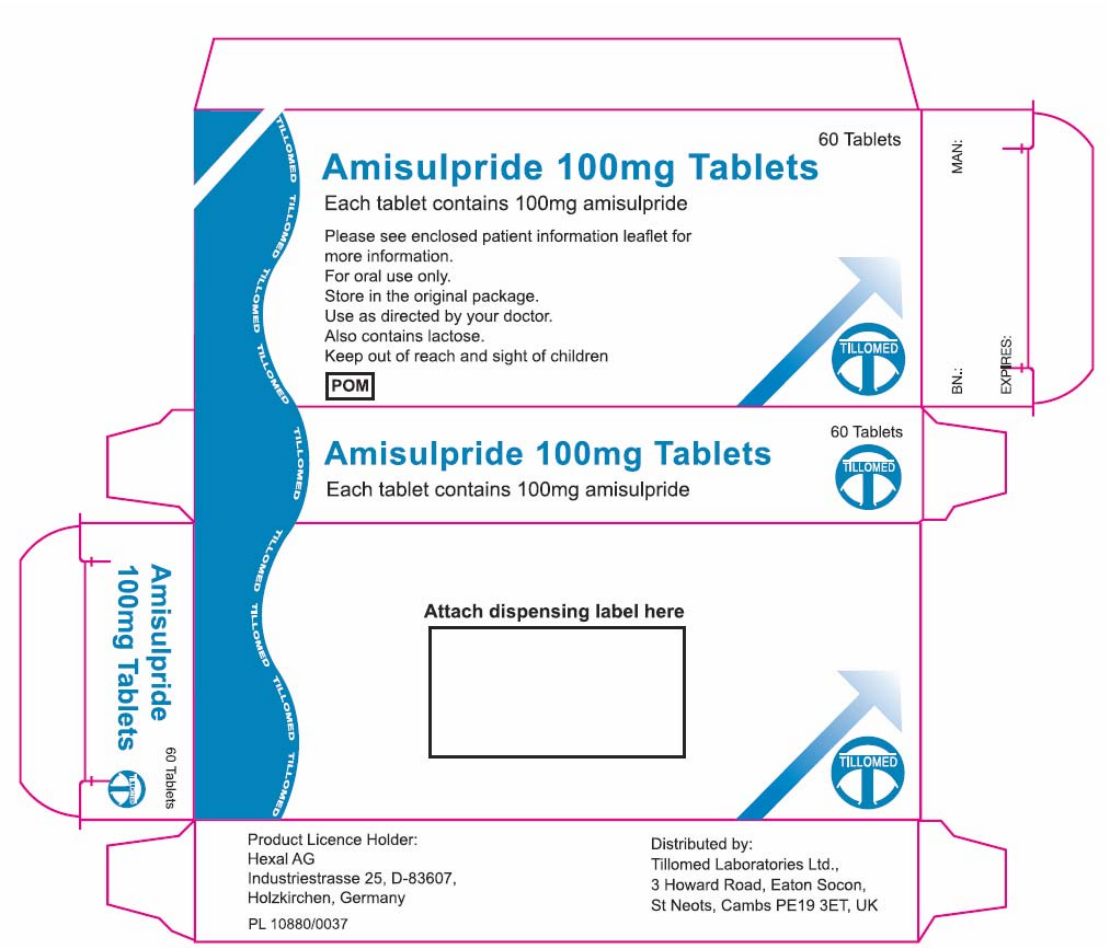
60 Tablets
Amisulpride 100mg Tablets
Each tablet contains 100mg amisulpride
Please see enclosed patient information leaflet for more information.
For oral use only.
Store in the original package.
Use as directed by your doctor.
Also contains lactose.
Keep out of reach and sight of children
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TILLOMED
60 Tablets
Amisulpride 100mg Tablets
Each tablet contains 100mg amisulpride
Attach dispensing label here
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60 Tablets
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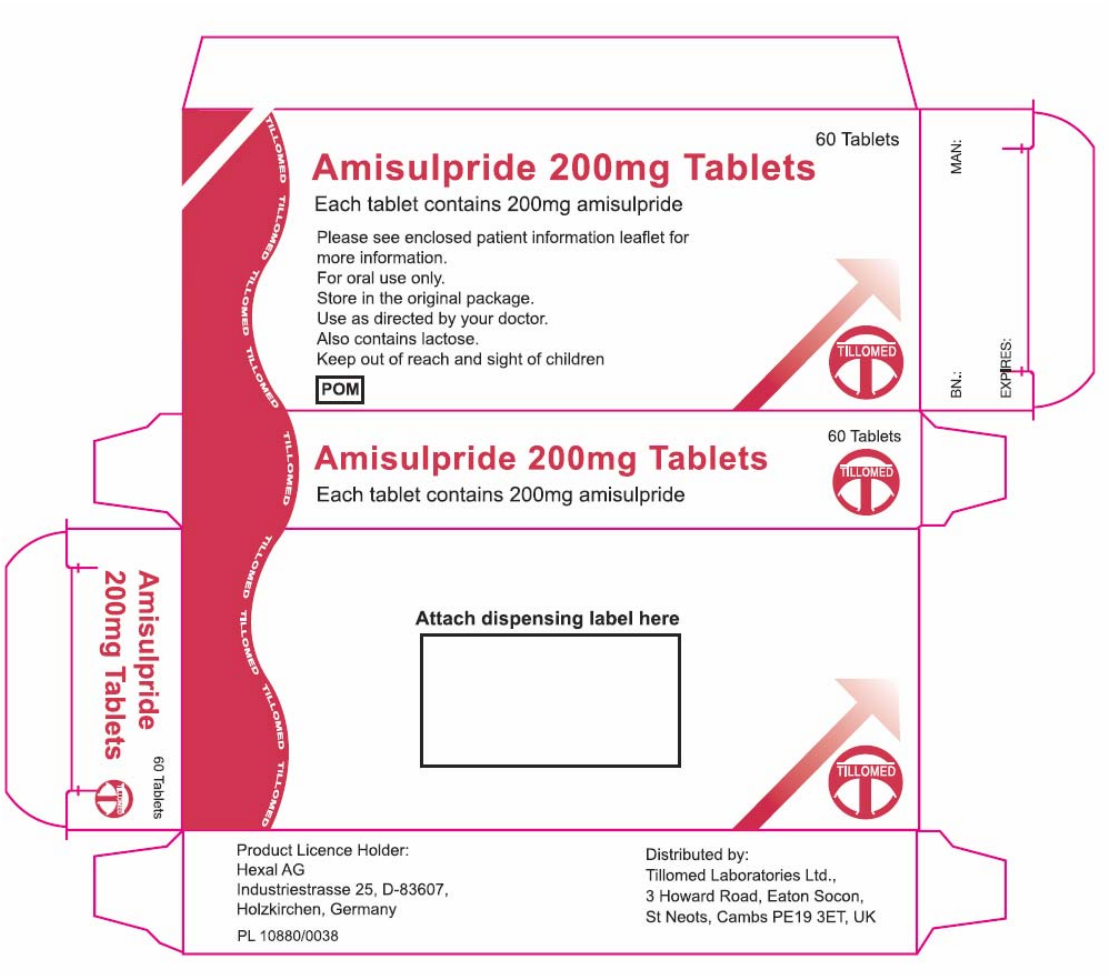
60 Tablets
Amisulpride 200mg Tablets
Each tablet contains 200mg amisulpride
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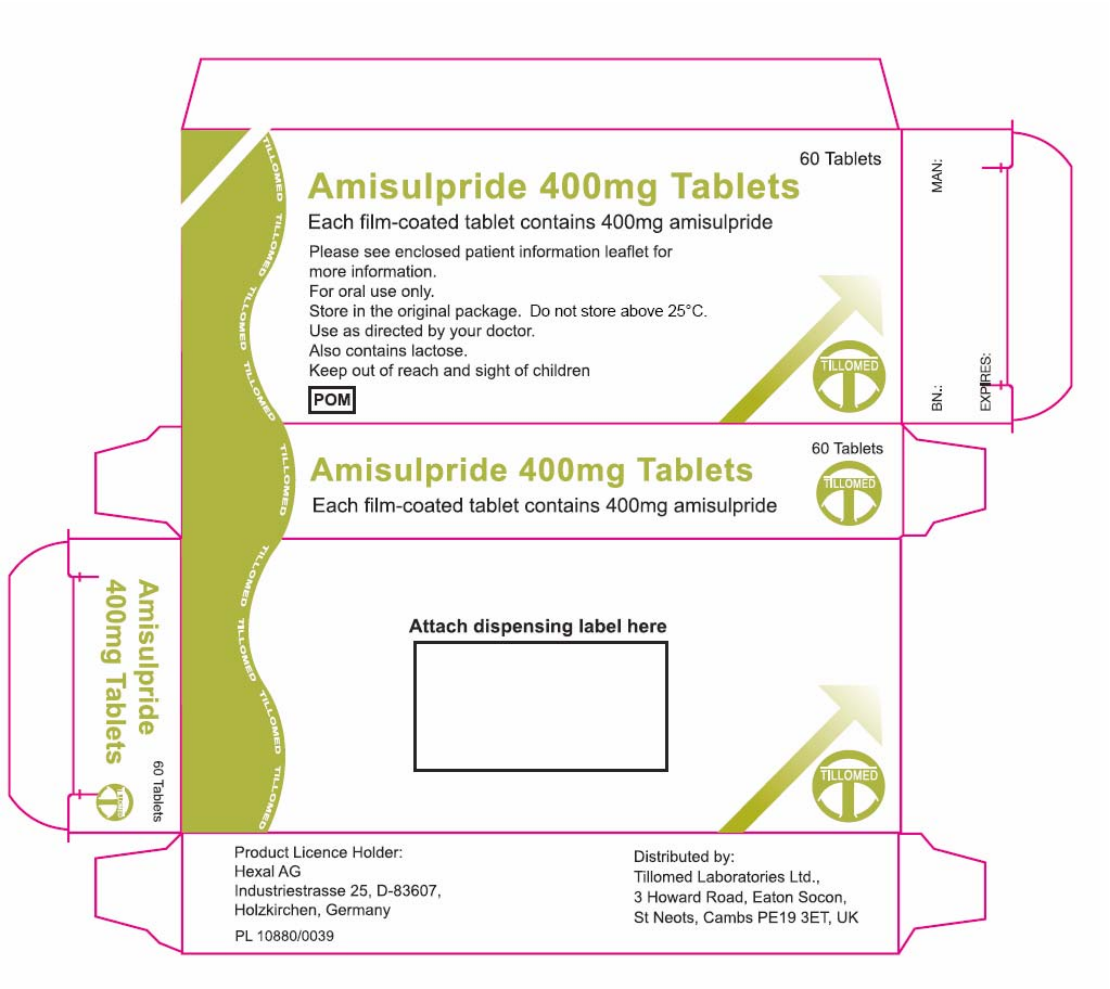
60 Tablets
Amisulpride 400mg Tablets
Each film-coated tablet contains 400mg amisulpride
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Also contains lactose.
Keep out of reach and sight of children
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Amisulpride 400mg Tablets PL HOLDER: HEXAL AG PL 10880/0039 Batch No./Exp. - embossed	**Amisulpride 400mg Tablets** PL HOLDER: HEXAL AG PL 10880/0039 Batch No./Exp. - embossed
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