**UKPAR**

**TABLE OF CONTENTS**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>2</td>
</tr>
<tr>
<td>Scientific discussion</td>
<td>3</td>
</tr>
<tr>
<td>Steps taken for assessment</td>
<td>12</td>
</tr>
<tr>
<td>Steps taken after authorisation – summary</td>
<td>13</td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td>14</td>
</tr>
<tr>
<td>Product Information Leaflet</td>
<td>42</td>
</tr>
<tr>
<td>Labelling</td>
<td>44</td>
</tr>
</tbody>
</table>
AMISULPRIDE 50MG, 100MG, 200MG & 400MG TABLETS
PL 00530/0727-30

LAY SUMMARY

The MHRA granted Norton Healthcare Limited Marketing Authorisations (licences) for the medicinal products Amisulpride 50mg Tablets (PL 00530/0727), Amisulpride 100mg Tablets (PL 00530/0728), Amisulpride 200mg Tablets (PL 00530/0729) and Amisulpride 4000mg Tablets (PL 00530/0730). These are prescription-only medicines (POM) for the treatment of schizophrenia.

Amisulpride Tablets contain the active ingredients 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.
AMISULPRIDE 50MG, 100MG, 200MG & 400MG TABLETS
PL 00530/0727-30

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction ........................................ Page 4
Pharmaceutical assessment ......................... Page 5
Preclinical assessment ................................ Page 9
Clinical assessment (including statistical assessment) ........................................ Page 10
Overall conclusions and risk benefit assessment ........................................ Page 11
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Amisulpride 50mg, 100mg, 200mg & 400mg Tablets (PL 00530/0727-30) on 24th April 2009. The products are prescription-only medicines.

These are national applications for four strengths of Amisulpride Tablets submitted under Article 10.1 of Directive 2001/83/EC, as amended, which have been shown to be generic medicinal products of Solian 50mg, 100mg, 200 & 400mg Tablets currently authorised to Sanofi-Synthelabo Ltd., UK following a change of ownership in July 2000. These products were originally authorised in July 1999 to Lorex Synthelabo UK & Ireland Limited. The reference product has therefore been authorised in the EU for more than 10 years.

The products contain the active ingredient amisulpride, a benzamide neuroleptic agent structurally related to sulpride 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 & 400mg tablets were submitted at the same time and depend on the bioequivalence study comparing the applicant’s 200mg and 400mg tablets against Solian Tablets of the same strength. Consequently, all 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-[(1 ethyl-2-pirrolidiny)methyl]-5-(ethylsulfonyl)-o-anisamide

Physical form: White or almost white, crystalline powder, bitter taste
Molecular formula: $\text{C}_{17}\text{H}_{31}\text{N}_{3}\text{O}_{4}\text{S}$
Molecular weight: 369.5
Steroisomerism/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 material 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

50mg, 100mg and 200mg 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.

400mg 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 used comply with their respective European Pharmacopoeial monograph or a suitable in-house monograph (polymethacrylate). Satisfactory certificates of analysis have been provided for all excipients.
The only excipients used that contain material of animal or human origin are lactose monohydrate and magnesium stearate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption. A satisfactory TSE certificate of suitability has been provided for the supplier of magnesium stearate.

**Dissolution and impurity profiles**
Dissolution and impurity profiles of the drug product were found to be similar to those for the reference product, Solian Tablets.

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on each strength of product and the results are satisfactory.

**Finished product specification**
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. 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**
The product is presented in a blister composed of aluminium and polyvinyl chloride (PVC). Specifications and certificates of analysis for the packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 60 tablets.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set for all strengths with no specific storage conditions, which is satisfactory.

**Patient Information Leaflet**
This is satisfactory. The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.
**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 strength it was not considered necessary for the 50mg 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.

<table>
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<tr>
<th>Parameter</th>
<th>Reference</th>
<th>Test</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>409 ± 151</td>
<td>424 ± 200</td>
<td>86.6-114.0</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (ng•h/ml)</td>
<td>3581 ± 929</td>
<td>3549 ± 959</td>
<td>93.5-104.0</td>
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</tbody>
</table>

<table>
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<tr>
<th>Parameter</th>
<th>Reference</th>
<th>Test</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>1391 ± 602</td>
<td>1269 ± 512</td>
<td>81.8-103.0</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (ng•h/ml)</td>
<td>8891 ± 2096</td>
<td>8808 ± 1962</td>
<td>94.7-104.0</td>
</tr>
</tbody>
</table>

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.

**MAA forms**

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

The requirements for a generic medicinal product for the proposed products have been met with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.
PRECLINICAL ASSESSMENT

These applications are generic medicinal products of 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 an application 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 \( C_{\text{max}} \) 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 50mg, 100mg, 200mg and 400mg 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 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 product 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 innovator 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.
AMISULPRIDE 50MG, 100MG, 200MG & 400MG TABLETS
PL 00530/0727-30

**STEPS TAKEN FOR ASSESSMENT**

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 1&lt;sup&gt;st&lt;/sup&gt; August 2003.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 13&lt;sup&gt;th&lt;/sup&gt; October 2003.</td>
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<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality on 30&lt;sup&gt;th&lt;/sup&gt; October 2003 and 8&lt;sup&gt;th&lt;/sup&gt; October 2004.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 28&lt;sup&gt;th&lt;/sup&gt; November 2008 for the quality sections.</td>
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<tr>
<td>5</td>
<td>The applications were determined on 24&lt;sup&gt;th&lt;/sup&gt; April 2009.</td>
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AMISULPRIDE 50MG, 100MG, 200MG & 400MG TABLETS
PL 00530/0727-30

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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AMISULPRIDE 50MG, 100MG, 200MG & 400MG TABLETS
PL 00530/0727-30

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Amisulpride 50 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Amisulpride 50 mg per tablet
For excipients, see 6.1.

3 PHARMACEUTICAL FORM
White to off-white, round uncoated tablet with a break-line on one side and A1 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.

The minimum effective dose should be used.

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 (CRCL) between 30-60 ml/min and to a third in patients with CRCL between 10-30 ml/min.

As there is no experience in patients with severe renal impairment (CRCL < 10 ml/min) particular care is recommended in these patients (see 4.4 Special 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 medicinal product.
Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer.
Phaeochromocytoma.
Children under 15 years of age.
Lactation.
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, sulotropride, thioridazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxicin.
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 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.
Hyperglycaemia has been reported in patients treated with some atypical antipsychotic agents, including amisulpride, therefore patients with an established diagnosis of diabetes mellitus or with risk factors for diabetes who are started on amisulpride, should get appropriate glycaemic monitoring.
Amisulpride is eliminated by the renal route. In cases of renal insufficiency, the dose should be decreased or intermittent treatment could be considered (see Section 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 akathisia, 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 (see Section 4.8 Undesirable effects). This effect is known to potentiate the risk of serious ventricular arrhythmias such as torsades de pointes.
Before any administration, and if possible according to the patient's clinical status, it is recommended to monitor factors which could favour the occurrence of this rhythm disorder:
- bradycardia less than 55 bpm,
- cardiac disease or family history of sudden death or QT prolongation,
- electrolyte imbalance, in particular 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 QT interval (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Baseline ECG is recommended prior to treatment in all patients especially in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination.

During therapy, the need for ECG monitoring (e.g. at dose escalation) should be assessed on an individual patient basis.

The dose of Amisulpride should be reduced if QT is prolonged and discontinued if QTc is >500ms.

Periodic electrolyte monitoring is recommended particularly if the patient is taking diuretics or during inter-current illness.

Concomitant antipsychotics should be avoided.

**Stroke**

In randomized clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic drugs, a 3-fold increase of the risk of cerebrovascular events has been observed. The mechanism of such risk increase is not known. An increase in the risk with other antipsychotic drugs, or other populations of patients cannot be excluded. Amisulpride should be used with caution in patients with stroke risk factors.

### 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, sulotropride, thioridazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparflaxacin.

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 or could prolong the QT interval:
- Bradycardia-inducing medications such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine, guanfacine; digitalis.
- Medications which induce hypokalaemia or electrolyte imbalance: 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.
Very limited clinical data on exposed pregnancies are available. Therefore, the safety of Amisulpride during human pregnancy has not been established.
Use of the drug is not recommended during pregnancy unless the benefits justify the potential risks. If amisulpride is used during pregnancy, neonates may show adverse effects of amisulpride and thus appropriate monitoring should be considered.
For women of childbearing potential, effective contraception should be fully discussed with the physician prior to treatment.

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 cause somnolence so that the ability to drive vehicles or operate machinery can be impaired (see Section 4.8 Undesirable effects).

4.8 UNDESIRABLE EFFECTS
Adverse effects have been ranked under headings of frequency using the following convention: very common (1/10); common (1/100; <1/10); uncommon (1/1,000; <1/100); rare (1/10,000; <1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data).
Clinical trials data
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.
• Nervous system disorders:
  Very common: Extrapyramidal symptoms may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia, dyskinesia. These symptoms are generally mild at optimal dosages and partially reversible without discontinuation of amisulpride upon administration of antiparkinsonian medication. The incidence of extrapyramidal symptoms which is dose related, remains very low in the treatment of patients with predominantly negative symptoms with doses of 50-300 mg/day.
  Common: Acute dystonia (spasm torticollis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon treatment with an antiparkinsonian agent. Somnolence.
  Uncommon: Tardive dyskinesia characterized by rhythmic, involuntary movements primarily of the tongue and/or face have been reported, usually after long term administration.
  Seizures

Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms.
• Psychiatric disorders:
  Common: Insomnia, anxiety, agitation, orgasmic dysfunction
• Gastrointestinal disorders
  Common: Constipation, nausea, vomiting, dry mouth
• Endocrine disorders:
  Common: Amisulpride causes an increase in plasma prolactin levels which is reversible after drug discontinuation. This may result in galactorrhoea, amenorrhoea, gynaecomastia, breast pain, and erectile dysfunction.
• Metabolism and nutrition disorders
  Uncommon: Hyperglycemia (see 4.4 Special warnings and precautions for use).
• Cardiovascular disorders
  Common: Hypotension
  Uncommon: Bradycardia
• Investigations:
  Common: Weight gain
  Uncommon: Elevations of hepatic enzymes, mainly transaminases
• Immune system disorders
  Uncommon: Allergic reaction
Post Marketing data
In addition, cases of the following adverse reactions have been reported through spontaneous reporting only:
• Nervous system disorders:
  Frequency not known: Neuroleptic Malignant Syndrome (see 4.4 Special warnings and precautions for use).
• Cardiac disorders:
  Frequency not known: QT interval prolongation and ventricular arrhythmias such as torsade de pointes, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, sudden death (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, 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 D2/D3 receptor subtypes whereas it is devoid of affinity for D1, D4 and D5 receptor subtypes.

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

In 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 D2/D3 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
Colloidal silica anhydrous
Magnesium stearate

6.2 INCOMPATIBILITIES
None known.

6.3 SHELF LIFE
3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions

6.5 NATURE AND CONTENTS OF CONTAINER
PVC/aluminium foil blister packs containing 60 tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special precautions.

7 MARKETING AUTHORISATION HOLDER
Norton Healthcare Limited
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8 MARKETING AUTHORISATION NUMBER(S)
PL 00530/0727

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/04/2009

10 DATE OF REVISION OF THE TEXT
24/04/2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Amisulpride 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Amisulpride 100 mg per tablet
For excipients, see 6.1.

3 PHARMACEUTICAL FORM
White to off-white, round uncoated tablet with a break-line on one side and A2 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.

The minimum effective dose should be used.

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 (CRCL) between 30-60 ml/min and to a third in patients with CRCL between 10-30 ml/min.

As there is no experience in patients with severe renal impairment (CRCL < 10 ml/min) particular care is recommended in these patients (see 4.4 Special 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 medicinal product.
Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer.
Phaeochromocytoma.
Children under 15 years of age.
Lactation.
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, sulproide, thioridazine, methadone, 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 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.
Hyperglycaemia has been reported in patients treated with some atypical antipsychotic agents, including amisulpride, therefore patients with an established diagnosis of diabetes mellitus or with risk factors for diabetes who are started on amisulpride, should get appropriate glycaemic monitoring.
Amisulpride is eliminated by the renal route. In cases of renal insufficiency, the dose should be decreased or intermittent treatment could be considered (see Section 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 akathisia, 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 (see Section 4.8 Undesirable effects). This effect is known to potentiate the risk of serious ventricular arrhythmias such as torsades de pointes.
Before any administration, and if possible according to the patient's clinical status, it is recommended to monitor factors which could favour the occurrence of this rhythm disorder:
- bradycardia less than 55 bpm,
- cardiac disease or family history of sudden death or QT prolongation,
-electrolyte imbalance, in particular 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 QT interval (see Section 4.5 Interaction with other medicinal products and other forms of interaction).
Baseline ECG is recommended prior to treatment in all patients especially in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination.
During therapy, the need for ECG monitoring (e.g. at dose escalation) should be assessed on an individual patient basis.
The dose of Amisulpride should be reduced if QT is prolonged and discontinued if QTc is >500ms.
Periodic electrolyte monitoring is recommended particularly if the patient is taking diuretics or during inter-current illness.
Concomitant antipsychotics should be avoided.
Stroke
In randomized clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic drugs, a 3-fold increase of the risk of cerebrovascular events has been observed. The mechanism of such risk increase is not known. An increase in the risk with other antipsychotic drugs, or other populations of patients cannot be excluded. Amisulpride should be used with caution in patients with stroke risk factors.

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, methadone, 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 or could prolong the QT interval:
- Bradycardia-inducing medications such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine, guanfacine; digitalis.
- Medications which induce hypokalaemia or electrolyte imbalance: 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.

Very limited clinical data on exposed pregnancies are available. Therefore, the safety of Amisulpride during human pregnancy has not been established.

Use of the drug is not recommended during pregnancy unless the benefits justify the potential risks. If amisulpride is used during pregnancy, neonates may show adverse effects of amisulpride and thus appropriate monitoring should be considered.

For women of childbearing potential, effective contraception should be fully discussed with the physician prior to treatment.

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 cause somnolence so that the ability to drive vehicles or operate machinery can be impaired (see Section 4.8 Undesirable effects).

4.8 UNDESIRABLE EFFECTS
Adverse effects have been ranked under headings of frequency using the following convention:
very common (≥1/10); common (≥1/100; <1/10); uncommon (≥1/1,000; <1/100); rare (≥1/10,000; <1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data).

Clinical trials data
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.

• Nervous system disorders:
  Very common: Extrapyramidal symptoms may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia, dyskinesia. These symptoms are generally mild at optimal dosages and partially reversible without discontinuation of amisulpride upon administration of antiparkinsonian medication. The incidence of extrapyramidal symptoms which is dose related, remains very low in the treatment of patients with predominantly negative symptoms with doses of 50-300 mg/day.
  Common: Acute dystonia (spasm torticollis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon treatment with an antiparkinsonian agent. Somnolence.
  Uncommon: Tardive dyskinesia characterized by rhythmic, involuntary movements primarily of the tongue and/or face have been reported, usually after long term administration. Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms. Seizures
• Psychiatric disorders:
  Common: Insomnia, anxiety, agitation, orgasmic dysfunction
• Gastrointestinal disorders
  Common: Constipation, nausea, vomiting, dry mouth
• Endocrine disorders:
  Common: Amisulpride causes an increase in plasma prolactin levels which is reversible after drug discontinuation. This may result in galactorrhoea, amenorrhoea, gynaecomastia, breast pain, and erectile dysfunction.
• Metabolism and nutrition disorders
  Uncommon: Hyperglycemia (see 4.4 Special warnings and precautions for use).
• Cardiovascular disorders
  Common: Hypotension
  Uncommon: Bradycardia
• Investigations:
  Common: Weight gain
  Uncommon: Elevations of hepatic enzymes, mainly transaminases
• Immune system disorders
  Uncommon: Allergic reaction

Post Marketing data
In addition, cases of the following adverse reactions have been reported through spontaneous reporting only:
• Nervous system disorders:
  Frequency not known: Neuroleptic Malignant Syndrome (see 4.4 Special warnings and precautions for use).
• Cardiac disorders:
  Frequency not known: QT interval prolongation and ventricular arrhythmias such as torsade de pointes, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, sudden death (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, 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 D2/D3 receptor subtypes whereas it is devoid of affinity for D1, D4 and D5 receptor subtypes.

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

In 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 D2/D3 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
Magnesium stearate (E572)
Colloidal silica anhydrous

6.2 INCOMPATIBILITIES
None known.

6.3 SHELF LIFE
3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions

6.5 NATURE AND CONTENTS OF CONTAINER
PVC/aluminium foil blister packs containing 60 tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special precautions.

7 MARKETING AUTHORISATION HOLDER
Norton Healthcare Limited
T/A IVAX Pharmaceuticals UK Limited
Regent House
5/7 Broadhurst Gardens
London
NW6 3RZ

8 MARKETING AUTHORISATION NUMBER(S)
PL 00530/0728

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/04/2009

10 DATE OF REVISION OF THE TEXT
24/04/2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Amisulpride 200 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Amisulpride 200 mg per tablet
For excipients, see 6.1.

3 PHARMACEUTICAL FORM
White to off-white, round uncoated tablet with a break-line on one side and A3 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.

The minimum effective dose should be used.

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 (CRCL) between 30-60 ml/min and to a third in patients with CRCL between 10-30 ml/min.

As there is no experience in patients with severe renal impairment (CRCL < 10 ml/min) particular care is recommended in these patients (see 4.4 Special 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 medicinal product.
Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer.
Phaeochromocytoma.
Children under 15 years of age.
Lactation.

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, sulotropride, thioridazine, methadone, 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 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.

Hyperglycaemia has been reported in patients treated with some atypical antipsychotic agents, including amisulpride, therefore patients with an established diagnosis of diabetes mellitus or with risk factors for diabetes who are started on amisulpride, should get appropriate glycaemic monitoring.

Amisulpride is eliminated by the renal route. In cases of renal insufficiency, the dose should be decreased or intermittent treatment could be considered (see Section 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 akathisia, 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 (see Section 4.8 Undesirable effects). This effect is known to potentiate the risk of serious ventricular arrhythmias such as torsades de pointes.

Before any administration, and if possible according to the patient's clinical status, it is recommended to monitor factors which could favour the occurrence of this rhythm disorder:
- bradycardia less than 55 bpm,
- cardiac disease or family history of sudden death or QT prolongation,
- electrolyte imbalance, in particular 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 QT interval (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Baseline ECG is recommended prior to treatment in all patients especially in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination.

During therapy, the need for ECG monitoring (e.g. at dose escalation) should be assessed on an individual patient basis.

The dose of Amisulpride should be reduced if QT is prolonged and discontinued if QTc is >500ms.

Periodic electrolyte monitoring is recommended particularly if the patient is taking diuretics or during inter-current illness.

Concomitant antipsychotics should be avoided.

Stroke

In randomized clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic drugs, a 3-fold increase of the risk of cerebrovascular events has been observed. The mechanism of such risk increase is not known. An increase in the risk with other antipsychotic drugs, or other populations of patients cannot be excluded. Amisulpride should be used with caution in patients with stroke risk factors.

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, sulotropride, thioridazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacín.

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 or could prolong the QT interval:

- Bradycardia-inducing medications such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine, guanfacine; digitalis.
- Medications which induce hypokalaemia or electrolyte imbalance: 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.
Very limited clinical data on exposed pregnancies are available. Therefore, the safety of Amisulpride during human pregnancy has not been established.
Use of the drug is not recommended during pregnancy unless the benefits justify the potential risks. If amisulpride is used during pregnancy, neonates may show adverse effects of amisulpride and thus appropriate monitoring should be considered.
For women of childbearing potential, effective contraception should be fully discussed with the physician prior to treatment.

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 cause somnolence so that the ability to drive vehicles or operate machinery can be impaired (see Section 4.8 Undesirable effects).

4.8 UNDESIRABLE EFFECTS
Adverse effects have been ranked under headings of frequency using the following convention:
very common (1/10); common (1/100; <1/10); uncommon (≥1/1,000; <1/100); rare (1/10,000; <1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data).

Clinical trials data
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.

• Nervous system disorders:
  Very common: Extrapyramidal symptoms may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia, dyskinesia. These symptoms are generally mild at optimal dosages and partially reversible without discontinuation of amisulpride upon administration of antiparkinsonian medication. The incidence of extrapyramidal symptoms which is dose related, remains very low in the treatment of patients with predominantly negative symptoms with doses of 50-300 mg/day.
  Common: Acute dystonia (spasm torticollis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon treatment with an antiparkinsonian agent. Somnolence.
  Uncommon: Tardive dyskinesia characterized by rhythmic, involuntary movements primarily of the tongue and/or face have been reported, usually after long term administration. Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms.
  Seizures
• Psychiatric disorders:
  Common: Insomnia, anxiety, agitation, orgasmic dysfunction

• Gastrointestinal disorders
  Common: Constipation, nausea, vomiting, dry mouth

• Endocrine disorders:
  Common: Amisulpride causes an increase in plasma prolactin levels which is reversible after drug discontinuation. This may result in galactorrhoea, amenorrhoea, gynaecomastia, breast pain, and erectile dysfunction.

• Metabolism and nutrition disorders
  Uncommon: Hyperglycemia (see 4.4 Special warnings and precautions for use).

• Cardiovascular disorders
  Common: Hypotension
  Uncommon: Bradycardia

• Investigations:
  Common: Weight gain
  Uncommon: Elevations of hepatic enzymes, mainly transaminases

• Immune system disorders
  Uncommon: Allergic reaction

Post Marketing data

In addition, cases of the following adverse reactions have been reported through spontaneous reporting only:

• Nervous system disorders:
  Frequency not known: Neuroleptic Malignant Syndrome (see 4.4 Special warnings and precautions for use).

• Cardiac disorders:
  Frequency not known: QT interval prolongation and ventricular arrhythmias such as torsade de pointes, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, sudden death (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, 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

Pharmcotherapeutic group: Antipsychotics

ATC Code: NO5A LO5
Amisulpride binds selectively with a high affinity to human dopaminergic D2/D3 receptor subtypes whereas it is devoid of affinity for D1, D4 and D5 receptor subtypes.

Unlike classical and atypical neuroleptics, amisulpride has no affinity for serotonin, β-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 pre-synaptic D2/D3 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.
**PHARMACEUTICAL PARTICULARS**

**6.1 LIST OF EXCIPIENTS**
Maize starch
Lactose monohydrate
Methylcellulose
Magnesium stearate (E572)
Colloidal silica anhydrous

**6.2 INCOMPATIBILITIES**
None known.

**6.3 SHELF LIFE**
3 years

**6.4 SPECIAL PRECAUTIONS FOR STORAGE**
This medicinal product does not require any special storage conditions

**6.5 NATURE AND CONTENTS OF CONTAINER**
PVC/aluminium foil blister packs containing 60 tablets

**6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**
No special precautions.

**7 MARKETING AUTHORISATION HOLDER**
Norton Healthcare Limited
T/A IVAX Pharmaceuticals UK Limited
Regent House
5/7 Broadhurst Gardens
London
NW6 3RZ

**8 MARKETING AUTHORISATION NUMBER(S)**
PL 00530/0729

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
24/04/2009

**10 DATE OF REVISION OF THE TEXT**
24/04/2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Amisulpride 400 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Amisulpride 400 mg per tablet
For excipients, see 6.1.

3 PHARMACEUTICAL FORM
White to off-white, film-coated, capsule-shaped tablet, with a break line on one side, plain on the other.

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.

The minimum effective dose should be used.

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 (CRCL) between 30-60 ml/min and to a third in patients with CRCL between 10-30 ml/min.

As there is no experience in patients with severe renal impairment (CRCL < 10 ml/min) particular care is recommended in these patients (see 4.4 Special 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 medicinal product.

Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer.
Phaeochromocytoma.
Children under 15 years of age.
Lactation.
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, sulotopride, thioridazine, methadone, 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 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.

Hyperglycaemia has been reported in patients treated with some atypical antipsychotic agents, including amisulpride, therefore patients with an established diagnosis of diabetes mellitus or with risk factors for diabetes who are started on amisulpride, should get appropriate glycaemic monitoring.

Amisulpride is eliminated by the renal route. In cases of renal insufficiency, the dose should be decreased or intermittent treatment could be considered (see Section 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 akathisia, 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 (see Section 4.8 Undesirable effects). This effect is known to potentiate the risk of serious ventricular arrhythmias such as torsades de pointes.

Before any administration, and if possible according to the patient's clinical status, it is recommended to monitor factors which could favour the occurrence of this rhythm disorder:
- bradycardia less than 55 bpm,
- cardiac disease or family history of sudden death or QT prolongation,
- electrolyte imbalance, in particular 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 QT interval (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Baseline ECG is recommended prior to treatment in all patients especially in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination.

During therapy, the need for ECG monitoring (e.g. at dose escalation) should be assessed on an individual patient basis.

The dose of Amisulpride should be reduced if QT is prolonged and discontinued if QTc is >500ms.

Periodic electrolyte monitoring is recommended particularly if the patient is taking diuretics or during inter-current illness.

Concomitant antipsychotics should be avoided.

Stroke

In randomized clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic drugs, a 3-fold increase of the risk of cerebrovascular events has been observed. The mechanism of such risk increase is not known. An increase in the risk with other antipsychotic drugs, or other populations of patients cannot be excluded. Amisulpride should be used with caution in patients with stroke risk factors.

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, sulotropride, thioridazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfluoxacin.

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 or could prolong the QT interval:
- Bradycardia-inducing medications such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine, guanfacine; digitalis.
- Medications which induce hypokalaemia or electrolyte imbalance: 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
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.

Very limited clinical data on exposed pregnancies are available. Therefore, the safety of Amisulpride during human pregnancy has not been established.

Use of the drug is not recommended during pregnancy unless the benefits justify the potential risks. If amisulpride is used during pregnancy, neonates may show adverse effects of amisulpride and thus appropriate monitoring should be considered.

For women of childbearing potential, effective contraception should be fully discussed with the physician prior to treatment.

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 cause somnolence so that the ability to drive vehicles or operate machinery can be impaired (see Section 4.8 Undesirable effects).

4.8 UNDESIRABLE EFFECTS

Adverse effects have been ranked under headings of frequency using the following convention: very common (1/10); common (1/100; <1/10); uncommon (1/1,000;<1/100); rare (1/10,000;<1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data).

Clinical trials data

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.

• Nervous system disorders:

  Very common: Extrapyramidal symptoms may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia, dyskinesia. These symptoms are generally mild at optimal dosages and partially reversible without discontinuation of amisulpride upon administration of antiparkinsonian medication. The incidence of extrapyramidal symptoms which is dose related, remains very low in the treatment of patients with predominantly negative symptoms with doses of 50-300 mg/day.

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

  Uncommon: Tardive dyskinesia characterized by rhythmic, involuntary movements primarily of the tongue and/or face have been reported, usually after long term administration. Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms.

  Seizures

• Psychiatric disorders:

  Common: Insomnia, anxiety, agitation, orgasmic dysfunction

• Gastrointestinal disorders
Common: Constipation, nausea, vomiting, dry mouth

• Endocrine disorders:
  Common: Amisulpride causes an increase in plasma prolactin levels which is reversible after drug discontinuation. This may result in galactorrhoea, amenorrhoea, gynaecomastia, breast pain, and erectile dysfunction.

• Metabolism and nutrition disorders
  Uncommon: Hyperglycemia (see 4.4 Special warnings and precautions for use).

• Cardiovascular disorders
  Common: Hypotension
  Uncommon: Bradycardia

• Investigations:
  Common: Weight gain
  Uncommon: Elevations of hepatic enzymes, mainly transaminases

• Immune system disorders
  Uncommon: Allergic reaction

Post Marketing data
In addition, cases of the following adverse reactions have been reported through spontaneous reporting only:

• Nervous system disorders:
  Frequency not known: Neuroleptic Malignant Syndrome (see 4.4 Special warnings and precautions for use).

• Cardiac disorders:
  Frequency not known: QT interval prolongation and ventricular arrhythmias such as torsade de pointes, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, sudden death (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, 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 D2/D3 receptor subtypes whereas it is devoid of affinity for D1, D4 and D5 receptor subtypes.
Unlike classical and atypical neuroleptics, amisulpride has no affinity for serotonin, α-adrenergic, histamine H1 and cholinergic receptors. In addition, amisulpride does not bind to sigma sites.

In 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 D2/D3 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
Sodium starch glycolate
Lactose monohydrate
Methycellulose
Microcrystalline cellulose (E460)
Magnesium stearate (E572)

Film-Coating
Basic butylated methacrylate polymers (Eudragit E100)
Titanium dioxide (E171)
Talc
Magnesium Stearate
Macrogol 6000

6.2 INCOMPATIBILITIES
None known.

6.3 SHELF LIFE
3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions

6.5 NATURE AND CONTENTS OF CONTAINER
PVC/aluminium foil blister packs containing 60 tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special precautions.

7 MARKETING AUTHORITY
Norton Healthcare Limited
T/A IVAX Pharmaceuticals UK Limited
Regent House
5/7 Broadhurst Gardens
London
NW6 3RZ
United Kingdom

8 MARKETING AUTHORIZATION NUMBER(S)
PL 00289/0730

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
24/04/2009

10 DATE OF REVISION OF THE TEXT
24/04/2009
AMISULPRIDE 50MG, 100MG, 200MG & 400MG TABLETS
PL 00530/0727-30

PATIENT INFORMATION LEAFLET

AMISULPRIDE 50 mg, 100 mg, 200 mg and 400 mg TABLETS

PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.

This medicine may be dangerous if you pass it on to others. It may harm them, even if their symptoms are the same as yours.

If any of the side effects gets serious, or if you notice any side effects that are not listed in this leaflet, get lost your doctor or pharmacist.

1 WHAT AMISULPRIDE TABLETS ARE AND WHAT THEY ARE USED FOR

Amisulpride belongs to a group of medicines called antipsychotics. The main purpose of these medicines is to treat schizophrenia and the symptoms of acute and chronic schizophrenic illness. This condition causes abnormalities such as becoming withdrawn, seeing or hearing things that aren't there, believing things that aren't true, and unexplained beliefs or unfounded suspicions.

2 BEFORE YOU TAKE AMISULPRIDE TABLETS

Do not take Amisulpride Tablets if you:
- are allergic or hypersensitive to amisulpride or any of the other ingredients of Amisulpride Tablets. Consult your doctor or pharmacist for advice.
- are breastfeeding (see section 4.4 'Effects on ability to drive and use machinery').
- have a pharyngoesophageal reflux disease.
- have a tumour on the adrenal gland or related to breast cancer.
- have a tumour on the adrenal gland or adrenal gland enlarged.
- have a history of Parkinson's disease under the age of 15.
- are taking any medicine within the 'taking other medicines' section which are listed under to not take Amisulpride Tablets.

Take special care with Amisulpride Tablets and tell your doctor or pharmacist before you start to take this medicine if:
- have kidney problems.
- have Parkinson's disease.
- have a history of epileptic seizures.
- have a heart problem, or a family history of heart problems or some relatives.
- have low potassium levels in your blood (hypokalaemia).
- have diabetes or you are at a higher risk of having diabetes.

Take other medicines

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed for you, including herbal medicines and other medicines available from your local supermarket, chemist, health food store, or from alternative medicine practitioners. This is because some medicines can affect the way Amisulpride works.

Consult your doctor or pharmacist before taking any other medication.

Do not take Amisulpride Tablets if you are taking any of the following:
- medicines to treat heart problems (antiarrhythmics), such as quinidine, disopyramide, procainamide, amiodarone, sotalol or flecainide.
- antibiotics such as IV 
  - amoxicillin, tetracycline, luteomycin, halofantrine or pantoprazole
- medicines to treat high blood pressure (antihypertensives), such as 
  - diuretics (used in Parkinson's disease).
- medicines to treat high blood pressure 
  - IV metoclopramide for heartburn
- methadone used for pain relief, 

In particular tell your doctor or pharmacist if you are taking any of the following:
- medicines that decrease potassium levels in your blood, e.g. water tablets (diuretics), 
  - laxatives, glucocorticoids (e.g. prednison, prednisolone), 
  - other inflammatory disease) 
  - antihypertensives (used to treat fungal disease), 
  - tricyclic antidepressants (used to treat anxiety) 
  - to sleep 
  - to lower your heart beat or cause heart failure 
  - to lower blood pressure such as diuretics and its derivatives 
  - digoxin (to treat cardiac heart failure 
  - any other medicines to treat mental disorders such as antidepressants, mood stabilizers, benzodiazepines 
  - taking antidepressants, 
  - Central nervous system depressants (medicines that act on the brain such as sleeping tablets, pain relievers, sedatives, hypnotics, 
  - analgesics, - anti allergic and hayfever), barbiturates and benzodiazepines (sleeping tablets) and medicine used to treat anxiety.

Taking Amisulpride Tablets with 

Food and Drink

- Some types of meal may affect how quickly the medicine works. If possible, it is best to take Amisulpride Tablets before meals on an empty stomach at the same time each day.
- You should not drink alcohol while you are taking Amisulpride Tablets as the effects of alcohol may be increased.

Pregnancy and breast-feeding

- Do not take Amisulpride Tablets if you are pregnant or are planning to become pregnant, or are breast-feeding, or are breastfeeding.
- The medicine should be used with caution if you are breastfeeding.
- Adequate contraception should be used when taking Amisulpride Tablets.
- Please read section 4.4 'Effects on ability to drive and use machinery'.

Important information about some of the ingredients of Amisulpride Tablets

- This medicinal product contains lactose. If you have been told by your doctor that you have an intolerance to certain sugars, please consult your pharmacist before taking this medicinal product.

3 HOW TO TAKE AMISULPRIDE TABLETS

You must take your tablets exactly as your doctor has told you. You should ask your doctor or pharmacist if you are not sure.
Always swallow your tablets whole with a large glass of water and about the same time each day.

- Adults and children over the age of 15 years old 
  - The usual dose of Amisulpride Tablets is 50 mg, 100 mg, 200 mg or 400 mg per day. The dose may be increased up to 1200 mg per day.
  - If you are taking 100 mg or less of amisulpride, you should take this once a day.
  - If you are taking more than 200 mg amisulpride a day you should divide this into two - take half in the morning and half in the evening. You are in any case not to exceed the maximum daily dose as instructed by your doctor or pharmacist.

- Elderly
  - Your doctor should monitor you closely when taking Amisulpride Tablets as you are more likely to react to side effects such as high blood pressure or drowsiness.

42
Reduced Kidney Function

Your doctor may decide to give you a lower dose.

Children

Amisulpride Tablets must not be used in children under 15 years of age.

If you take more Amisulpride Tablets

If you or anyone else swallows too much Amisulpride Tablets, contact your nearest hospital casualty department or a doctor immediately. Always take any remaining tablets and this leaflet with you. Symptoms of an overdose may include coma, low blood pressure, slowness, restlessness, sleepiness, shaking or slow movement.

If you forget to take Amisulpride Tablets

If you forget to take a dose, take it as soon as you remember, unless it is nearly time for your next dose. Do not take a double dose to make up for the one you have missed.

If you stop taking Amisulpride Tablets

You should only stop taking your tablets if advised by your doctor. Stopping Amisulpride abruptly may cause withdrawal effects such as feeling sick, vomiting, sweats, sweating, sleeplessness, extreme restlessness, muscle stiffness or abnormal movements of your original condition may come back. Always follow your doctor’s instructions carefully.

Possible Side Effects

Like all medicines, Amisulpride Tablets can cause side effects, although not everybody gets them.

If the following happens, stop taking the tablets and tell your doctor immediately or go to the casualty department of your nearest hospital:

- an allergic reaction (swelling of the face, lips, or tongue, skin rash, or hives)
- slow heart beat
- changes in the level of liver enzymes
- an allergic reaction (swelling of the lips, face or neck leading to severe difficulty in breathing; skin rash or hives)
- involuntary movement of the face and or tongue.

The following have also been reported at an unknown frequency:

- dizziness
- abnormal heart rhythm and sudden unusual death
- convulsions
- skin rash or hives
- severe difficulty in breathing: skin rash or hives
- changes in the level of liver enzymes
- an allergic reaction (swelling of the lips, face or neck leading to severe difficulty in breathing; skin rash or hives)
- involuntary movement of the face and or tongue.

If any of the side effects get serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.

FURTHER INFORMATION

What Amisulpride Tablets contain

The active substance is amisulpride. Each tablet contains either 50 mg, 100 mg, 200 mg or 400 mg of amisulpride.

- Amisulpride 50 mg, 100 mg and 200 mg tablets also contain starch, lactose monohydrate, magnesium stearate.
- Amisulpride 400 mg Tablets also contain: starch, lactose monohydrate, magnesium stearate.
- The tablet coating contains: purified water, polyvinylalcohol, magnesium stearate, and microcrystalline cellulose.
- Amisulpride Tablets look like and are similar to the other tablets of the pack.

Marketing Authorisation Holder and Manufacturer

The marketing authorisation holder is TEVA UK Limited, Regent House, 5-7 Broadhurst Gardens, London, NW8 3SZ.

Company responsible for manufacture is TEVA UK Limited, Eastbourne, BN22 9AG.

Distributed by: TEVA UK, Leeds, LS17 6UG.

This leaflet was last revised: October 2008.
AMISULPRIDE 100MG TABLETS
PL 00530/0728
LABEL

Each tablet contains 100 mg of amisulpride. Amisulpride is an antipsychotic.

DOSAGE:
Use as directed by the doctor. Please read the enclosed package leaflet before use.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

There are no special storage conditions.

BLISTER FOIL
AMISULPRIDE 200MG TABLETS
PL 00530/0729
LABEL

BLISTER FOIL
AMISULPRIDE 400MG TABLETS
PL 00530/0730
LABEL

BLISTER FOIL

Each tablet contains 400mg of amisulpride. Store below 25°C in the blister foil pack.

Keep out of the reach and sight of children.

Do not exceed the recommended dose.

Contraindications...

Side effects...

Use with caution in patients with primary depression.

Consult a doctor if you have any concerns.

Return any unused tablets here.