Public Assessment Report

Decentralised Procedure

AMISULPRIDE 50MG, 100MG AND 200MG TABLETS
AMISULPRIDE 400MG FILM-COATED TABLETS

Procedure No: UK/H/2385/001-004/DC
Procedure No: UK/H/2386/001-004/DC
Procedure No: UK/H/2387/001-004/DC

UK Licence No: PL 16866/0043-54

YES Pharmaceutical Development Services GmbH
LAY SUMMARY

On 14 and 21 June 2010, the MHRA granted to YES Pharmaceutical Development Services GmbH, Marketing Authorisations for the medicinal products Amisulpride 50mg, 100mg, 200mg Tablets, and Amisulpride 400mg Film-Coated Tablets (PL 16866/0043-54; UK/H/2385-7/001-4/DC).

Amisulpride belongs to a group of medicines called antipsychotics and is used to treat schizophrenia, when it starts and also over the long-term. Symptoms of this disorder include:

- so called positive symptoms: hallucinations, such as feeling, seeing or hearing things which do not exist; strange and/or frightening thoughts and changes in your behaviour, which can be aggressive
- so called negative symptoms: becoming withdrawn and subdued.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Amisulpride 50mg, 100mg and 200mg Tablets, and Amisulpride 400mg Film-Coated Tablets outweigh the risks, hence Marketing Authorisations have been granted.
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3 Non-clinical aspects
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Module 6 Steps taken after initial procedure
## Module 1

| **Product Name** | Amisulpride 50mg Tablets  
| | Amisulpride 100mg Tablets  
| | Amisulpride 200mg Tablets  
| | Amisulpride 400mg Film-coated Tablets  
| **Type of Application** | Generic, Article 10.1  
| **Active Substances** | Amisulpride  
| **Form** | Tablet/Film-coated Tablet  
| **Strength** | 50mg, 100mg and 200mg tablets, and 400mg film-coated tablets  
| **MA Holder** | YES Pharmaceutical Development Services GmbH  
| | Bahnstrasse 42-46, 61381 Friedrichsdorf, Germany  
| **Reference Member State (RMS)** | UK  
| **Concerned Member States (CMS)** | UK/H/2385/001-004/DC: Belgium, Germany, Greece, Italy (50, 200 and 400mg only), Portugal, Romania (200 and 400mg only) and Slovakia (200mg and 400mg only)  
| | UK/H/2386/001-004/DC: Germany  
| | UK/H/2387/001-004/DC: Germany  
| **Procedure Numbers** | UK/H/2385-7/001-4/DC  
| **Timetable** | Day 210 – 12 May 2010  

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINE
Amisulpride 50 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 50 mg amisulpride
Excipients: 23.75 mg lactose/tablet
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
White, round (6 mm diameter), bi-convex tablet with score line. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Amisulpride is indicated for the treatment of acute and chronic schizophrenic disorders with:
- positive symptoms such as delusions, hallucinations, thought disorders, hostility, suspiciousness
- negative symptoms (deficit syndrome) such as blunted affect, emotional and social withdrawal.
This includes patients with predominant negative symptoms.

4.2 Posology and method of administration
Posology
For acute psychotic episodes, oral doses between 400 mg/day and 800 mg/day are recommended. In individual cases, the daily dose may be increased up to 1200 mg. Doses above 1200 mg/day 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 in example between 400-800mg/day. Maintenance treatment should be established individually with the minimally effective dose.

For patients characterised by predominant negative symptoms, oral doses between 50 mg/day and 300 mg/day are recommended. Doses should be adjusted individually.

Amisulpride can be administered once daily at oral doses up to 300 mg, higher doses should be administered bid.
The minimum effective dose and appropriate strength tablets should be used.

Special populations
Elderly patients over 65 years: Treatment of elderly patients is not recommended as there is no sufficient clinical experience. If treatment with amisulpride is absolutely necessary particular caution is required due to a possible risk of hypotension or sedation.

Children and adolescents: Efficacy and safety of amisulpride in children and adolescents under 18 years of age have not been established. There are only limited data available on the use of amisulpride in adolescents in schizophrenia. Therefore, amisulpride should not be used in adolescents from 15 to 18 years of age until further data are available. If absolutely required treatment of adolescents must be initiated and performed by a physician experienced in treating schizophrenia in this age group. The use of amisulpride is contraindicated in children and adolescents under 15 years of age (see section 4.3).

Renal impairment: Amisulpride is eliminated by the renal route. In renal insufficiency, the dose should be reduced to half in patients with creatinine clearance (CR\text{CL}) between 30-60 ml/min and to a third in patients with CR\text{CL} between 10-30 ml/min.
As there is no experience in patients with severe renal impairment (CRCL < 10 ml/min) amisulpride should not be used in these patients (see section 4.4).

Hepatic impairment: since amisulpride is weakly metabolised a dosage reduction should not be necessary.

Duration of treatment
Data from controlled clinical trials covering a period of 1 year is available. The duration of treatment should be determined by the treating physician.

Method of administration
Amisulpride can be administered with or without food. The tablets should be taken without chewing with a sufficient amount of water.

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

4.3 Contraindications
- hypersensitivity to the active substance or to any of the excipients of the medicinal product
- concomitant prolactin-dependent tumours, e.g. pituitary gland prolactinomas and breast cancer
- phaeochromocytoma
- children and adolescents under 15 years of age
- lactation (see section 4.6)
- combination with levodopa (see section 4.5)
- combination with the following medicinal products which could induce torsades de pointes:
  - class I antiarrhythmics such as quinidine, disopyramide, procainamide, flecainide and propafenone
  - class III antiarrhythmics such as amiodarone and sotalol
  - other medicinal products such as bepridil, cisapride, sulthiame, thioridazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin, azole antifungals.

(see section 4.5)

4.4 Special warnings and precautions for use
As with other antipsychotics, neuroleptic malignant syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK, may occur. In the event of hyperthermia, particularly with high daily doses, all antipsychotic medicinal products 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).

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

In elderly patients (over 65 years), amisulpride, like other antipsychotics, 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 antipsychotic treatment cannot be avoided.
Acute withdrawal symptoms including nausea, vomiting and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotics. 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). This effect is known to potentiate the risk of serious ventricular arrhythmias such as torsades de pointes. Before any administration, and if possible according to the patient's clinical status, it is recommended to exclude the following factors which could favour the occurrence of this rhythm disorder:

- 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 medicinal product likely to produce pronounced bradycardia (< 55 bpm), hypokalaemia, decreased intracardiac conduction, or prolongation of the QT interval (see section 4.5).

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 (see section 4.5).

**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.

**Increased mortality in elderly people with dementia**
Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known. Amisulpride is not licensed for the treatment of dementia-related behavioural disturbances.

**Venous thromboembolism**
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with amisulpride and preventive measures undertaken.

**Lactose**
Amisulpride tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
4.5 Interaction with other medicinal products and other forms of interaction

Combinations which are contraindicated (see also section 4.3)

Medicinal products which could induce torsades de pointes:
- class I antiarrhythmics such as quinidine, disopyramide, procainamide, flecainide and propafenone
- class III antiarrhythmics such as amiodarone and sotalol
- other medicinal products such as bepridil, cisapride, sulpropride, thioridazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin, azole antifungals.

Levodopa: reciprocal antagonism of effects between levodopa and antipsychotics.

Combinations which are not recommended

Medicinal products which enhance the risk of torsades de pointes or could prolong the QT interval:
- bradycardia-inducing medicinal products such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine, guanfacine; and digitalis
- medicinal products which induce hypokalaemia or electrolyte imbalance: hypokalemic diuretics, stimulant laxatives, IV amphotericin B, glucocorticoids, and tetracosactides.
  Hypokalaemia should be corrected.
- antipsychotics such as pimozide, and haloperidol
- imipramine antidepressants
- lithium
- some antihistamines such as astemizole, and terfenadine.

Amisulpride may enhance the central effects of alcohol. Therefore, alcohol should not be consumed during treatment.

Combinations which require precautions for use

Concomitant use of the following agents can lead to potentiation of the effect:
- CNS depressants including narcotics, anaesthetics, analgesics, sedative H1 antihistamines, barbiturates, benzodiazepines and other anxiolytic drugs, clonidine and derivatives
- antihypertensive and other hypotensive medicinal products

4.6 Pregnancy and lactation

Pregnancy

In animals, amisulpride did not show reproductive toxicity. A decrease in fertility linked to its pharmacological effects (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 this medicinal product 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 contraindicated.

4.7 Effects on ability to drive and use machines

This medicinal product can have minor or moderate influence on the ability to drive and use machines. Even used as recommended, amisulpride may affect reaction time (e.g. caused by somnolence) so that the ability to drive vehicles or operate machinery can be impaired (see section 4.8). This effect is enhanced by the consumption of alcohol.
4.8 Undesirable effects

The following frequency estimates are used in assessing adverse effects:

- **Very common:** (≥1/10)
- **Common:** (≥1/100 to <1/10)
- **Uncommon:** (≥1/1,000 to <1/100)
- **Rare:** (≥1/10,000 to <1/1,000)
- **Very rare:** (<1/10,000)
- **Not known:** (cannot be estimated from the available data)

**CLINICAL TRIALS DATA**

The following adverse 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.

**Immune system disorders**
- **Uncommon:** Allergic reaction

**Endocrine disorders**
- **Common:** Increase in plasma prolactin levels which is reversible after discontinuation of amisulpride. This may result in galactorrhoea, amenorrhoea or menstrual disorders, gynaecomastia, breast pain or breast enlargement, prolactinoma (see section 4.3) and erectile dysfunction.

**Metabolism and nutrition disorders**
- **Uncommon:** Hyperglycemia (see section 4.4)

**Psychiatric disorders**
- **Common:** Insomnia, anxiety, agitation, orgasmic dysfunction

**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 should not be used as it is ineffective or may induce aggravation of the symptoms. Seizures

**Cardiac disorders**
- **Uncommon:** Bradycardia

**Vascular disorders**
- **Common:** Hypotension

**Gastrointestinal disorders**
- **Common:** Constipation, nausea, vomiting, dry mouth
General disorders

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

Investigations

Common:
Weight gain

Uncommon:
Elevations of hepatic enzymes, mainly transaminases

POST MARKETING DATA

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

Nervous system disorders

Not known:
Neuroleptic malignant syndrome (see section 4.4)

Cardiac disorders

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 section 4.4)

Vascular disorders

Not known:
Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein
thrombosis have been reported with antipsychotic drugs.

Skin and subcutaneous tissue disorders

Not known:
Angioedema, urticaria

4.9 Overdose

Symptoms

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

Fatal outcomes have been reported mainly in combination with other psychotropic agents.

Treatment

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 it. 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 until the patient recovers.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antipsychotics: benzamides
ATC code: N05AL05

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
antipsychotics, amisulpride has no affinity for serotonin, alpha-adrenergic, histamine H1 and
cholinergic receptors. In addition, amisulpride does not bind to sigma sites. In animal studies, at high
doses, amisulpride blocks dopamine receptors located in the limbic structures in preference to those in
the striatum. At low doses it preferentially blocks 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 ng/ml and 54 ± 4 ng/ml after a 50 mg dose.

The volume of distribution is 5.8 l/kg bodyweight, plasma protein binding is low (16%) and no drug interactions are suspected.

Absolute bioavailability is 48%. Amisulpride is weakly metabolised: two inactive metabolites, accounting for approximately 4% of the dose, have been identified. There is no accumulation of amisulpride and its pharmacokinetics remain unchanged after the administration of repeated doses. The elimination half-life of amisulpride is approximately 12 hours after an oral dose.

Amisulpride is eliminated unchanged in the urine. Fifty percent of an intravenous dose is excreted via the urine, of which 90% is eliminated in the first 24 hours. Renal clearance is in the order of 20 l/h or 330 ml/min.

A carbohydrate rich meal (containing 68% fluids) significantly decreases the AUCs, \( T_{\text{max}} \) and \( C_{\text{max}} \) of amisulpride but no changes were seen after a high fat meal. However, the significance of these findings in routine clinical use is not known.

Hepatic impairment
Since amisulpride is weakly metabolised a dosage reduction should not be necessary in patients with hepatic insufficiency.

Renal impairment
The elimination half-life is increased in patients with renal insufficiency while systemic clearance is reduced by a factor of 2.5 to 3. The AUC of amisulpride in mild renal failure increased two fold and almost tenfold in moderate renal failure (see section 4.2). Experience is however limited and there is no data with doses greater than 50 mg.

Amisulpride is very weakly dialysed.

Elderly patients over 65 years
Limited pharmacokinetic data in this patient group show that a 10-30% rise occurs in \( C_{\text{max}} \), \( T_{\text{1/2}} \) and AUC after a single oral dose of 50 mg. No data are available after repeat dosing.

5.3 Preclinical safety data
An overall review of the completed safety studies indicates that amisulpride is devoid of any general, organ-specific, teratogenic, mutagenic or carcinogenic risk. Changes observed in rats and dogs at doses below the maximum tolerated dose are either pharmacological effects or are devoid of major toxicological significance under these conditions. Compared with the maximum recommended dosages in man, maximum tolerated doses are 2 and 7 times greater in the rat (200 mg/kg/day) and dog (120 mg/kg/day) respectively in terms of AUC. No carcinogenic risk, relevant to man, was identified in the rat at up to 1.5 to 4.5 times the expected human AUC. A mouse carcinogenicity study (120 mg/kg/day) and reproductive studies (160, 300 and 500 mg/kg/day respectively in rat, rabbit and mouse) were performed. The exposure of the animals to amisulpride during these latter studies was not evaluated.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
- Lactose monohydrate
- Magnesium stearate
- Methylcellulose
- Microcrystalline cellulose
- Sodium starch glycolate (type A)

6.2 Incompatibilities
Not applicable.
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 blister

Pack sizes of 10, 12, 14, 20, 21, 30, 42, 50, 60, 98, 100, 150 and 198 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
YES Pharmaceutical Development Services GmbH
Bahnstraße 42 – 46
61381 Friedrichsdorf,
Germany.

8 MARKETING AUTHORISATION NUMBER(S)
PL 16866/0043
PL 16866/0047
PL 16866/0051

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
PL 16866/0043 - 21/06/2010
PL 16866/0047 - 14/06/2010
PL 16866/0051 - 14/06/2010

10 DATE OF REVISION OF THE TEXT
PL 16866/0043 - 21/06/2010
PL 16866/0047 - 14/06/2010
PL 16866/0051 - 14/06/2010
1 NAME OF THE MEDICINAL PRODUCT
Amisulpride 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 100 mg amisulpride

Excipients: 47.50 mg lactose/tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet

White, round (8 mm diameter), flat tablet with score line. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Amisulpride is indicated for the treatment of acute and chronic schizophrenic disorders with:
- positive symptoms such as delusions, hallucinations, thought disorders, hostility, suspiciousness
- negative symptoms (deficit syndrome) such as blunted affect, emotional and social withdrawal.

This includes patients with predominant negative symptoms.

4.2 Posology and method of administration
Posology
For acute psychotic episodes, oral doses between 400 mg/day and 800 mg/day are recommended. In individual cases, the daily dose may be increased up to 1200 mg. Doses above 1200 mg/day 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 in example between 400-800mg/day.

Maintenance treatment should be established individually with the minimally effective dose.

For patients characterised by predominant negative symptoms, oral doses between 50 mg/day and 300 mg/day are recommended. Doses should be adjusted individually.

Amisulpride can be administered once daily at oral doses up to 300 mg, higher doses should be administered bid. The minimum effective dose and appropriate strength tablets should be used.

Special populations
Elderly patients over 65 years: Treatment of elderly patients is not recommended as there is no sufficient clinical experience. If treatment with amisulpride is absolutely necessary particular caution is required due to a possible risk of hypotension or sedation.

Children and adolescents: Efficacy and safety of amisulpride in children and adolescents under 18 years of age have not been established. There are only limited data available on the use of amisulpride in adolescents in schizophrenia. Therefore, amisulpride should not be used in adolescents from 15 to 18 years of age until further data are available. If absolutely required treatment of adolescents must be initiated and performed by a physician experienced in treating schizophrenia in this age group. The use of amisulpride is contraindicated in children and adolescents under 15 years of age (see section 4.3).

Renal impairment: Amisulpride is eliminated by the renal route. In renal insufficiency, the dose should be reduced to half in patients with creatinine clearance (CR\textsubscript{CL}) between 30-60 ml/min and to a third in patients with CR\textsubscript{CL} between 10-30 ml/min.

As there is no experience in patients with severe renal impairment (CR\textsubscript{CL} < 10 ml/min) amisulpride should not be used in these patients (see section 4.4).

Hepatic impairment: since amisulpride is weakly metabolised a dosage reduction should not be necessary.
**Duration of treatment**
Data from controlled clinical trials covering a period of 1 year is available. The duration of treatment should be determined by the treating physician.

**Method of administration**
Amisulpride can be administered with or without food. The tablets should be taken without chewing with a sufficient amount of water.

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

### 4.3 Contraindications
- hypersensitivity to the active substance or to any of the excipients of the medicinal product
- concomitant prolactin-dependent tumours, e.g. pituitary gland prolactinomas and breast cancer
- phaeochromocytoma
- children and adolescents under 15 years of age
- lactation (see section 4.6)
- combination with levodopa (see section 4.5)
- combination with the following medicinal products which could induce torsades de pointes:
  - class I antiarrhythmics such as quinidine, disopyramide, procainamide, flecainide and propafenone
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(see section 4.5)

### 4.4 Special warnings and precautions for use
As with other antipsychotics, neuroleptic malignant syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK, may occur. In the event of hyperthermia, particularly with high daily doses, all antipsychotic medicinal products 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).

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

In elderly patients (over 65 years), amisulpride, like other antipsychotics, 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 antipsychotic treatment cannot be avoided.

Acute withdrawal symptoms including nausea, vomiting and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotics. 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). This effect is known to potentiate the risk of serious ventricular arrhythmias such as torsades de pointes. Before any administration, and if possible according to the patient's clinical status, it is recommended to exclude the following factors which could favour the occurrence of this rhythm disorder:
- 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 medicinal product likely to produce pronounced bradycardia (< 55 bpm), hypokalaemia, decreased intracardiac conduction, or prolongation of the QT interval (see section 4.5).

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 (see section 4.5).

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.

Increased mortality in elderly people with dementia

Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known. Amisulpride is not licensed for the treatment of dementia-related behavioural disturbances.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with amisulpride and preventive measures undertaken.

Lactose

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

4.5 Interaction with other medicinal products and other forms of interaction

Combinations which are contraindicated (see also section 4.3)

Medicinal products which could induce torsades de pointes:
- class I antiarrhythmics such as quinidine, disopyramide, procainamide, flecainide and propafenone
- class III antiarrhythmics such as amiodarone and sotalol
- other medicinal products such as bepridil, cisapride, sulotropride, thioridazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin, azole antifungals.
Levodopa: reciprocal antagonism of effects between levodopa and antipsychotics.
Combinations which are not recommended
Medicinal products which enhance the risk of torsades de pointes or could prolong the QT interval:
- bradycardia-inducing medicinal products such as beta-blockers, bradycardia-inducing calcium
  channel blockers such as diltiazem and verapamil, clonidine, guanfacine; and digitalis.
- medicinal products which induce hypokalaemia or electrolyte imbalance: hypokalemic diuretics,
  stimulant laxatives, IV amphotericin B, glucocorticoids, and tetracosactides.
  Hypokalaemia should be corrected.
- antipsychotics such as pimozide, and haloperidol
- imipramine antidepressants
- lithium
- some antihistamines such as astemizole, and terfenadine.

Amisulpride may enhance the central effects of alcohol. Therefore, alcohol should not be consumed
during treatment.

Combinations which require precautions for use
Concomitant use of the following agents can lead to potentiation of the effect:
- CNS depressants including narcotics, anaesthetics, analgesics, sedative H1 antihistamines,
  barbiturates, benzodiazepines and other anxiolytic drugs, clonidine and derivatives
- antihypertensive and other hypotensive medicinal products

4.6 Pregnancy and lactation

Pregnancy
In animals, amisulpride did not show reproductive toxicity. A decrease in fertility linked to it’s
pharmacological effects (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 this medicinal product 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
This medicinal product can have minor or moderate influence on the ability to drive and use machines.
Even used as recommended, amisulpride may affect reaction time (e.g. caused by somnolence) so that
the ability to drive vehicles or operate machinery can be impaired (see section 4.8). This effect is
enhanced by the consumption of alcohol.

4.8 Undesirable effects
The following frequency estimates are used in assessing adverse effects:

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>(≥1/10)</td>
</tr>
<tr>
<td>Common</td>
<td>(≥1/100 to &lt;1/10)</td>
</tr>
<tr>
<td>Uncommon</td>
<td>(≥1/1,000 to &lt;1/100)</td>
</tr>
<tr>
<td>Rare</td>
<td>(≥1/10,000 to &lt;1/1,000)</td>
</tr>
<tr>
<td>Very rare</td>
<td>(&lt;1/10,000)</td>
</tr>
<tr>
<td>Not known</td>
<td>(cannot be estimated from the available data)</td>
</tr>
</tbody>
</table>

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.
Amisulpride 50, 100 and 200mg Tablets, and 400mg Film-Coated Tablets

Immune system disorders
Uncommon:
Allergic reaction

Endocrine disorders
Common:
Increase in plasma prolactin levels which is reversible after discontinuation of amisulpride. This may result in galactorrhoea, amenorrhoea or menstrual disorders, gynaecomastia, breast pain or breast enlargement, prolactinoma (see section 4.3) and erectile dysfunction.

Metabolism and nutrition disorders
Uncommon:
Hyperglycemia (see section 4.4)

Psychiatric disorders
Common:
Insomnia, anxiety, agitation, orgasmic dysfunction

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 should not be used as it is ineffective or may induce aggravation of the symptoms. Seizures

Cardiac disorders
Uncommon:
Bradycardia

Vascular disorders
Common:
Hypotension

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

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

Investigations
Common:
Weight gain

Uncommon:
Elevations of hepatic enzymes, mainly transaminases
POST MARKETING DATA
In addition, cases of the following adverse reactions have been reported through spontaneous reporting only:

Nervous system disorders
Not known:
Neuroleptic malignant syndrome (see section 4.4)

Cardiac disorders
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 section 4.4)

Vascular disorders
Not known:
Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs.

Skin and subcutaneous tissue disorders
Not known:
Angioedema, urticaria

4.9 Overdose
Symptoms
Experience with amisulpride in overdosage is limited. Exaggeration of the known pharmacological effects of amisulpride has been reported. These include drowsiness and sedation, coma, hypotension and extrapyramidal symptoms.

Fatal outcomes have been reported mainly in combination with other psychotropic agents.

Treatment
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 it. 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 until the patient recovers.

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

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antipsychotics: benzamides
ATC code: N05AL05

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 antipsychotics, amisulpride has no affinity for serotonin, alpha-adrenergic, histamine H1 and cholinergic receptors. In addition, amisulpride does not bind to sigma sites. In animal studies, at high doses, amisulpride blocks dopamine receptors located in the limbic structures in preference to those in the striatum. At low doses it preferentially blocks 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 ng/ml and 54 ± 4 ng/ml after a 50 mg dose.
The volume of distribution is 5.8 l/kg bodyweight, plasma protein binding is low (16%) and no drug interactions are suspected.

Absolute bioavailability is 48%. Amisulpride is weakly metabolised: two inactive metabolites, accounting for approximately 4% of the dose, have been identified. There is no accumulation of amisulpride and its pharmacokinetics remain unchanged after the administration of repeated doses. The elimination half-life of amisulpride is approximately 12 hours after an oral dose.

Amisulpride is eliminated unchanged in the urine. Fifty percent of an intravenous dose is excreted via the urine, of which 90% is eliminated in the first 24 hours. Renal clearance is in the order of 20 l/h or 330 ml/min.

A carbohydrate rich meal (containing 68% fluids) significantly decreases the AUCs, $T_{\text{max}}$ and $C_{\text{max}}$ of amisulpride but no changes were seen after a high fat meal. However, the significance of these findings in routine clinical use is not known.

**Hepatic impairment**
Since amisulpride is weakly metabolised a dosage reduction should not be necessary in patients with hepatic insufficiency.

**Renal impairment**
The elimination half-life is increased in patients with renal insufficiency while systemic clearance is reduced by a factor of 2.5 to 3. The AUC of amisulpride in mild renal failure increased two fold and almost tenfold in moderate renal failure (see section 4.2). Experience is however limited and there is no data with doses greater than 50 mg.

Amisulpride is very weakly dialysed.

**Elderly patients over 65 years**
Limited pharmacokinetic data in this patient group show that a 10-30% rise occurs in $C_{\text{max}}$, $T_{\frac{1}{2}}$ and AUC after a single oral dose of 50 mg. No data are available after repeat dosing.

### 5.3 Preclinical safety data
An overall review of the completed safety studies indicates that amisulpride is devoid of any general, organ-specific, teratogenic, mutagenic or carcinogenic risk. Changes observed in rats and dogs at doses below the maximum tolerated dose are either pharmacological effects or are devoid of major toxicological significance under these conditions. Compared with the maximum recommended dosages in man, maximum tolerated doses are 2 and 7 times greater in the rat (200 mg/kg/day) and dog (120 mg/kg/day) respectively in terms of AUC. No carcinogenic risk, relevant to man, was identified in the rat at up to 1.5 to 4.5 times the expected human AUC. A mouse carcinogenicity study (120 mg/kg/day) and reproductive studies (160, 300 and 500 mg/kg/day respectively in rat, rabbit and mouse) were performed. The exposure of the animals to amisulpride during these latter studies was not evaluated.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients
- Lactose monohydrate
- Magnesium stearate
- Methylcellulose
- Microcrystalline cellulose
- Sodium starch glycolate (type A)

#### 6.2 Incompatibilities
Not applicable.

#### 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 blister

Pack sizes of 10, 12, 14, 20, 21, 30, 42, 50, 60, 98, 100, 150 and 198 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
YES Pharmaceutical Development Services GmbH
Bahnstraße 42 – 46
61381 Friedrichsdorf,
Germany.

8 MARKETING AUTHORISATION NUMBER(S)
PL 16866/0044
PL 16866/0048
PL 16866/0052

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY
PL 16866/0044 - 21/06/2010
PL 16866/0048 - 14/06/2010
PL 16866/0052 - 14/06/2010

10 DATE OF REVISION OF THE TEXT
PL 16866/0044 - 21/06/2010
PL 16866/0048 - 14/06/2010
PL 16866/0052 - 14/06/2010
1 **NAME OF THE MEDICINAL PRODUCT**
Amisulpride 200 mg Tablets

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each tablet contains 200 mg amisulpride

Excipients: 95.00 mg lactose/tablet

For a full list of excipients, see section 6.1.

3 **PHARMACEUTICAL FORM**
Tablet

White, round (11 mm diameter), flat tablet with score line. The tablet can be divided into equal halves.

4 **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**
Amisulpride is indicated for the treatment of acute and chronic schizophrenic disorders with:
- positive symptoms such as delusions, hallucinations, thought disorders, hostility, suspiciousness
- negative symptoms (deficit syndrome) such as blunted affect, emotional and social withdrawal.
This includes patients with predominant negative symptoms.

4.2 **Posology and method of administration**

**Posology**
For acute psychotic episodes, oral doses between 400 mg/day and 800 mg/day are recommended. In individual cases, the daily dose may be increased up to 1200 mg. Doses above 1200 mg/day 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 in example between 400-800mg/day. Maintenance treatment should be established individually with the minimally effective dose.

For patients characterised by predominant negative symptoms, oral doses between 50 mg/day and 300 mg/day are recommended. Doses should be adjusted individually.

Amisulpride can be administered once daily at oral doses up to 300 mg, higher doses should be administered bid. The minimum effective dose and appropriate strength tablets should be used.

**Special populations**

*Elderly patients over 65 years:* Treatment of elderly patients is not recommended as there is no sufficient clinical experience. If treatment with amisulpride is absolutely necessary particular caution is required due to a possible risk of hypotension or sedation.

*Children and adolescents:* Efficacy and safety of amisulpride in children and adolescents under 18 years of age have not been established. There are only limited data available on the use of amisulpride in adolescents in schizophrenia. Therefore, amisulpride should not be used in adolescents from 15 to 18 years of age until further data are available. If absolutely required treatment of adolescents must be initiated and performed by a physician experienced in treating schizophrenia in this age group. The use of amisulpride is contraindicated in children and adolescents under 15 years of age (see section 4.3).

*Renal impairment:* Amisulpride is eliminated by the renal route. In renal insufficiency, the dose should be reduced to half in patients with creatinine clearance ($\text{CR}_{\text{CL}}$) between 30-60 ml/min and to a third in patients with $\text{CR}_{\text{CL}}$ between 10-30 ml/min.
As there is no experience in patients with severe renal impairment ($\text{CR}_{\text{CL}} < 10$ ml/min) amisulpride should not be used in these patients (see section 4.4).

*Hepatic impairment:* since amisulpride is weakly metabolised a dosage reduction should not be necessary.
**Duration of treatment**
Data from controlled clinical trials covering a period of 1 year is available. The duration of treatment should be determined by the treating physician.

**Method of administration**
Amisulpride can be administered with or without food. The tablets should be taken without chewing with a sufficient amount of water.

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

**4.3 Contraindications**
- hypersensitivity to the active substance or to any of the excipients of the medicinal product
- concomitant prolactin-dependent tumours, e.g. pituitary gland prolactinomas and breast cancer
- phaeochromocytoma
- children and adolescents under 15 years of age
- lactation (see section 4.6)
- combination with levodopa (see section 4.5)
- combination with the following medicinal products which could induce torsades de pointes:
  - class I antiarrhythmics such as quinidine, disopyramide, procainamide, flecainide and propafenone
  - class III antiarrhythmics such as amiodarone and sotalol
  - other medicinal products such as bepridil, cisapride, sultopride, thioridazine, methadone, IV erythromycin, halofantrine, pentamidine, sparfloxacin, azole antifungals.
(see section 4.5)

**4.4 Special warnings and precautions for use**
As with other antipsychotics, neuroleptic malignant syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK, may occur. In the event of hyperthermia, particularly with high daily doses, all antipsychotic medicinal products 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).

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

In elderly patients (over 65 years), amisulpride, like other antipsychotics, 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 antipsychotic treatment cannot be avoided.

Acute withdrawal symptoms including nausea, vomiting and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotics. 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). This effect is known to potentiate the risk of serious ventricular arrhythmias such as torsades de pointes. Before any administration, and if possible according to the patient’s clinical status, it is recommended to exclude the following factors which could favour the occurrence of this rhythm disorder:
- 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 medicinal product likely to produce pronounced bradycardia (< 55 bpm), hypokalaemia, decreased intracardiac conduction, or prolongation of the QT interval (see section 4.5).

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 (see section 4.5).

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.

Increased mortality in elderly people with dementia
Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

Amisulpride is not licensed for the treatment of dementia-related behavioural disturbances.

Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with amisulpride and preventive measures undertaken.

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

4.5 Interaction with other medicinal products and other forms of interaction
Combinations which are contraindicated (see also section 4.3)
Medicinal products which could induce torsades de pointes:
- class I antiarrhythmics such as quinidine, disopyramide, procainamide, flecainide and propafenone
- class III antiarrhythmics such as amiodarone and sotalol
- other medicinal products such as bepridil, cisapride, sultopride, thioridazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin, azole antifungals.

Levodopa: reciprocal antagonism of effects between levodopa and antipsychotics.
Combinations which are not recommended
Medicinal products which enhance the risk of torsades de pointes or could prolong the QT interval:
- bradycardia-inducing medicinal products such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine, guanfacine; and digitalis
- medicinal products which induce hypokalaemia or electrolyte imbalance: hypokalemic diuretics, stimulant laxatives, IV amphotericin B, glucocorticoids, and tetracosactides. Hypokalaemia should be corrected.
- antipsychotics such as pimozide, and haloperidol
- imipramine antidepressants
- lithium
- some antihistamines such as astemizole, and terfenadine.

Amisulpride may enhance the central effects of alcohol. Therefore, alcohol should not be consumed during treatment.

Combinations which require precautions for use
Concomitant use of the following agents can lead to potentiation of the effect:
- CNS depressants including narcotics, anaesthetics, analgesics, sedative H1 antihistamines, barbiturates, benzodiazepines and other anxiolytic drugs, clonidine and derivatives
- antihypertensive and other hypotensive medicinal products

4.6 Pregnancy and lactation

Pregnancy
In animals, amisulpride did not show reproductive toxicity. A decrease in fertility linked to it’s pharmacological effects (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 this medicinal product 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
This medicinal product can have minor or moderate influence on the ability to drive and use machines. Even used as recommended, amisulpride may affect reaction time (e.g. caused by somnolence) so that the ability to drive vehicles or operate machinery can be impaired (see section 4.8). This effect is enhanced by the consumption of alcohol.

4.8 Undesirable effects
The following frequency estimates are used in assessing adverse effects:
Very common: \((\geq 1/10)\)
Common: \((\geq 1/100 \text{ to } <1/10)\)
Uncommon: \((\geq 1/1,000 \text{ to } <1/100)\)
Rare: \((\geq 1/10,000 \text{ to } <1/1,000)\)
Very rare: \(<1/10,000)\)
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.
Immune system disorders
Uncommon:
Allergic reaction

Endocrine disorders
Common:
Increase in plasma prolactin levels which is reversible after discontinuation of amisulpride. This may result in galactorrhoea, amenorrhoea or menstrual disorders, gynaecomastia, breast pain or breast enlargement, prolactinoma (see section 4.3) and erectile dysfunction.

Metabolism and nutrition disorders
Uncommon:
Hyperglycemia (see section 4.4)

Psychiatric disorders
Common:
Insomnia, anxiety, agitation, orgasmic dysfunction

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 should not be used as it is ineffective or may induce aggravation of the symptoms. Seizures

Cardiac disorders
Uncommon:
Bradycardia

Vascular disorders
Common:
Hypotension

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

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

Investigations
Common:
Weight gain

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Elevations of hepatic enzymes, mainly transaminases
POST MARKETING DATA
In addition, cases of the following adverse reactions have been reported through spontaneous reporting only:

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Not known:
Neuroleptic malignant syndrome (see section 4.4)

Cardiac disorders
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 section 4.4)

Vascular disorders
Not known:
Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs.

Skin and subcutaneous tissue disorders
Not known:
Angioedema, urticaria

4.9 Overdose
Symptoms
Experience with amisulpride in overdosage is limited. Exaggeration of the known pharmacological effects of amisulpride has been reported. These include drowsiness and sedation, coma, hypotension and extrapyramidal symptoms.

Fatal outcomes have been reported mainly in combination with other psychotropic agents.

Treatment
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 it. 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 until the patient recovers.

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

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antipsychotics: benzamides
ATC code: N05AL05

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 antipsychotics, amisulpride has no affinity for serotonin, alpha-adrenergic, histamine H1 and cholinergic receptors. In addition, amisulpride does not bind to sigma sites. In animal studies, at high doses, amisulpride blocks dopamine receptors located in the limbic structures in preference to those in the striatum. At low doses it preferentially blocks 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 ng/ml and 54 ± 4 ng/ml after a 50 mg dose.

The volume of distribution is 5.8 l/kg bodyweight, 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 impairment
Since amisulpride is weakly metabolised a dosage reduction should not be necessary in patients with hepatic insufficiency.

Renal impairment
The elimination half-life is increased in patients with renal insufficiency while systemic clearance is reduced by a factor of 2.5 to 3. The AUC of amisulpride in mild renal failure increased two fold and almost tenfold in moderate renal failure (see section 4.2). Experience is however limited and there is no data with doses greater than 50 mg. Amisulpride is very weakly dialysed.

Elderly patients over 65 years
Limited pharmacokinetic data in this patient group show that a 10-30% rise occurs in Cmax, T½ and AUC after a single oral dose of 50 mg. No data are available after repeat dosing.

5.3 Preclinical safety data
An overall review of the completed safety studies indicates that amisulpride is devoid of any general, organ-specific, teratogenic, mutagenic or carcinogenic risk. Changes observed in rats and dogs at doses below the maximum tolerated dose are either pharmacological effects or are devoid of major toxicological significance under these conditions. Compared with the maximum recommended dosages in man, maximum tolerated doses are 2 and 7 times greater in the rat (200 mg/kg/day) and dog (120 mg/kg/day) respectively in terms of AUC. No carcinogenic risk, relevant to man, was identified in the rat at up to 1.5 to 4.5 times the expected human AUC. A mouse carcinogenicity study (120 mg/kg/day) and reproductive studies (160, 300 and 500 mg/kg/day respectively in rat, rabbit and mouse) were performed. The exposure of the animals to amisulpride during these latter studies was not evaluated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Magnesium stearate
Methylcellulose
Microcrystalline cellulose
Sodium starch glycolate (type A)

6.2 Incompatibilities
Not applicable.

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 blister

Pack sizes of 10, 12, 14, 20, 21, 30, 42, 50, 60, 98, 100, 150 and 198 tablets

Not all pack sizes may be marketed.
6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
YES Pharmaceutical Development Services GmbH
Bahnstraße 42 – 46
61381 Friedrichsdorf,
Germany.

8 MARKETING AUTHORISATION NUMBER(S)
PL 16866/0045
PL 16866/0049
PL 16866/0053

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
PL 16866/0045 - 21/06/2010
PL 16866/0049 - 14/06/2010
PL 16866/0053 – 14/06/2010

10 DATE OF REVISION OF THE TEXT
PL 16866/0045 - 21/06/2010
PL 16866/0049 - 14/06/2010
PL 16866/0053 - 14/06/2010
1 NAME OF THE MEDICINAL PRODUCT
Amisulpride 400 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 400 mg amisulpride

Excipients: 190.00 mg lactose/film-coated tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

White to off white, oval (18 mm length and 8 mm width) film-coated tablet with score line. The film-coated tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Amisulpride is indicated for the treatment of acute and chronic schizophrenic disorders with:
- positive symptoms such as delusions, hallucinations, thought disorders, hostility, suspiciousness
- negative symptoms (deficit syndrome) such as blunted affect, emotional and social withdrawal.
This includes patients with predominant negative symptoms.

4.2 Posology and method of administration
Posology
For acute psychotic episodes, oral doses between 400 mg/day and 800 mg/day are recommended. In individual cases, the daily dose may be increased up to 1200 mg. Doses above 1200 mg/day 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 in example between 400-800mg/day. Maintenance treatment should be established individually with the minimally effective dose.

For patients characterised by predominant negative symptoms, oral doses between 50 mg/day and 300 mg/day are recommended. Doses should be adjusted individually.

Amisulpride can be administered once daily at oral doses up to 300 mg, higher doses should be administered bid.
The minimum effective dose and appropriate strength tablets should be used.

Special populations
Elderly patients over 65 years: Treatment of elderly patients is not recommended as there is no sufficient clinical experience. If treatment with amisulpride is absolutely necessary particular caution is required due to a possible risk of hypotension or sedation.

Children and adolescents: Efficacy and safety of amisulpride in children and adolescents under 18 years of age have not been established. There are only limited data available on the use of amisulpride in adolescents in schizophrenia. Therefore, amisulpride should not be used in adolescents from 15 to 18 years of age until further data are available. If absolutely required treatment of adolescents must be initiated and performed by a physician experienced in treating schizophrenia in this age group. The use of amisulpride is contraindicated in children and adolescents under 15 years of age (see section 4.3).

Renal impairment: Amisulpride is eliminated by the renal route. In renal insufficiency, the dose should be reduced to half in patients with creatinine clearance (CR\text{CL}) between 30-60 ml/min and to a third in patients with CR\text{CL} between 10-30 ml/min.
As there is no experience in patients with severe renal impairment (CR\text{CL} < 10 ml/min) amisulpride should not be used in these patients (see section 4.4).

Hepatic impairment: since amisulpride is weakly metabolised a dosage reduction should not be necessary.
Duration of treatment
Data from controlled clinical trials covering a period of 1 year is available. The duration of treatment should be determined by the treating physician.

Method of administration
Amisulpride can be administered with or without food. The tablets should be taken without chewing with a sufficient amount of water.

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

4.3 Contraindications
- hypersensitivity to the active substance or to any of the excipients of the medicinal product
- concomitant prolactin-dependent tumours, e.g. pituitary gland prolactinomas and breast cancer
- phaeochromocytoma
- children and adolescents under 15 years of age
- lactation (see section 4.6)
- combination with levodopa (see section 4.5)
- combination with the following medicinal products which could induce torsades de pointes:
  - class I antiarrhythmics such as quinidine, disopyramide, procainamide, flecainide and propafenone
  - class III antiarrhythmics such as amiodarone and sotalol
  - other medicinal products such as bepridil, cisapride, sulthiophene, thioridazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin, azole antifungals.
(see section 4.5)

4.4 Special warnings and precautions for use
As with other antipsychotics, neuroleptic malignant syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK, may occur. In the event of hyperthermia, particularly with high daily doses, all antipsychotic medicinal products 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).

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

In elderly patients (over 65 years), amisulpride, like other antipsychotics, 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 antipsychotic treatment cannot be avoided.

Acute withdrawal symptoms including nausea, vomiting and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotics. 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). This effect is known to potentiate the risk of serious ventricular arrhythmias such as torsades de pointes. Before any administration, and if possible according to the patient's clinical status, it is recommended to exclude the following factors which could favour the occurrence of this rhythm disorder:
- 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 medicinal product likely to produce pronounced bradycardia (< 55 bpm), hypokalaemia, decreased intracardiac conduction, or prolongation of the QT interval (see section 4.5).

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 (see section 4.5).

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.

Increased mortality in elderly people with dementia
Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known. Amisulpride is not licensed for the treatment of dementia-related behavioural disturbances.

Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with amisulpride and preventive measures undertaken.

Lactose
Amisulpride film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction
Combination which are contraindicated (see also section 4.3)
Medicinal products which could induce torsades de pointes:
- class I antiarrhythmics such as quinidine, disopyramide, procainamide, flecainide and propafenone
- class III antiarrhythmics such as amiodarone and sotalol
- other medicinal products such as bepridil, cisapride, sulotropride, thioridazine, methadone, IV erythromycin, IV vincampine, halofantrine, pentamidine, sparfloxacin, azole antifungals.

Levodopa: reciprocal antagonism of effects between levodopa and antipsychotics.
Combinations which are not recommended
Medicinal products which enhance the risk of torsades de pointes or could prolong the QT interval:
- bradycardia-inducing medicinal products such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine, guanfacine; and digitalis
- medicinal products which induce hypokalaemia or electrolyte imbalance: hypokalemic diuretics, stimulant laxatives, IV amphotericin B, glucocorticoids, and tetracosactides. Hypokalaemia should be corrected.
- antipsychotics such as pimozide, and haloperidol
- imipramine antidepressants
- lithium
- some antihistamines such as astemizole, and terfenadine.

Amisulpride may enhance the central effects of alcohol. Therefore, alcohol should not be consumed during treatment.

Combinations which require precautions for use
Concomitant use of the following agents can lead to potentiation of the effect:
- CNS depressants including narcotics, anaesthetics, analgesics, sedative H1 antihistamines, barbiturates, benzodiazepines and other anxiolytic drugs, clonidine and derivatives
- antihypertensive and other hypotensive medicinal products

4.6 Pregnancy and lactation

Pregnancy
In animals, amisulpride did not show reproductive toxicity. A decrease in fertility linked to its pharmacological effects (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 this medicinal product 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 contraindicated.

4.7 Effects on ability to drive and use machines
This medicinal product can have minor or moderate influence on the ability to drive and use machines. Even used as recommended, amisulpride may affect reaction time (e.g. caused by somnolence) so that the ability to drive vehicles or operate machinery can be impaired (see section 4.8). This effect is enhanced by the consumption of alcohol.

4.8 Undesirable effects
The following frequency estimates are used in assessing adverse effects:
Very common: (≥1/10)
Common: (≥1/100 to <1/10)
Uncommon: (≥1/1,000 to <1/100)
Rare: (≥1/10,000 to <1/1,000)
Very rare: (<1/10,000)
Not known: (cannot be estimated from the available data)

CLINICAL TRIALS DATA
The following adverse 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.

Immune system disorders
Uncommon:
Allergic reaction
Endocrine disorders
Common:
Increase in plasma prolactin levels which is reversible after discontinuation of amisulpride. This may result in galactorrhoea, amenorrhoea or menstrual disorders, gynaecomastia, breast pain or breast enlargement, prolactinoma (see section 4.3) and erectile dysfunction.

Metabolism and nutrition disorders
Uncommon:
Hyperglycemia (see section 4.4)

Psychiatric disorders
Common:
Insomnia, anxiety, agitation, orgasmic dysfunction

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 should not be used as it is ineffective or may induce aggravation of the symptoms. Seizures

Cardiac disorders
Uncommon:
Bradycardia

Vascular disorders
Common:
Hypotension

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

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

Investigations
Common:
Weight gain

Uncommon:
Elevations of hepatic enzymes, mainly transaminases

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

Nervous system disorders
Not known:
Neuroleptic malignant syndrome (see section 4.4)
Cardiac disorders
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 section 4.4)

Vascular disorders
Not known:
Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs.

Skin and subcutaneous tissue disorders
Not known:
Angioedema, urticaria

4.9 Overdose

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

Fatal outcomes have been reported mainly in combination with other psychotropic agents.

Treatment
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 it. 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 until the patient recovers.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antipsychotics: benzamides
ATC code: N05AL05

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 antipsychotics, amisulpride has no affinity for serotonin, alpha-adrenergic, histamine H1 and cholinergic receptors. In addition, amisulpride does not bind to sigma sites. In animal studies, at high doses, amisulpride blocks dopamine receptors located in the limbic structures in preference to those in the striatum. At low doses it preferentially blocks 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 ng/ml and 54 ± 4 ng/ml after a 50 mg dose.

The volume of distribution is 5.8 l/kg bodyweight, plasma protein binding is low (16%) and no drug interactions are suspected.

Absolute bioavailability is 48%. Amisulpride is weakly metabolised: two inactive metabolites, accounting for approximately 4% of the dose, have been identified. There is no accumulation of amisulpride and its pharmacokinetics remain unchanged after the administration of repeated doses. The elimination half-life of amisulpride is approximately 12 hours after an oral dose.

Amisulpride is eliminated unchanged in the urine. Fifty percent of an intravenous dose is excreted via the urine, of which 90% is eliminated in the first 24 hours. Renal clearance is in the order of 20 l/h or 330 ml/min.
A carbohydrate rich meal (containing 68% fluids) significantly decreases the AUCs, $T_{\text{max}}$ and $C_{\text{max}}$ of amisulpride but no changes were seen after a high fat meal. However, the significance of these findings in routine clinical use is not known.

**Hepatic impairment**
Since amisulpride is weakly metabolised a dosage reduction should not be necessary in patients with hepatic insufficiency.

**Renal impairment**
The elimination half-life is increased in patients with renal insufficiency while systemic clearance is reduced by a factor of 2.5 to 3. The AUC of amisulpride in mild renal failure increased two fold and almost tenfold in moderate renal failure (see section 4.2). Experience is however limited and there is no data with doses greater than 50 mg.

Amisulpride is very weakly dialysed.

**Elderly patients over 65 years**
Limited pharmacokinetic data in this patient group show that a 10-30% rise occurs in $C_{\text{max}}$, $T_{\frac{1}{2}}$ and AUC after a single oral dose of 50 mg. No data are available after repeat dosing.

5.3 **Preclinical safety data**
An overall review of the completed safety studies indicates that amisulpride is devoid of any general, organ-specific, teratogenic, mutagenic or carcinogenic risk. Changes observed in rats and dogs at doses below the maximum tolerated dose are either pharmacological effects or are devoid of major toxicological significance under these conditions. Compared with the maximum recommended dosages in man, maximum tolerated doses are 2 and 7 times greater in the rat (200 mg/kg/day) and dog (120 mg/kg/day) respectively in terms of AUC. No carcinogenic risk, relevant to man, was identified in the rat at up to 1.5 to 4.5 times the expected human AUC. A mouse carcinogenicity study (120 mg/kg/day) and reproductive studies (160, 300 and 500 mg/kg/day 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**

*Tablet core:*
- Lactose monohydrate
- Magnesium stearate
- Methylcellulose
- Microcrystalline cellulose
- Sodium starch glycolate (type A)

*Tablet coat:*
- Macrogol 6000
- Magnesium stearate
- Basic butylated methacrylate copolymer (Eudragit E 100)
- Talc
- Titanium dioxide (E 171)

6.2 **Incompatibilities**
Not applicable.

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 blister

Pack sizes of 10, 12, 14, 20, 21, 30, 42, 50, 60, 98, 100, 150 and 198 film-coated tablets

Not all pack sizes may be marketed.
6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
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Bahnstraße 42 – 46
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8 MARKETING AUTHORISATION NUMBER(S)
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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
PL 16866/0046 - 21/06/2010
PL 16866/0050 - 14/06/2010
PL 16866/0054 - 14/06/2010

10 DATE OF REVISION OF THE TEXT
PL 16866/0046 - 21/06/2010
PL 16866/0050 - 14/06/2010
PL 16866/0054 - 14/06/2010
Amisulpride belongs to a group of medicines called antipsychotics. 
Amisulpride is used to treat schizophrenia, when it starts and also over the long term. Symptoms of this disorder include: changes in your thinking; hallucinations, such as hearing, seeing or feeling things which do not exist; changes in your behaviour, which can be aggressive; changes in your appetite; becoming withdrawn and sad.

What Amisulpride is and what it is used for
Amisulpride belongs to a group of medicines called antipsychotics. It is used to treat schizophrenia, when it starts and also over the long term. Symptoms of this disorder include:

- changes in your thinking; 
- hallucinations, such as hearing, seeing or feeling things which do not exist;
- changes in your behaviour, which can be aggressive;
- changes in your appetite;
- becoming withdrawn and sad.

Do not take Amisulpride
If you have:
- an allergy to any of the ingredients of Amisulpride or any of the other medicines listed at section 6. Further information;
- a history of taking or something called “proteins-dependent” medicines;
- a tumour on the adrenal gland;
- under 18 years old;
- breast-fasting;
- any of the following medicines:
  - levodopa: a medicine to treat Parkinson's disease;
- medicines which may cause severe heart disease;

Taking Amisulpride with food and drink
Do not drink alcohol during treatment as it can affect the way Amisulpride works.

Pregnancy and breast-feeding
Do not take Amisulpride if you are pregnant unless your doctor has told you to do so. Ask your doctor immediately if you are pregnant or think you may be.

Breast-feeding
You must not take Amisulpride when breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Only drive or operate machines if your doctor has approved it. This will depend upon how this therapy affects your mental alertness and makes you feel drowsy or sleepy.

Important information about some of the ingredients of Amisulpride
Amisulpride contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Amisulpride.

How to take Amisulpride
Always take Amisulpride exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will tell you how many Amisulpride tablets/film-coated tablets you should take and how long you should continue to take them.

Adults (and adolescents from 18 years of age, if treatment is absolutely required)

If you suffer from positive symptoms, the usual dose is between 400 mg and 800 mg amisulpride daily, and it will be adjusted individually by your doctor depending on the nature and severity of your illness.

If you suffer from both positive and negative symptoms, your doctor will adjust your dose individually so that there is adequate control of both the positive and negative symptoms. Depending on your doctor’s treatment, your doctor will use the lowest possible dose that is effective for you.

If you suffer from negative symptoms, the usual dose is between 50 mg and 200 mg amisulpride daily, and it will be adjusted individually by your doctor depending on the nature and severity of your illness.
Children and adolescents

Efficacy and safety of amisulpride in children and adolescents under 18 years of age have not been established. If absolutely required treatment of adolescents from 15 to 18 years of age may be initiated and performed by a physician experienced in treating schizophrenia in this age group; children and adolescents under 15 years of age must not take amisulpride (see section 2 ‘Do not take Amisulpride’).

Patients with impaired kidney function

Your doctor will treat you with a lower dose, half or a third of the usual daily dose, depending on the impairment grade of your kidney.

Patients with impaired liver function

No changes to the usual daily dose are necessary.

Method of administration

- Swallow the tablets with a glass of water.
- You can take them during or between meals.
- Doses up to 300 mg amisulpride per day can be taken as a single dose, preferably at the same time each day.
- Doses above 360 mg amisulpride should be taken at half in the morning and half in the evening.

If you take more Amisulpride than you should

Contact your doctor or the nearest hospital straight away. Always take the tablets/film-coated tablets (400mg only), tablet and/or carton with you so the doctor will know what you have taken. Immediate medical care is necessary if the following signs occur: tachycardia, agitation, loss of consciousness, unusual body movements, rigid muscles and low blood pressure.

If you forget to take Amisulpride

Continue treatment by taking your next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Amisulpride

Do not stop taking Amisulpride unless advised by your doctor, as this may harm the success of therapy. Stopping treatment suddenly can cause withdrawal symptoms such as nausea, vomiting, sleeplessness, rigid muscles, unusual body movements, and a faster heartbeat than usual.

Reported side effects listed according to the frequency are:

Very common, occurs in more than 1 per 10 users

- tremor
- muscle stiffness or spasm
- slow movement
- feeling more or less alert than usual
- feeling restless

Consult your doctor if this occurs. These symptoms are generally mild and can be reduced by lowering your dose, or by treating with an additional medicine.

Common, occurs in 1 to 10 per 100 users

- muscle cramps, mainly of the neck, eyes and jaws
- Consult your doctor if this occurs. These effects are reversible by adequate treatment with an additional medicine.
- feeling sleepy
- difficulty sleeping
- feeling drowsy or dazed
- feeling having orgasms
- constipation
- nausea and vomiting
- dry mouth
- increased values of a hormone called prolactin in your blood, which can lead to:
  - unusual growth of breast milk in men and women
  - breast enlargement

Uncommon, occurs in 1 to 10 per 1000 users

- unusual growth of breast milk in men and women
- breast enlargement
- breast pain or breast tenderness
- prolactin-dependent tumour

These symptoms disappear after ending therapy with Amisulpride.

- low blood pressure
- weight gain

- irritable or abnormal movements of the tongue, mouth and face

These occur only when you start or stop taking Amisulpride, especially if you have taken high doses of this medicine.

Frequency unknown, according to the available data

- so-called ‘neuroleptic malignant syndrome’ (see first paragraph in this chapter)
- heart attack, specific heart rhythm disorders, sudden unexpected death
- blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), may travel through blood vessels to the lungs causing chest pain and difficulty in breathing

If you notice any of these symptoms seek medical advice immediately.

In elderly people with dementia, a small increase in the number of deaths has been reported for patients taking antipsychotics compared with those not receiving antipsychotics.

- swelling of the skin associated with pain, redness and itching

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

5 How to store Amisulpride

Keep out of the reach and sight of children.

Do not use Amisulpride after the expiry date which is stated on the carton and on the blister. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 Further information

What Amisulpride contains

The active substance is amisulpride.

- Amisulpride 50 mg tablets: Each tablet contains 50 mg amisulpride.
- Amisulpride 100 mg tablets: Each tablet contains 100 mg amisulpride.
- Amisulpride 200 mg tablets: Each tablet contains 200 mg amisulpride.
- Amisulpride 400 mg film-coated tablets: Each film-coated tablet contains 400 mg amisulpride.

The other ingredients are:

- Lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium starch glycolide (type A).
- Lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium starch glycolide (type A).
- Microcrystalline cellulose, magnesium stearate, hydroxypropyl cellulose.
- Microcrystalline cellulose, magnesium stearate, hydroxypropyl cellulose.
- Microcrystalline cellulose, magnesium stearate, hydroxypropyl cellulose.
- Microcrystalline cellulose, magnesium stearate, hydroxypropyl cellulose.
- Microcrystalline cellulose, magnesium stearate, hydroxypropyl cellulose.

What Amisulpride looks like and contents of the pack

Amisulpride 50 mg tablets are white, round with a diameter of 5 mm and rounded on the upper and lower side. They have a score line and can be divided into equal halves.

Amisulpride 100 mg tablets are white, round with an 8 mm diameter and flat. They have a score line and can be divided into equal halves.

Amisulpride 200 mg tablets are white, round with 11 mm diameter and flat. They have a score line and can be divided into equal halves.

Amisulpride 400 mg film-coated tablets are white to off white, 18 mm long and 8 mm wide. They have a score line and can be divided into equal halves.

Amisulpride 50 mg, 100 mg and 200 mg tablets are available in blister packs of 10, 12, 14, 20, 21, 30, 42, 50, 60, 80, 100, 150 and 218 tablets.

Amisulpride 400 mg film-coated tablets are available in blister packs of 10, 12, 14, 20, 21, 30, 42, 50, 60, 80, 90, 100, 150 and 198 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Vaccinates Pharmaceuticals and Meds, A Pharmaceutical Development Services GmbH, Bystrastraße 42 - 46, 61381 Friedberg, Germany.

Manufacturer

Inis Pharmaceuticals D.O. Lubiana, IJse or Lek S.A., Warsaw, Poland or

Svenska Firma GmbH, Berne, Germany or

Svenska Firma GmbH (Gerling), Gerling, Germany.

This leaflet was last approved in 05/2010 (to be amended after approval).
Module 4
Labelling

Amisulpride 50 mg Tablets
60 tablets

Amisulpride 50 mg Tablets

for use by adults and adolescents from 15 years of age
60 tablets
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Amisulpride, 50mg, 100mg and 200mg Tablets and Amisulpride, 400mg Film-Coated Tablets (PL 16866/0043-54; UK/H/2385-7/001-4/DC) could be approved. The products are prescription-only medicines (POM) and are indicated for the treatment of acute and chronic schizophrenic disorders with:
- positive symptoms such as delusions, hallucinations, thought disorders, hostility and suspiciousness
- negative symptoms (deficit syndrome) such as blunted affect, emotional and social withdrawal.
This includes patients with predominant negative symptoms.

The applications were submitted using the decentralised procedure, with the UK as reference member state (RMS), and Belgium, Germany, Greece, Italy, Portugal, Romania and Slovakia as concerned member states (CMS).

The applications were submitted under Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of Solian 50mg, 100mg, 200mg and 400mg Tablets (Sanofi-Aventis, UK), which were first authorised in the EU to Laboratoires Synthelabo in 1986.

No new non-clinical studies were performed, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

Two single-dose, fasting, bioequivalence studies were submitted to support the applications, one with the 200mg tablet and the other with the 400mg film-coated tablet. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence studies, no new clinical studies were performed, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for these products at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The marketing authorisation holder has provided adequate justification for not submitting a Risk Management Plan (RMP) and Environmental Risk Assessment (ERA).
The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 12 May 2010. After a subsequent national phase, licences were granted in the UK on 14 June 2010 (PL 16866/0047-54; UK/H/2386-7/001-4/DC) and 21 June 2010 (PL 16866/0043-6; UK/H/2385/001-4/DC).
## II. ABOUT THE PRODUCT

| Name of the products in the Reference Member State | Amisulpride 50mg Tablets  
| | Amisulpride 100mg Tablets  
| | Amisulpride 200mg Tablets  
| | Amisulpride 400mg Film-Coated Tablets  |
| Name(s) of the active substance(s) (INN) | Amisulpride  
| Pharmacotherapeutic classification (ATC code) | Antipsychotic, benzamide  
| | N05 AL05  
| Pharmaceutical form and strength(s) | Tablets: 50mg, 100mg and 200mg  
| | Film-Coated Tablets: 400mg  
| Reference numbers for the Mutual Recognition Procedure | UK/H/2385/001-004/DC  
| | UK/H/2386/001-004/DC  
| | UK/H/2387/001-004/DC  
| Reference Member State | United Kingdom  
| Member States concerned | UK/H/2385/001-004/DC: Belgium, Germany, Greece, Italy (50, 200 and 400mg only), Portugal, Romania (200 and 400mg only) and Slovakia (200mg and 400mg only)  
| | UK/H/2386/001-004/DC: Germany  
| | UK/H/2387/001-004/DC: Germany  
| Marketing Authorisation Number(s) | PL 16866/0043-54  
| Name and address of the authorisation holder | YES Pharmaceutical Development Services GmbH  
| | Bahnstraße 42-46  
| | 61381 Friedrichsdorf  
| | Germany  

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

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

Molecular formula: C_{17}H_{27}N_{3}O_{4}S
Molecular weight: 369.5
Appearance: A white, odourless powder, poorly soluble in water. Amisulpride has one chiral centre.

Amisulpride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance amisulpride are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Medicinal Product
Other Ingredients
Other ingredients consist of the pharmaceutical excipients lactose monohydrate, magnesium stearate, methylcellulose, microcrystalline cellulose and sodium starch glycolate (type A).

The tablet film-coating on the 400mg tablet consists of the pharmaceutical excipients macrogol 6000, magnesium stearate, basic butylated methacrylate copolymer (Eudragit E 100), talc and titanium dioxide (E 171).

All excipients comply with their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monographs.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate 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. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to produce safe, efficacious products containing 50, 100, 200 and 400mg amisulpride, that could be considered generic medicinal products of Solian 50, 100, 200 and 400mg Tablets (Sanofi-Aventis, France).

A satisfactory account of the pharmaceutical development has been provided.
Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of all strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. In-process controls are satisfactory based on process validation data and controls on the finished product.

**Finished Product Specification**
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Container-Closure System**
All strengths of the tablets are packaged in polyvinylchloride/aluminium blister strips in pack sizes 10, 12, 14, 20, 21, 30, 42, 50, 60, 98, 100, 150 and 198 tablets.

Not all pack sizes may be marketed. However, Marketing Authorisation Holder has committed to submitting the mock-ups to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials suitable for contact with food.

**Stability of the Product**
Stability studies were performed in accordance with current guidelines on batches of all strengths of the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years, with no special storage conditions.

**Bioequivalence/Bioavailability**
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence studies.

**Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels**
The SPC, PILs and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflets are 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 they contain.

**MAA Forms**
The MAA forms are satisfactory.

**Expert Report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.
Conclusion
The grant of Marketing Authorisations is recommended.
III.2 NON-CLINICAL ASPECTS
No new non-clinical studies were performed, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the non-clinical aspects of the dossier.

The marketing authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment.

There are no objections to the approval of these products from a non-clinical viewpoint.
III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence studies:

**Study 1**
A randomised, open-label, two-way, single-dose, crossover study comparing the test product Amisulpride 200mg Tablets and the reference product Solian 200mg Tablets (Sanofi-Aventis) in healthy male subjects under fasting conditions.

Subjects were dosed with either treatment after at least a 10-hour fast. Blood sampling was performed pre- and up to 72 hours post dose in each treatment period. The washout period between the two treatment arms was 6 days. Pharmacokinetic parameters were measured from plasma and statistically analysed. The pharmacokinetic results (presented as ratios and 90% confidence intervals) are presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters (arithmetic mean ± SD, ratio and confidence intervals [CI]) of amisulpride</th>
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</thead>
<tbody>
<tr>
<td>Amisulpride 200mg (Test)</td>
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<tr>
<td>AUC$_{0-t}$ (ng/ml h)</td>
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<tr>
<td>AUC$_{0-inf}$ (ng/ml h)</td>
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<tr>
<td>C$_{max}$ (ng/ml)</td>
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</tbody>
</table>

AUC$_{0-t}$ area under the plasma concentration-time curve from time zero to infinity
AUC$_{0-inf}$ area under the plasma concentration-time curve from time zero to infinity
C$_{max}$ maximum plasma concentration
90% geometric CI calculated from ln-transformed data

The 90% confidence interval of the test/reference ratio of geometric means for AUC$_{0-t}$ and C$_{max}$ lie within the acceptable limits. Thus, the data support the claim that the test product is bioequivalent to the reference product.

As the 50mg, 100mg and 200mg strength products meet all the criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions from the bioequivalence study with the 200mg tablet strength can be extrapolated to the 50mg and 100mg tablet strengths.

**Study 2**
A randomised, open-label, two-way, single-dose, crossover study comparing the test product Amisulpride 400mg Film-Coated Tablets and the reference product Solian 400mg Film-Coated Tablets (Sanofi-Aventis) in healthy male subjects under fasting conditions.

Subjects were dosed with either treatment after an overnight fast of at least 10 hours. Blood sampling was performed, pre- and up to 60 hours post dose in each treatment period. The washout period between the two treatment arms was 7 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed. Pharmacokinetic results (presented as ratios and 90% confidence intervals) from the study are presented below:

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<tr>
<th>Pharmacokinetic parameters (arithmetic mean ± SD, ratio and confidence intervals [CI]) of amisulpride</th>
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</thead>
<tbody>
<tr>
<td>Amisulpride 400mg (Test)</td>
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</table>

50
The 90% confidence interval of the test/reference ratio of geometric means for AUC\textsubscript{0-t} and C\textsubscript{max} lie within the acceptable limits. Thus, the data support the claim that the test product is bioequivalent to the reference product.

**Efficacy**
No new data on the efficacy have been submitted and none are required for these types of applications.

**Safety**
No new or unexpected safety issues were raised by the bioequivalence data.

**Pharmacovigilance System and Risk Management Plan**
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for these products.

**Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels**
The SPC, PILs and labels are medically acceptable. The SPCs are consistent with those for the originator products.

**Clinical Expert Report**
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Conclusion**
The grant of Marketing Authorisations is recommended.
IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Amisulpride 50mg, 100mg and 200mg Tablets, and Amisulpride 400mg Film-Coated Tablets, are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the risk-benefit 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 200mg and 400mg strength tablets and the respective reference products. As the 50mg, 100mg and 200mg strengths of the product meet the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study with the 200mg tablet strength can be extrapolated to the 50mg and 100mg tablet strengths.

SAFETY
The safety profile of amisulpride is well-known.

PRODUCT LITERATURE
The approved SPCs are satisfactory and consistent with those for the reference products.

The final PIL and labelling text are satisfactory and consistent with those for the reference products and with the approved SPCs.

RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable, and no new preclinical or clinical safety concerns have been identified. The data provided support the claim that these products are generic medicinal products of the reference products, Solian 50mg, 100mg, 200mg and 400mg Tablets (Sanofi-Aventis). 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.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Application type</th>
<th>Scope</th>
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