Public Assessment Report

Decentralised Procedure

AMISULPRIDE 100MG/ML ORAL SOLUTION

UK/H/2028/001/DC
UK Licence No: PL 20046/0074

FOCUS PHARMACEUTICALS LIMITED
LAY SUMMARY

On 22nd February 2011, the UK granted Focus Pharmaceuticals Limited a Marketing Authorisation (licence) for the prescription only medicinal product Amisulpride 100mg/ml Oral Solution.

Amisulpride 100mg/ml Oral Solution belongs to a group of medicines called neuroleptics. Amisulpride 100mg/ml Oral Solution is used to treat acute and chronic schizophrenia. Symptoms of this condition can include sensing, seeing or hearing things that do not exist, becoming withdrawn and having mistaken beliefs or suspicions.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Amisulpride 100mg/ml Oral Solution outweigh the risks; hence a Marketing Authorisation has been granted.
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Module 1

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Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Amisulpride 100mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1ml of solution contains 100mg of Amisulpride.
For a full list of excipients, see Section 6.1.
It also contains 1mg/ml methyl parahydroxybenzoate (E218), 0.5mg/ml propyl parahydroxybenzoate (E216) and sodium (4.02mg/ml).

3 PHARMACEUTICAL FORM
Oral Solution.
A colourless to brown yellowish clear solution.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Amisulpride Oral Solution is indicated for the treatment of acute and chronic schizophrenic disorders, in which positive symptoms (such as delusions, hallucinations, thought disorders) and/or negative symptoms (such as blunted affect, emotional and social withdrawal) are prominent, including patients characterised by predominant negative symptoms.

4.2 Posology and method of administration
For acute psychotic episodes, oral doses between 400 mg/day and 800 mg/day are recommended. In individual cases, the daily dose may be increased up to 1200 mg/day. 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 Oral Solution. 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 i.e. between 400-800 mg/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 Oral Solution can be administered once daily at oral doses up to 300 mg, higher doses should be administered bid.

The minimum effective dose should be used.

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

Children: Amisulpride Oral Solution is contra-indicated in children under 15 years of age as its safety has not yet been established.

Renal insufficiency: Amisulpride Oral Solution is eliminated by the renal route. In renal insufficiency, the dose should be reduced to half in patients with creatinine clearance (CRCL) between 30-60 ml/min and to a third in patients with CRCL between 10-30 ml/min.
As there is no experience in patients with severe renal impairment (CRCL <10 ml/min) particular care is recommended in these patients (see 4.4 Special warnings and precautions for use).

Hepatic insufficiency: since the drug is weakly metabolised a dosage reduction should not be necessary.

Method of administration (Amisulpride Oral Solution): The graduations on the dosage syringe measure the millilitres of oral solution. After introducing the measuring syringe into the bottle, draw the plunger of the measuring syringe up to the graduation mark corresponding to the number of millilitres to be administered. The oral solution should be drunk with a liquid, which does not contain alcohol.
4.3 Contraindications
- Hypersensitivity to the active ingredient or to other ingredients of the medicinal product;
- Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer;
- Phaeochromocytoma;
- Children under 15 years of age;
- Lactation.

Combination with the following medications which could induce torsades de pointes:
- Class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide;
- Class III antiarrhythmic agents such as amiodarone, sotalol;
- Other medications such as bepridil, cisapride, sulthiame, thioridazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparflaxacin.
This list is not exhaustive.
- Combination with levodopa (see 4.5 Interactions with other medicinal products and other forms of interaction)

4.4 Special warnings and precautions for use
As with other neuroleptics, Neuroleptic Malignant Syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK, may occur. In the event of hyperthermia, particularly with high daily doses, all antipsychotic drugs including Amisulpride Oral Solution 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 Oral Solution is eliminated by the renal route. In cases of renal insufficiency, the dose should be decreased or intermittent treatment could be considered (see Section 4.2 Posology and method of administration).

Amisulpride Oral Solution may lower the seizure threshold. Therefore patients with a history of epilepsy should be closely monitored during Amisulpride Oral Solution therapy. In elderly patients, Amisulpride Oral Solution, like other neuroleptics, should be used with particular caution because of a possible risk of hypotension or sedation.

As with other antidopaminergic agents, caution should also be exercised when prescribing Amisulpride Oral Solution to patients with Parkinson’s disease since it may cause worsening of the disease. Amisulpride Oral Solution should be used only if neuroleptic treatment cannot be avoided.

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

Prolongation of the QT interval
Amisulpride induces a dose-dependent prolongation of the QT interval (see Section 4.8 Undesirable effects). This effect is known to potentiate the risk of serious ventricular arrhythmias such as torsades de pointes.

Before any administration, and if possible according to the patient’s clinical status, it is recommended to monitor factors which could favour the occurrence of this rhythm disorder:
- bradycardia less than 55 bpm,
- cardiac disease or family history of sudden death or QT prolongation,
- electrolyte imbalance, in particular hypokalaemia,
- congenital prolongation of the QT interval,
- on-going treatment with a medication likely to produce pronounced bradycardia (< 55 bpm), hypokalaemia, decreased intracardiac conduction, or prolongation of the QT interval (see Section 4.5 Interaction with other medicinal products and other forms of interaction).
Baseline ECG is recommended prior to treatment in all patients especially in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination.

During therapy, the need for ECG monitoring (e.g. at dose escalation) should be assessed on an individual patient basis.
The dose of Amisulpride Oral Solution should be reduced if QT is prolonged and discontinued if QTc is <500ms.

Periodic electrolyte monitoring is recommended particularly if the patient is taking diuretics or during inter-current illness. Concomitant antipsychotics should be avoided.

Stroke.
In randomised 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 Oral Solution 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 Oral Solution 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 Oral Solution and preventative measures undertaken.

Excipients with recognised action or effect
Amisulpride 100mg/ml Oral Solution contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed).

This medicinal product contains 0.17mmol (4.02mg) sodium per 1ml of oral solution. A dose of up to 500mg amisulpride contains less than 1mmol of sodium, essentially sodium free. A dose of 600mg amisulpride or greater, contains more than 1mmol of sodium. Care should be taken with patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction
COMBINATIONS WHICH ARE CONTRAINDICATED
Medications which could induce torsades de pointes:
- Class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide;
- Class III antiarrhythmic agents such as amiodarone, sotalol;
- Other medications such as bepridil, cisapride, sulpriproide, thioridazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacim.

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

COMBINATIONS WHICH ARE NOT RECOMMENDED
Amisulpride Oral Solution may enhance the central effects of alcohol.

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

COMBINATIONS TO BE TAKEN INTO ACCOUNT
CNS depressants including narcotics, anaesthetics, analgesics, sedative H1 antihistamines, barbiturates, benzodiazepines and other anxiolytic drugs, clonidine and derivatives; Antihypertensive drugs and other hypotensive medications; Dopamine agonists (e.g. levodopa) since it may attenuate their action.
4.6 Pregnancy and lactation
For women of child bearing potential, effective contraception should be fully discussed with the physician prior to treatment.

Pregnancy
There is a very limited amount of data from the use of amisulpride in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Amisulpride Oral Solution 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.

Lactation
It is unknown whether amisulpride is excreted in human milk. A risk to newborns/infants cannot be excluded. Amisulpride Oral Solution is contraindicated during breast feeding (see Section 4.3).

4.7 Effects on ability to drive and use machines
Even used as recommended, Amisulpride Oral Solution may cause somnolence so that the ability to drive vehicles or operate machinery can be impaired (see Section 4.8 Undesirable effects).

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

Clinical trials data
The following adverse effects have been observed in controlled clinical trials. It should be noted that in some instances it can be difficult to differentiate adverse events from symptoms of the underlying disease.

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

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

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

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

- Metabolism and nutrition disorders
  Uncommon: Hyperglycemia (see 4.4 Special warnings and precautions for use).
- Cardiovascular disorders
  *Common:* Hypotension
  *Uncommon:* Bradycardia

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

- Immune system disorders
  *Uncommon:* Allergic reaction

Post Marketing data

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

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

- Cardiac disorders:
  *Frequency not known:* QT interval prolongation and ventricular arrhythmias such as torsade de pointes, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, sudden death (see 4.4 Special warnings and precautions for use).

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

### 4.9 Overdose

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

In cases of acute overdosage, the possibility of multiple drug intake should be considered. Since amisulpride is weakly dialysed, haemodialysis is of no use to eliminate the drug. There is no specific antidote to amisulpride.

Appropriate supportive measures should therefore be instituted with close supervision of vital functions including continuous cardiac monitoring due to the risk of prolongation of the QT interval. If severe extrapyramidal symptoms occur, anticholinergic agents should be administered.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics

ATC Code: NO5A LO5

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

Unlike classical and atypical neuroleptics, amisulpride has no affinity for serotonin, α-adrenergic, histamine H_1 and cholinergic receptors. In addition, amisulpride does not bind to sigma sites. In animal studies, at high doses, amisulpride blocks dopamine receptors located in the limbic structures in preference to those in the striatum.

At low doses it preferentially blocks pre-synaptic D_2/D_3 receptors, producing dopamine release responsible for its disinhibitory effects. This pharmacological profile explains the clinical efficacy of amisulpride against both negative and positive symptoms of schizophrenia.

#### 5.2 Pharmacokinetic properties

In man, amisulpride shows two absorption peaks: one which is attained rapidly, one hour post-dose and a second between 3 and 4 hours after administration. Corresponding plasma concentrations are 39 ± 3 and 54 ± 4 ng/ml after a 50 mg dose.

The volume of distribution is 5.8 l/kg, plasma protein binding is low (16%) and no drug interactions are suspected.
Absolute bioavailability is 48%. Amisulpride is weakly metabolised: two inactive metabolites, accounting for approximately 4% of the dose, have been identified. There is no accumulation of amisulpride and its pharmacokinetics remain unchanged after the administration of repeated doses. The elimination half-life of amisulpride is approximately 12 hours after an oral dose. Amisulpride is eliminated unchanged in the urine. Fifty percent of an intravenous dose is excreted via the urine, of which 90% is eliminated in the first 24 hours. Renal clearance is in the order of 20 l/h or 330 ml/min.

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

**Hepatic insufficiency:** since the drug is weakly metabolised a dosage reduction should not be necessary in patients with hepatic insufficiency.

**Renal insufficiency:** The elimination half-life is unchanged in patients with renal insufficiency while systemic clearance is reduced by a factor of 2.5 to 3. The AUC of amisulpride in mild renal failure increased two fold and almost tenfold in moderate renal failure. Experience is however limited and there is no data with doses greater than 50mg. Amisulpride is very weakly dialysed. Limited pharmacokinetic data in elderly subjects (>65 years) shows that a 10-30 % rise occurs in Cmax, T1/2 and AUC after a single oral dose of 50mg. 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 (200mg/kg/day) and dog (120mg/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

- Saccharin sodium,
- Sodium gluconate,
- Gluconolactone,
- Hydrochloric acid, concentrated (pH adjuster),
- Methyl parahydroxybenzoate (E218),
- Propyl parahydroxybenzoate (E216),
- Potassium sorbate,
- Caramel flavour, (containing glycerol (E422) and ethyl alcohol),
- Purified water.

#### 6.2 Incompatibilities

None known.

#### 6.3 Shelf life

2 years unopened. Once the bottle is opened, use within 2 months.

#### 6.4 Special precautions for storage

The medicinal product does not require any special storage conditions.

#### 6.5 Nature and contents of container

Amber (Ph. Eur. type III), 60ml glass bottle with a child resistant, tamper evident plastic screw cap with a LDPE liner, and a 5ml graduated oral dosing syringe.
6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Focus Pharmaceuticals Ltd
Unit 5 Faraday Court
First Avenue
Centrum 100
Burton upon Trent
Staffordshire
DE14 2WX
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20046/0074

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/02/2011

10 DATE OF REVISION OF THE TEXT
22/02/2011
Module 3
Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Amisulpride 100mg/ml Oral Solution
Amisulpride

Read all of this leaflet carefully before you start taking this medicine.
• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Amisulpride Oral Solution is and what it is used for
2. Before you take Amisulpride Oral Solution
3. How to take Amisulpride Oral Solution
4. Possible side effects
5. How to store Amisulpride Oral Solution
6. Further information

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

Your medicine is called Amisulpride 100mg/ml Oral Solution (called Amisulpride Oral Solution throughout this leaflet).

What this medicine does
Amisulpride Oral Solution is one of a group of medicines called neuroleptics. These are used to treat acute and chronic schizophrenia. Symptoms of this condition can include sensing, seeing or hearing things that do not exist, becoming withdrawn and having mistaken beliefs or suspicions.
2. Before you take Amisulpride Oral Solution

Do not take Amisulpride Oral Solution

- if you are allergic (hypersensitive) to amisulpride or any of the other ingredients of Amisulpride Oral Solution (see section 6, Further information);
- if you have a tumour of the pituitary gland or breast cancer;
- if you have phaeochromocytoma (a tumour of the adrenal gland);
- if you are under 15 years of age;
- if you are breast-feeding;
- if you are taking a dopamine agonist e.g. levodopa used in Parkinson’s disease;
- if you are taking any medicines to treat an irregular heartbeat (arrhythmias) e.g. quinidine, disopyramide, procainamide, amiodarone, or sotalol;
- if you are taking any antibiotics e.g. erythromycin, halofantrine, pentamidine, or sparfloxacin;
- if you are taking sultopride (an antidepressant);
- if you are taking cisapride which can be used to treat stomach problems e.g. heartburn;
- if you are taking thiadiazine which can be used as a tranquiliser or to treat conditions such as schizophrenia;
- if you are taking bepridil which can be used to treat angina;
- if you are taking methadone which can be used to treat opioid drug addiction or to treat moderate to severe pain;
- if you are taking vincamine which can be used to increase the blood flow and amount of oxygen in the brain.

Talk to your doctor or pharmacist if any of the following apply to you:

- if you suffer from kidney problems;
- if you have a history of epilepsy;
- if you suffer from Parkinson’s disease;
- if you have a slow pulse (less than 55 beats per minute);
- if you have an inherited heart problem;
- if you have low levels of potassium in your blood (hypokalaemia);
- if you are a diabetic or have been told you have an increased risk of having diabetes;
- if you are elderly. This is because elderly people would be more likely to get low blood pressure or feel sleepy;
- if you have an unusual heart rate (rhythm);
- if you have had a stroke or your doctor has told you that you may be at risk from a stroke;
- if you are taking any antipsychotic medicines used to treat certain mental and emotional conditions (see the next section, Using other medicines).

Take special care with Amisulpride Oral Solution:
If you or someone else in your family has a history of blood clots, as medicines like these have been associated with formation of blood clots.
Using other medicines
Tell your doctor or pharmacist if you are taking any medicines listed under section 2, Do not take Amisulpride Oral Solution. Please also tell your doctor or pharmacist if you are taking any of the following medicines:

- medicines that act on the brain (CNS depressants) including anaesthetics, some antihistamines, medicines used to relieve pain (narcotics), medicines to help you sleep (barbiturates, benzodiazepines), or medicines that treat anxiety;
- clonidine (used to treat high blood pressure, migraine and menopausal flushing), its derivatives or other medicines to slow your heartbeat e.g. verapamil, or medicines which can cause your heartbeat to slow;
- medicines which may lower the levels of potassium in your blood such as:
  - water tablets (diuretics) which increase the amount of urine you pass;
  - amphotericin B (medicine used to treat fungal infections);
  - some laxatives;
  - glucocorticoids (used to treat severe asthma and other inflammatory disorders);
  - tetracosides (used to treat ulcerative colitis, Crohn’s disease and rheumatoid arthritis).
- medicines used to treat certain mental and emotional conditions (antipsychotics) or medicines used to treat depression such as pimozide, haloperidol, imipramine, thiouridazine and lithium;
- medicines which lower your blood pressure e.g. diltiazem.

You must also inform your doctor or dentist that you are taking Amisulpride Oral Solution before you have an anaesthetic.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Amisulpride Oral Solution with food, drink and alcohol
A carbohydrate rich (starchy/sugary) meal may adversely effect how this medicine works. Therefore you should take Amisulpride Oral Solution before a meal and at about the same time(s) each day. Do not drink alcohol whilst you are taking this medicine as the effects of alcohol may be increased.

Pregnancy and breast-feeding
- Do not take Amisulpride Oral Solution if you are breast-feeding.
- If you are a woman of child bearing age, you should talk to your doctor about the use of appropriate contraception while taking this medicine.
- If you are pregnant, or thinking of becoming pregnant, ask your doctor or pharmacist for advice before taking Amisulpride Oral Solution.
Driving and using machines
When taking this medicine you may feel drowsy or find that your reaction time is impaired. Do not drive and do not use any tools or machines until you are sure that you are not affected.

Important information about some of the other ingredients in Amisulpride Oral Solution
Amisulpride Oral Solution contains parahydroxybenzoates (E216 propyl parahydroxybenzoate and E218 methyl parahydroxybenzoate). These may cause allergic reactions (possibly delayed). This medicinal product contains 0.17mmol [4.02mg] sodium (salt) per 1ml of oral solution. To be taken into consideration by patients on a controlled sodium (salt) diet.

3. How to take Amisulpride Oral Solution
Your doctor will prescribe the most appropriate dose to treat your condition. Always take Amisulpride Oral Solution exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
• Take your medicine by mouth.
• Take your medicine with a drink that does not contain alcohol.
• Take before a meal.

A 5ml graduated syringe is provided with your medicine. Use the syringe to withdraw, from the bottle, the amount of Amisulpride Oral Solution that has been prescribed for you by your doctor.

Each 1ml of solution contains 100mg of your medicine. Each 0.5ml of solution contains 50mg of your medicine (see Figure A).

Figure A
The conversion of milligrams (mg) to millilitres (ml) is provided in the table below:

<table>
<thead>
<tr>
<th>Amount of solution (ml)</th>
<th>Amount of medicine (mg)</th>
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<tr>
<td>0.5</td>
<td>50</td>
</tr>
<tr>
<td>1</td>
<td>100</td>
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<tr>
<td>2</td>
<td>200</td>
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<tr>
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<td>300</td>
</tr>
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<td>4</td>
<td>400</td>
</tr>
<tr>
<td>5</td>
<td>500</td>
</tr>
</tbody>
</table>

**Adults, children over 15 years of age and the elderly**
- The usual dose is between 0.5ml (50mg amisulpride) and 8ml (800mg amisulpride) each day.
- This may be increased to 12ml (1200mg amisulpride) daily.
- Dosages up to 3ml (300mg amisulpride) can be taken once daily.
- Dosages greater than 3ml (300mg amisulpride) should not be taken all at once. Your doctor will tell you how much to take and when to take it.

In the elderly, Amisulpride Oral Solution may increase the risk of low blood pressure or may make you feel sleepier; therefore your doctor may want to monitor you more closely.

**Children**
- Amisulpride Oral Solution should **not** be given to children under 15 years of age.

**Patients with kidney problems**
- If you suffer from kidney problems, your doctor may choose to give you a lower dose of Amisulpride Oral Solution.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

**If you take more Amisulpride Oral Solution than you should**
If you or someone else takes more Amisulpride Oral Solution than has been prescribed, or you think a child has swallowed any Amisulpride Oral Solution, contact your doctor, pharmacist or hospital emergency department immediately and take your Amisulpride Oral Solution with you.

- Symptoms of overdose may include sleepiness, coma, low blood pressure, shaking, slowed movement, increased saliva, stiffness and restlessness.
If you forget to take Amisulpride Oral Solution
• If you forget to take a dose, do not worry. Take the next dose when it is due.
• Do not take double the amount to make up for a forgotten dose.

If you stop taking Amisulpride Oral Solution
• Do not stop taking Amisulpride Oral Solution suddenly as this may cause side effects.
• Speak to your doctor before you stop taking Amisulpride Oral Solution.
• Your doctor will tell you how to reduce your dose slowly over a number of weeks or months to help lower the chance of you getting withdrawal symptoms.
• Stopping Amisulpride Oral Solution suddenly can lead to withdrawal symptoms such as:
  - feeling or being sick
  - problems sleeping
  - feeling restless
  - unusual body movements or muscle stiffness
  - your original condition may come back

4. Possible side effects
Like all medicines, Amisulpride Oral Solution can cause side effects, although not everybody gets them.

If you experience any of the following symptoms, contact your doctor immediately and stop taking this medicine:
• You have a high temperature, sweating, stiff muscles, fast heartbeat, fast breathing and feel confused, drowsy, or agitated. These could be the symptoms of a serious but rare side effect called ‘neuroleptic malignant syndrome’.
• You have an unusual heart rate, very fast heart rate or chest pain which could result in a heart attack or life-threatening heart disorder.
• Severe allergic reaction (affecting fewer than 1 in 100 people). You may have a red lumpy rash, difficulty breathing, swelling of face, lips or eyelids, unexplained high temperature (fever) and feel faint. If the swelling affects your throat and makes breathing and swallowing difficult, go to hospital straight away.
• You have blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which 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.

Very common side effects (affecting more than 1 in 10 people):
• Trembling, muscle stiffness, excess saliva, slowed movement or restlessness. Your doctor may give you another medicine to reduce these symptoms. The effects are generally mild at low doses.
Common side effects (affecting up to 1 in 10 people):
- Neck spasms, rolling of the eyes, lockjaw. Your doctor may give you another medicine to treat these symptoms
- Feeling drowsy
- Sleeplessness, agitation, anxiety
- Difficulty in reaching orgasm
- Problems with digestion such as constipation, feeling or being sick, dry mouth
- Weight gain
- Milk production from the breasts (in women), breast pain
- Stopping of menstrual periods
- Enlarged breasts in men
- Difficulty in getting, or maintaining, an erection (impotence)
- Feeling dizzy when you stand up if sitting, or sit up after lying down (which can be due to low blood pressure)

Uncommon side effects (affecting fewer than 1 in 100 people):
- Uncontrollable movements of the face or tongue (tardive dyskinesia)
- Seizures, convulsions. If you have a history of epilepsy your doctor will monitor you closely while taking this medicine as your seizure threshold may be reduced and you may experience more seizures
- Liver enzyme test changes (you may get increased levels of certain liver enzymes)
- High blood sugar (hyperglycaemia) which may result in the need to urinate more frequently, feeling tired, feeling thirsty or experiencing blurred vision
- Slowing of the heartbeat

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

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

5. How to store Amisulpride Oral Solution

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the carton and the bottle label. The expiry date refers to the last day of that month.

The medicinal product does not require any special storage conditions.

Once opened, use within 2 months.

Do not use if you notice any visible signs of damage to the bottle or deterioration in your medicine. Return it to your pharmacist. Medicines should not be disposed of via wastewater or household
waste. Ask your pharmacist how to dispose of medicines that have passed the expiry date or have been open for more than 2 months. These measures will help to protect the environment.

6. Further information

**What Amisulpride Oral Solution contains**
- The active substance is amisulpride. Each 1ml of oral solution contains 100mg amisulpride.
- The other ingredients are saccharin sodium, sodium gluconate, gluconolactone, hydrochloric acid (used to adjust the pH), methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), potassium sorbate, caramel flavour (containing glycerol (E422) and ethyl alcohol) and purified water (see section 2, **Before you take Amisulpride Oral Solution**).

**What Amisulpride Oral Solution looks like and contents of the pack**
Amisulpride Oral Solution is a colourless to brown yellowish clear solution. It is available in an amber glass bottle containing 60ml of medicine. The pack also contains a 5ml, plastic oral dosing syringe.

**Marketing Authorisation Holder**
Focus Pharmaceuticals Limited, Unit 5, Faraday Court, First Avenue, Centrum 100, Burton upon Trent, Staffordshire, DE14 2WX, UK.
Tel: 00 44 (0)1283 495 280 Fax: 00 44 (0)1283 495 290
Email: medinfo@focuspharma.co.uk

**Manufacturer**
Pharmanel Pharmaceuticals S.A. 60th km of the Athens-Lamia Highway (Schimatari), Greece.
Or
P. N. G. Gerolymatos S.A. Plant B, 4 Asklepiou Str.,
145 68 Kryoneri, Athens, Greece.

For any information about this medicinal product, please contact the Marketing Authorisation Holder, details provided above.

For information in large print, audio CD or Braille please telephone 00 44 (0)1283 495 280 or email medinfo@focuspharma.co.uk.

This leaflet was last approved in February 2011
Module 4
Labelling

Amisulpride 100mg/ml Oral Solution

Each 1ml of oral solution contains 100mg Amisulpride.
It also contains methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216) and sodium.

For oral use. Use only as directed by a doctor.
Read the enclosed package leaflet before taking your medicine.
Once opened, use within 2 months.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

PL 20046/0074
PA 1338/006/001
PL Holder:
Focus Pharmaceuticals Ltd.
Unit 5, Feraday Court,
Burton upon Trent,
DE24 1WX, UK.
Amisulpride 100mg/ml Oral Solution

Each 1ml of oral solution contains 100mg Amisulpride. It also contains methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216) and sodium.

For oral use. Use only as directed by a doctor. Read the enclosed package leaflet before taking your medicine.

Once opened, use within 2 months.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Ireland and the UK considered that the application for Amisulpride 100mg/ml Oral Solution could be approved. The product is a prescription only medicine (POM) and is indicated for the treatment of acute and chronic schizophrenic disorders, in which positive symptoms (such as delusions, hallucinations, and thought disorders) and/or negative symptoms (such as blunted affect, emotional and social withdrawal) are prominent, including patients characterised by predominant negative symptoms.

This application for Amisulpride 100mg/ml Oral Solution is submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product of Solian 100mg and 200mg Tablets (PL 15819/0037 and 0002, respectively) first authorised in the UK to Lorex Sythelabo UK and Ireland Limited on 6th July 1999 and 11th August 1997, respectively.

The UK reference product is Solian Solution 100mg/ml (PL 11723/0377), first authorised in the UK to Sanofi-Synthelabo Limited on 16th May 2001. This then underwent a change of ownership to Aventis pharma Limited (PL 04425/0654) on 16th May 2001.

No new non-clinical studies were conducted, which is acceptable given that the product contains a widely-used, well-known active substance. No clinical studies have been performed and none are required for this application as the pharmacology of amisulpride is well-established.

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.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Amisulpride 100mg/ml Oral Solution</th>
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<tr>
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<td>Focus Pharmaceuticals Ltd</td>
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<td>Unit 5 Faraday Court</td>
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III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

Amisulpride
INN/Ph.Eur name: Amisulpride
Chemical name: 4-Amino-N-[(2RS)-1-ethylpyrrolidin-2-yl]methyl]-5-(ethylsulphonyl)-2-methoxybenzamide

Structural formula:

![Structural formula of Amisulpride]

Molecular formula: C_{17}H_{27}N_{3}O_{4}S

Appearance: White to almost white crystalline powder.
Solubility: Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in anhydrous ethanol.

Amisulpride complies with the European Pharmacopoeia monograph.

All aspects of the manufacture of the active substance from its starting materials are controlled by a Certificate of Suitability.

All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance amisulpride, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Suitable Certificates of Analysis have been provided for all reference standards used. Batch analysis data are provided and comply with the proposed specification.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product

Other Ingredients

Other ingredients are pharmaceutical excipients saccharin sodium, sodium gluconate, gluconolactone, hydrochloric acid, concentrated (pH adjuster), methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), potassium sorbate, Caramel flavour, (glycerol (E422) and ethyl alcohol) and purified water.
All excipients comply with their European Pharmacopoeia monographs with the exception of Gesweet 2023 (saccharin sodium, sodium gluconate, gluconolactone) and Caramel flavour (glycerol (E422) and ethyl alcohol). Gesweet 2023 (saccharin sodium, sodium gluconate, gluconolactone) and Caramel flavour (glycerol (E422) and ethyl alcohol) comply with in-house specifications.

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**
The objective of the development programme was to produce a product containing amisulpride that could be considered a generic medicinal product of Solian Solution 100mg/ml.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on pilot-scale batches have been provided. The applicant has committed to perform process validation with future commercial-scale batches of the drug product.

**Finished Product Specification**
The finished product specification proposed for the product is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container-Closure System**
This product is packaged in 60ml bottles composed of amber (European Pharmacopoeia) Type III glass. The bottles are closed with child resistant, tamper evident plastic screw caps with a low-density polyethylene (LDPE) liner. The product comes with a 5ml graduated oral dosing syringe.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the European Pharmacopoeia and relevant regulations regarding use of materials in contact with food.

**Stability of the product**
Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 2 years for an unopened product with no special storage instructions. Once the bottle has been opened, the product should be used within 2 months.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labelling are pharmaceutically acceptable.
User testing results have been submitted for Section 3 (‘How to take Amisulpride Oral Solution’) of the PIL for this product. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

An appropriate bridging report has been provided for the remainder of the text. The PIL is satisfactory.

**MAA forms**
The MAA form is pharmaceutically 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**
It is recommended that a Marketing Authorisation is granted for this application.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of amisulpride are well-known. As this is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required.

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment.
III.3 CLINICAL ASPECTS
This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

CLINICAL PHARMACOLOGY
No new pharmacokinetic or pharmacodynamic data were submitted with this application and none were required, as per the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, if the test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived, if the excipients contained in it do not affect gastrointestinal transit, absorption, solubility or in-vivo stability of the active substance.

EFFICACY
No new efficacy data were submitted with this application and none were required.

SAFETY
No new safety data were submitted with this application and none were required.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference product, where appropriate.

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.

MAA FORM
The MAA form is medically satisfactory.

CONCLUSIONS
It is recommended that a Marketing Authorisation is granted for this application.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Amisulpride 100mg/ml Oral Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Amisulpride 100mg/ml Oral Solution and the reference product Solian Solution 100mg/ml.

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with that for the reference product.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. 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 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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