Public Assessment Report

Decentralised Procedure

Amisulpride Oral Solution 100mg/ml

Amisulpride

UK/H/1875/001/DC

UK licence no: PL 20620/0040

NRIM Limited
Amisulpride Oral Solution 100mg/ml
PL 20620/0040

LAY SUMMARY

On 27th October 2010, Germany, France and the UK agreed to grant marketing authorisation to NRIM Limited for the medicinal product Amisulpride Oral Solution 100mg/ml. The marketing authorisation was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a licence was granted in the UK on 26th November 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:

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

● so called negative symptoms:
  - becoming withdrawn and subdued.

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

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<td><strong>Type of Application</strong></td>
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<td><strong>Active Substance</strong></td>
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<td><strong>Strength</strong></td>
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<td><strong>MA Holder</strong></td>
<td>NRIM Ltd. Marlborough House 298, Regents Park Road Finchley London N3 2UA UK</td>
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Module 2
Summary of Product Characteristics

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
1ml of Amisulpride Oral Solution contains 100mg of amisulpride.

1ml of Amisulpride Oral Solution also contains 1.0 mg of Methyl parahydroxybenzoate and 0.1mg of Propyl parahydroxybenzoate

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Oral Solution

A clear yellow liquid with an odour of caramel.

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, animosity, unusual suspiciousness
and/or 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

Route of administration
Oral use

Method of administration
The graduations on the dosage pipette measure the milligrams of active ingredient. 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 milligrams to be administered. The oral solution should be drunk with a liquid, which does not contain alcohol.

Recommended dosage
Positive symptoms:
For acute psychotic episodes a daily dose of 400 mg to 800 mg of amisulpride is recommended. In individual cases, the daily dose may be increased up to 1200 mg/day of amisulpride. Doses above 1200 mg/day have not been extensively evaluated for safety and should therefore not be used. For daily doses over 300 mg/day amisulpride, the daily dose should be divided in several administrations.
No specific titration is required when initiating the treatment with amisulpride. For patients with mixed positive and negative symptoms, doses should be adjusted to obtain optimal control of positive symptoms i.e. between 400-800mg/day.
Maintenance treatment should be established individually with the minimally effective dose.

Predominant negative symptoms (deficit syndrome):
A daily dose of 50 mg to 300 mg of amisulpride. Doses should be adjusted according to individual response.
Amisulpride can be administered once daily at oral doses up to 300 mg.

Dosage for particular patient groups

Patients with renal impairment:
The dose should be reduced to half in patients with creatinine clearance between 30 to 60 ml/min and to a third in patients with creatinine clearance between 10 to 30 ml/min. As there is no experience in patients with severe renal impairment (creatinine clearance < 10 ml/min), the use of amisulpride is not recommended in these patients (see section 4.4).

Patients with hepatic impairment:
Since the drug is weakly metabolized, a dosage reduction should not be necessary for patients with hepatic insufficiency.

Children and adolescents
Amisulpride is contra-indicated in children and adolescents under 15 years of age (see section 4.3)
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 preformed by a physician experienced in treating schizophrenia in this age group.

**Patients over 65 years**

Treatment of elderly patients is not recommended as there is insufficient clinical experience. If treatment with amisulpride is absolutely necessary particular caution is required due to a possible risk of hypotension or sedation.

**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.

### 4.3 Contraindications

- **Hypersensitivity to amisulpride or to other ingredients of the drug**
- **Concomitant prolactin-dependent tumours: 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)**

### 4.4 Special warnings and precautions for use

**Neuroleptic Malignant Syndrome**, characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK, may occur. In the event of hyperthermia, particularly with high daily doses, all antipsychotic drugs including amisulpride should be discontinued.

**Hyperglycaemia** has been reported in patients treated with some atypical antipsychotic agents, including amisulpride, therefore patients with an established diagnosis of diabetes mellitus or with risk factors for diabetes who are started on amisulpride, should get appropriate glycaemic monitoring. Amisulpride is eliminated by the renal route. In cases of mild to moderate renal insufficiency, the dose should be decreased or intermittent treatment should 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 (patients over 65 years), amisulpride should be used with caution in this patient group owing to a lack of experience. It may lead to sedation and hypotension in this patient population (section 5.2). Caution should be also exercised when prescribing Amisulpride to patients with Parkinson’s disease since it may cause worsening of the disease. Amisulpride should be used only if neuroleptic treatment cannot be avoided.

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

**Prolongation of the QT interval**

Caution should be exercised when amisulpride is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and concomitant use with neuroleptics should be avoided.

**Stroke**

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

Diabetic patients and patients with risk factors for diabetes and who start treatment with amisulpride should receive appropriate blood glucose monitoring.

**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.

**Notice for Amisulpride Oral Solution**
Allergic reactions can be caused by Methyl parahydroxybenzoate and Propyl parahydroxybenzoate (possibly delayed).

### 4.5 Interaction with other medicinal products and other forms of interaction

#### COMBINATIONS WHICH ARE CONTRAINDICATED (see section 4.3)
Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics. In the case of neuroleptic-induced extrapyramidal symptoms, do not treat with a dopaminergic agonist but use an anticholinergic.

#### COMBINATIONS WHICH ARE NOT RECOMMENDED
Amisulpride may enhance the central effects of alcohol. Therefore alcohol should not be consumed during treatment.

#### COMBINATIONS WHICH REQUIRE PRECAUTIONS FOR USE
Caution is required when using the following agents concomitantly (due to potentiation of effect):
- CNS depressants including narcotics, anaesthetics, analgesics, sedative H1 antihistamines, barbiturates, benzodiazepines and other anxiolytic drugs, clonidine and derivatives.
- Antihypertensive drugs and other hypotensive medications. Antihypertensive effect and increase risk of orthostatic hypotension (additive effect).
- Caution is advised when prescribing amisulpride with medicines known to prolong the QT interval, e.g., class IA antiarrhythmics (e.g., quinidine, disopyramide) and class III antiarrhythmics (e.g., amiodarone, sotalol), some antihistamines, some other antipsychotics and some antimalarials (e.g., mefloquine) (see section 4.4).
- Possible interactions with medicines causing electrolyte imbalance.

### 4.6 Pregnancy and lactation

#### Pregnancy:
In animals, Amisulpride did not show reproductive toxicity. A decrease in fertility linked to the pharmacological effects of the drug (prolactin mediated effect) was observed. No teratogenic effects of Amisulpride were noted.
Very limited clinical data on exposed pregnancies are available. Therefore, the safety of Amisulpride during human pregnancy has not been established.
Use of the drug is not recommended during pregnancy unless the benefits justify the potential risks. If amisulpride is used during pregnancy, neonates may show adverse effects of amisulpride and thus appropriate monitoring should be considered.
For women of childbearing potential, effective contraception should be fully discussed with the physician prior to treatment.

#### Lactation:
It is not known whether amisulpride is excreted in breast milk, breast-feeding is therefore 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 cause somnolence so that the ability to drive vehicles or operate machinery can be impaired (see section 4.8). This is especially true when used concomitantly with alcohol.

### 4.8 Undesirable effects
Adverse events have been ranked under headings of frequency using the following convention: very common \((\geq 1/10)\); 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 events 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: Amisulpride causes an increase in plasma prolactin levels which is reversible after drug discontinuation. This may result in galactorrhoea, amenorrhoea or menstrual disorders, gynaecomastia, breast pain or enlargement, prolactinoma 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 and dizziness.

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 is ineffective or may induce aggravation of the symptoms.

Seizures

Cardiovascular disorders
Common: Hypotension
Uncommon: Bradycardia

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:
Frequency not known: Neuroleptic Malignant Syndrome (see section 4.4).

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.

Skin and subcutaneous tissue disorders
Frequency Not known: Angioedema, urticaria

4.9 Overdose
Experience with amisulpride in over-dosage is limited. Exaggeration of the known pharmacological effects of the drug has been reported. These include drowsiness and sedation, coma, hypotension and extrapyramidal symptoms.
Actions to be taken by overdose
In cases of acute over-dosage, the possibility of intoxication by multiple drug intake should be considered.
Since amisulpride is weakly dialysed, hemodialysis should not be used to eliminate the drug.
There is no specific antidote to amisulpride.
Appropriate supportive measures should therefore be instituted with close supervision of vital functions including continuous cardiac monitoring due to the risk of prolongation of the QT interval. If severe extrapyramidal symptoms occur, anticholinergic agents should be administered.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmcotherapeutic group: Antipsychotics, Benzamides
ATC Code: NO5A LO5
Amisulpride binds selectively with a high affinity to human dopaminergic D2/D3 receptor subtypes whereas it is devoid of affinity for D1, D4 and D5 receptor subtypes.
Unlike classical and atypical neuroleptics, amisulpride has no affinity for serotonin, α-adrenergic, histamine H1 and cholinergic receptors. In addition, amisulpride does not bind to sigma sites.
In animal studies, at high doses, amisulpride blocks dopamine receptors located in the limbic structures in preference to those in the striatum.
At low doses it preferentially blocks pre-synaptic D2/D3 receptors, producing dopamine release responsible for its disinhibitory effects.
This pharmacological profile explains the clinical efficacy of Amisulpride against both negative and positive symptoms of schizophrenia.

5.2 Pharmacokinetic properties
In man, amisulpride shows two absorption peaks: one which is attained rapidly, one hour post-dose and a second between 3 and 4 hours after administration. Corresponding plasma concentrations are 39 ± 3 and 54 ± 4 ng/ml after a 50 mg dose.
The volume of distribution is 5.8 l/kg, plasma protein binding is low (16%) and no drug interactions are suspected.
Absolute bioavailability is 48%. Amisulpride is weakly metabolised: two inactive metabolites, accounting for approximately 4% of the dose, have been identified. There is no accumulation of amisulpride and its pharmacokinetics remains 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 the drug is weakly metabolised a dosage reduction should not be necessary in patients with hepatic insufficiency.
Renal impairment: The elimination half-life may increase in patients with renal insufficiency while systemic clearance is reduced by a factor of 2.5 to 3. The AUC of amisulpride in mild renal failure increased two fold and almost tenfold in moderate renal failure (see chapter 4.2). Experience is however limited and there is no data with doses greater than 50 mg.
Amisulpride is very weakly dialysed.
Limited pharmacokinetic data in elderly subjects (> 65 years) show that a 10-30 % rise occurs in Cmax, T1/2 and AUC after a single oral dose of 50 mg. No data are available after repeat dosing.

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

6.1 List of excipients
- Propylene Glycol
- Saccharin Sodium
- Sodium Gluconate
- Glucono-delta-lactone
- Methyl parahydroxybenzoate (E218)
- Propyl parahydroxybenzoate (E216)
- Potassium Sorbate (E202)
- Hydrochloric Acid (for pH-adjustment)
- Purified water
- Caramel flavour consisting of the following: -
  - Propylene glycol E1520 75,
  - Nature-identical flavouring substance(s),
  - Water,
  - Flavouring preparation
  - Ascorbic acid E300

6.2 Incompatibilities
Not applicable

6.3 Shelf life
- Shelf life: 2 years
- Shelf life after first opening the container: 2 months

6.4 Special precautions for storage
Store in the original bottle.

6.5 Nature and contents of container
- 60ml Amber colored EP type III glass bottle with 28 mm polypropylene child resistance cap having tamper evident ring with a 4ml graduated oral syringe.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
NRIM Limited
Marlborough House
298, Regents Park Road
Finchley N3 2UA
London, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20620/0040

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
26/11/2010

10 DATE OF REVISION OF THE TEXT
26/11/2010
Module 3

AMISULPRIDE ORAL SOLUTION 100MG/ML
PATIENT INFORMATION LEAFLET

READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU START USING 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 gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

THE LEAFLET CONTAINS INFORMATION ON:
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?

The name of your medicine is Amisulpride Oral Solution 100mg/ml (called Amisulpride throughout this leaflet). 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:

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

2 BEFORE YOU TAKE AMISULPRIDE ORAL SOLUTION

You should not take Amisulpride until you are sure it is safe for you to do so.

Do not take Amisulpride and tell your doctor if:
- you are allergic (hypersensitive) to amisulpride or any of the other ingredients of Amisulpride listed in Section 6 below)

Signs of an allergic reaction include: a rash, swelling or breathing problems, swelling of your lips, face, throat or tongue
- you are breast-feeding (see 'Pregnancy and breast-feeding' section)
- you have breast cancer or something called 'a prolactin dependent tumour'
- you have a tumour on the adrenal gland (called phaeochromocytoma)
- you have severely impaired kidney function
- you are taking levodopa, a medicine used to treat Parkinson's disease (See 'Taking other medicines' section)
- the patient is under 15 years old

Do not take this medicine if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Amisulpride.

Take special care with Amisulpride.

Check with your doctor or pharmacist before taking this medicine if:
- you have kidney problems
- you have Parkinson's disease, as Amisulpride can make this condition worse
- you have ever had fits (epileptic seizures)
- you have an unusual heart rate (rhythm)
- You have or have had heart disease or family history of heart problems
- You are at risk for a stroke or a temporary reduction of blood flow to the brain (transient ischemic attack)
- you are diabetic or have been told you have an increased risk of having diabetes
- you are over 65 years old. This is because elderly people are more likely to get low blood pressure or feel sleepy
- you have been told you have a low amount of potassium or magnesium in your blood or you are taking other medicines that cause these side effects
- someone else in your family has a history of blood clots, as medicines like these have been associated with formation of blood clots
- you have any involuntary or abnormal movements especially of the tongue, mouth and face while taking this medicine (extrapyramidal symptoms)

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking Amisulpride.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes
medicines you buy without a prescription, including herbal medicines. This is because Amisulpride can affect the way some other medicines work. Also some medicines can affect the way Amisulpride works.

Do not take Amisulpride, and tell your doctor if you are taking any of the following medicines:
- L-dopa, a medicine to treat Parkinson's disease

Tell your doctor if you are taking any of the following medicines:
- Medicines used to control your heart beat such as quinidine, disopyramide, procainamide, amiodarone, sotalol, flecaïnide, and propafenone
- Medicines for depression or to calm emotional and mental illnesses such as thioridazine
- Medicines for severe pain called opiates such as morphine, pethidine or methadone
- Medicines used to treat high blood pressure, that could slow your heart rate down, such as clonidine
- Medicines to help you sleep such as barbiturates and benzodiazepines
- Anaesthetics
- Medicines to treat malaria
- Medicines causing electrolyte imbalance
- Some antidepressants

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking Amisulpride.

Taking Amisulpride with food or drink
Amisulpride should be taken with a drink that does not contain alcohol. Do not drink alcohol while you are taking Amisulpride because it can affect the way the medicine works.

Pregnancy and breast-feeding
Do not take this medicine if you are breast-feeding or planning to breast-feed. Talk to your doctor before taking this medicine if you are pregnant, might become pregnant or think you may be pregnant.

Driving and using machines:
You may feel less alert, dizzy or sleepy while taking this medicine. If this happens, do not drive or use any tools or machines. Please note that alcohol will make your reactions even slower.

Important information about some of the ingredients of Amisulpride
Amisulpride contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

3. HOW TO TAKE AMISULPRIDE ORAL SOLUTION
Always take Amisulpride exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults
- If you suffer from positive symptoms, the usual dose is between 400mg (4ml) to 800mg (8ml) a day and will be adjusted individually by your doctor depending on the nature and severity of your illness and your kidney function. The maximum daily dose is 1,200 mg (12ml).
- If you suffer from both positive and negative symptoms, your doctor will adjust your dose individually so that there is adequate control of the positive symptoms. To maintain 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 (0.5ml) and 300 mg (3ml) amisulpride daily, and will be adjusted individually by your doctor depending on the nature and severity of your illness and your kidney function.

Patients over 65 years old
Your doctor will need to keep a close check on you as you are more likely to have low blood pressure or sleepiness due to this medicine.

Children and adolescents
Efficacy and safety of amisulpride in children and adolescents under 18 years of age have not been established. It absolutely required treatment of adolescents from 16 to 18 years of age must 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.

Patients with kidney problems
If you suffer from kidney problems, your doctor will normally prescribe a lower dose. This may be reduced to half or a third of the normal dose depending on the impairment grade of your kidney.

Patients with impaired liver function
No changes to the normal dose should be necessary.

Method of administration
If you are taking up to 300mg of Amisulpride a day, this can be taken as a single dose preferably at the same time each day. Larger doses should usually be divided up with part of the
dose given in the morning and the other part later in the day. Your doctor will tell you how and when to take your medicine.

Use the graduated syringe to measure your medicine. Each 1ml of solution contains 100mg of your medicine. The graduations on the dosage pipette measure the milligrams of active ingredient. 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 milligrams to be administered. Wipe off excess solution from the outside of the syringe with a tissue prior to administration of the dose. The oral solution should be drunk with a liquid, which does not contain alcohol.

Your doctor will tell you how much Amisulpride you should take and how long you should continue to take it.

If you take more Amisulpride than you should
It is important to stick to the dose on the label of the medicine. If you or someone else takes too much medicine, contact your doctor or nearest hospital emergency department immediately. Always take any medicine left over with you and also the box, as this will allow easier identification of the medicine.

Signs of overdose may include feeling restless or shaky, rigidity, muscle, feeling drowsy or sleepy which could lead to a loss of consciousness.

If you forget to take Amisulpride
If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose do not take a double dose to make up for a forgotten dose, just carry on as before.

If you stop taking Amisulpride
Keep taking Amisulpride until your doctor tells you to stop. Do not stop taking Amisulpride just because you feel better. If you stop, your illness may get worse or come back. Unless your doctor tells you otherwise Amisulpride Oral Solution should not be stopped suddenly. Stopping treatment suddenly may cause withdrawal effects such as feeling or being sick, sweating, difficulty sleeping or feeling very restless, muscle stiffness or unusual body movements or your original condition may come back.

Blood tests
Taking Amisulpride may affect the results of some blood tests. These include tests to measure the hormone called 'prolactin' and liver tests. If you are going to have a blood test, it is important to tell your doctor you are taking Amisulpride.

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

4. POSSIBLE SIDE EFFECTS
Like all medicines, Amisulpride can cause side effects although not everybody gets them.

Stop taking Amisulpride and see a doctor or go to a hospital straight away if:
- You have a high temperature, sweating, stiff muscles, fast heartbeat, fast breathing and feel confused, drowsy or agitation. 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.
- 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.

Uncommon (affects less than 1 in 100 people)
- You have an allergic reaction. The signs may include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
- You have a fit (seizure).

Tell your doctor as soon as possible if you have any of the following side effects:

Very Common (affects more than 1 in 10 people)
- Trembling, pronounced muscle stiffness or spasm, slow movement, producing more saliva than usual or feeling restless. (These symptoms can be reduced if your doctor lowers your dose of Amisulpride or prescribes an additional medicine).

Common (affects less than 1 in 10 people)
- Movements that you cannot control, mainly of the arms and legs. (These symptoms can be reduced if your doctor lowers your dose of Amisulpride or prescribes an additional medicine).

Uncommon (affects less than 1 in 100 people)
- Movements you cannot control, mainly of the face or tongue.

Other side effects include:

Common (affects less than 1 in 10 people)
- Difficulty sleeping (insomnia) or feeling anxious or agitated.
- Feeling drowsy or sleepy.
• Constipation, feeling or being sick, dry mouth
• Putting on weight
• Unusual production of breast milk in women and men, breast pain
• Increased levels of the hormone prolactin which can lead to milk secretion from the breasts, breast pain or enlargement, menstrual period disorders, impotence, which will gradually disappear after you stop taking Amisulpride. Prolactin-dependent tumours may also appear.
• Feeling dizzy (which can be due to low blood pressure)
• Ovarian disorders

Uncommon (affects less than 1 in 100 people)
• Slowing of the heart beat
• Increased liver enzyme levels, high blood sugar (hyperglycaemia)
• Convulsions (fits)
• Allergic reactions such as skin rashes, itching or swelling

Frequency not known (cannot be estimated from the available data)
• Abnormal heart rhythms, which may be life-threatening and lead to cardiac arrest and sudden death

If any of the side effects get serious or lasts longer than a few days, or if you notice any other unwanted effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE AMISULPRIDE ORAL SOLUTION
• Keep out of the reach and sight of children.
• Do not use Amisulpride after the expiry date, which is stated on the label and carton. The expiry date refers to the last day of the month.
• Store in the original bottle.
• Amisulpride should be disposed of 2 months after opening.
• 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 Oral Solution contains?
The name of this medicine is Amisulpride Oral Solution. The active substance is amisulpride. 1ml of Amisulpride Oral Solution contains 100mg of amisulpride. The other ingredients are propylene glycol, saccharin sodium, sodium gluconate, gluten-dextrose, methylparahydroxybenzoate (E219), propyl parahydroxybenzoate (E216), potassium sorbate (E202), hydrochloric acid and caramel flavour. Caramel flavour consists of propylene glycol, E150d 75%, nature-identical flavouring substances, water, flavouring preparation and ascorbic acid E300.

What Amisulpride Oral Solution looks like and contents of the pack
Amisulpride is a clear yellow liquid with an odour of caramel. Each bottle contains 60ml of oral solution.

Marketing Authorisation Holder and Manufacturer
The Marketing Authorisation holder and manufacturer of this oral solution is NRM Limited Marlborough House, 293 Regents Park Road, Finchley, London, N3 2UA, United Kingdom.

This leaflet was last approved in 11/2010.
Module 4
Labelling

Amisulpride Oral Solution - 60 ml Ctn Cutter Guide
Size: 53 x 45 x 120 mm

For oral administration
Use as directed by your physician
Store in the original bottle.
Keep out of the reach and sight of children.
Read the package leaflet before use.
Shelf-life after first opening the container is 2 months.

BN:  
Exp:

POM PL 20620/0040
PL Holder: NRIM Limited, Marlborough House, 298 Regents Park Road, Finchley, London N3 2UA, UK

Each 1 ml dose of oral solution contains 100mg of amisulpride
Also contains Methyl parahydroxybenzoate (E218), Propyl parahydroxybenzoate (E216)
See leaflet for further information.

NRIM
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the application for Amisulpride Oral Solution 100mg/ml, in the treatment of acute and chronic schizophrenic disorders with positive symptoms (delusions, hallucinations, thought disorders, animosity, unusual suspiciousness) and/or negative symptoms (blunted affect, emotional and social withdrawal), could be approved.

This application was submitted under Article 10.1, claiming to be a generic medicinal product of Solian Solution 100 mg/ml (PL 04425/0654), which was originally granted in the UK to Sanofi-Aventis in May 2001.

With UK as the RMS in this Decentralised Procedure (UK/H/1875/001/DC), NRIM Limited applied for a Marketing Authorisation for Amisulpride Oral Solution 100mg/ml in Germany and France.

Amisulpride binds selectively with a high affinity to human dopaminergic D2/D3 receptor subtypes whereas it is devoid of affinity for D1, D4 and D5 receptor subtypes. Unlike classical and atypical neuroleptics, amisulpride has no affinity for serotonin, α-adrenergic, histamine H1 and cholinergic receptors. In addition, amisulpride does not bind to sigma sites.

No new non-clinical or clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of the originator product that has been licensed for over 10 years. Since both test and originator products are oral solutions, no bioequivalence study has been performed.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

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. A suitable justification has been provided for non-submission of a Risk Management Plan.

All member states agreed to grant a respective licence for the above product at the end of procedure (Day 210 – 27th October 2010). After a subsequent national phase, the UK granted a licence for this product on 26th November 2010 (PL 20620/0040).
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Amisulpride Oral Solution 100 mg/ml</th>
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</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s)</td>
<td>Amisulpride</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Antipsychotics, N05A L05</td>
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<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Oral Solution, 100 mg/ml</td>
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<td>Reference numbers for the Decentralised Procedure</td>
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<tr>
<td>Reference Member State</td>
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<td>Concerned Member States</td>
<td>Germany and France</td>
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<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 20620/0040</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>NRIM Limited</td>
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<tr>
<td></td>
<td>Marlborough House</td>
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<td></td>
<td>298, Regents Park Road</td>
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<td>Finchley, London N3 2UA, UK</td>
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</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Amisulpride

Chemical Names: 4-amino-N-[(2RS)-1-ethylpyrrolidin-2-yl]methyl]-5-(ethylsulfonyl)-2-methoxybenzamide
4-amino-N-[(ethyl-2-pyrrolidinyl)methyl]-5-(ethylsulfonyl)-o-anisamide

Structure:

\[
\begin{align*}
\text{Molecular formula: } & C_{17}H_{27}N_3O_4S \\
\text{Molecular weight: } & 369.5 \\
\text{Physical form: A white, odourless powder, with a bitter taste. Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol.}
\end{align*}
\]

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

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients propylene glycol, saccharin sodium, sodium gluconate, glucono-delta-lactone, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), potassium sorbate (E202), hydrochloric acid (for pH-adjustment), purified water and caramel flavour (consisting of propylene glycol E1520 75, nature-identical flavouring substance(s), water, flavouring preparation and ascorbic acid E300).

All excipients comply with the European Pharmacopoeia monograph with the exception of caramel flavour which complies with an in-house specification and glucono-delta-lactone and sodium gluconate which comply with United Stated Pharmacopoeia. Satisfactory Certificates of Analysis have been provided for these excipients.

The above excipients do not contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the pharmaceutical development programme was to obtain a stable product containing amisulpride that could be considered a generic medicinal product of Solian Solution 100 mg/ml (PL 04425/0654), which was granted in the UK to Sanofi-Aventis in May 2001.

Suitable pharmaceutical development data have been provided for this application.

Manufacture
A description and flow-chart of the manufacturing method have been provided. Process validation has been carried out on batches of the product and results are satisfactory.

**Finished Product Specifications**
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
The finished product is packaged in amber coloured, EP type III, glass bottles with polypropylene child resistance caps having tamper evident rings and supplied with a 4ml graduated oral syringe.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging, including the oral syringe, is controlled to appropriate EU quality standards and complies with guidelines.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been set when the product is unopened and after first opening 2 months, with the storage condition “Store in the original bottle”. This is acceptable.

**Bioequivalence**
As this is an oral solution, bioequivalence data are not necessary to support the application. This is acceptable and in line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1 Corr**).

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labelling are pharmaceutically satisfactory.

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

**Marketing Authorisation Application (MAA) Forms**
The MAA form is pharmaceutically satisfactory.

**Expert Report**
A pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
There are no objections to the approval of this product from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS
The pharmacological, pharmacokinetic and toxicological properties of amisulpride are well-known.

No further non-clinical data have been supplied with this application and none are required for applications of this type. 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.

A suitable justification has been provided for non-submission of the environmental risk assessment.

There are no objections to the approval of this product from a non-clinical point of view.

III.3 CLINICAL ASPECTS
Pharmacokinetics
No new data have been submitted and none are required for an application of this type.

This application is for a generic medicinal product of Solian Solution 100 mg/ml (PL 04425/0654), which was originally granted to Sanofi-Aventis in May 2001. The applicant’s product and the reference product contain the same quantitative and qualitative composition of the active substance, amisulpride.

In accordance with the Committee for Proprietary Medicinal Products (CHMP) guideline on “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**), there is no requirement for a bioequivalence study for products which are oral solutions.

Pharmacodynamics
No new data have been submitted and none are required for an application of this type.

Clinical efficacy
No new data have been submitted and none are required for an application of this type.

Clinical safety
Amisulpride has an acceptable adverse events profile. No new safety data are supplied or required for this generic application. Amisulpride has a well-established side-effect profile and is generally well-tolerated.

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.
Clinical Expert Report
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Marketing Authorisation Application (MAA) Forms
The MAA form is medically satisfactory.

Clinical Conclusion
There are no objections to the approval of this product from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Amisulpride Oral Solution 100mg/ml are well-defined and controlled. The specifications are satisfactory 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
This application is for a generic medicinal product of Solian Solution 100 mg/ml (PL 04425/0654), which was originally granted to Sanofi-Aventis in May 2001. The applicant’s product and the reference product contain the same quantitative and qualitative composition of the active substance, amisulpride.

According to the CHMP guideline on “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**), there is no requirement for a bioequivalence study for products which are oral solutions.

No new safety data are supplied or required for this generic application. Amisulpride has a well-established side-effect profile and is generally well-tolerated.

The SmPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s product and the innovator product are interchangeable. Extensive clinical experience with amisulpride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
# Module 6

## STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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