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.

It also contains 1mg/ml methyl parahydroxybenzoate (E218), 0.5mg/ml propyl parahydroxybenzoate (E216), sodium (4.02mg/ml) and ethanol (less than 0.5mg/ml).

For a full list of excipients, see Section 6.1.

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

Posology

For acute psychotic episodes

Oral doses between 400 mg/day and 800 mg/day are recommended. In individual cases, the daily dose may be increased up to 1200 mg/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. Maintenance treatment should be established individually with the minimally effective dose.

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:

The safety of amisulpride has been examined in a limited number of elderly patients. Amisulpride Oral Solution should be used with particular caution because of a possible risk of hypotension or sedation. Reduction in dosage may also be required because of renal insufficiency.

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 (CR_{CL}) between 30-60 ml/min and to a third in patients with CR_{CL} between 10-30 ml/min. As there is no experience in patients with severe renal impairment (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

Paediatric population:
The efficacy and safety of amisulpride from puberty to the age of 18 years have not been established: There are limited data available on the use of amisulpride in adolescents in schizophrenia. Therefore, the use of amisulpride from puberty to the age of 18 years is not recommended; in children up to puberty amisulpride is contraindicated, as its safety has not yet been established (see Section 4.3).

Method of administration :

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 listed in section 6.1.

- Concomitant prolactin-dependent tumours (e.g pituitary gland prolactinomas and breast cancer) (see section 4.4 and 4.8);

- Phaeochromocytoma;

- Children before the onset of puberty;

- Combination with levodopa (see 4.5).

4.4 Special warnings and precautions for use

As with other neuroleptics, Neuroleptic Malignant Syndrome, a potentially fatal complication, 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).

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. Reduction in dosage may also be required because of renal insufficiency.

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 been described after abrupt cessation of high therapeutic 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 with amisulpride. Therefore, gradual withdrawal is advisable.

<u>Prolongation of the QT interval:</u>

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.

<u>Stroke:</u>

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.

Elderly patients with dementia:

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analysis of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death in clinical trials with atypical antipsychotics were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature.

Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality.

The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

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.

Breast cancer

Amisulpride may increase prolactin levels. Therefore, caution should be exercised and patients with a history or a family history of breast cancer should be closely monitored during Amisulpride Oral Solution therapy.

Benign pituitary tumour

Amisulpride may increase prolactin levels. Cases of benign pituitary tumours such as prolactinoma have been observed during amisulpride therapy (see section 4.8). In case of very high levels of prolactin or clinical signs of pituitary tumour (such as visual field defect and headache), pituitary imaging should be performed. If the diagnosis of pituitary tumour is confirmed, the treatment with amisulpride must be stopped (see section 4.3).

Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics, including amisulpride. Unexplained infections or fever may be evidence of blood dyscrasia (see section 4.8), and requires immediate haematological investigation.

Severe liver toxicity has been reported with amisulpride use. Patients should be instructed to report immediately signs such as asthenia, anorexia, nausea, vomiting, abdominal pain or icterus to a physician. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately (see section 4.8).

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

This medicinal product contains 0.18mmol (4.02mg) sodium per 1ml of oral solution equivalent to 0.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult. 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. A dose of 600mg amisulpride contains 24.12 mg (1.04 mmol) sodium per 6 ml equivalent to 1.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult. A maximum dose of 1200 mg amisulpride contains 48.24 mg (2.08 mmol) sodium per 12 ml equivalent to 2.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult. Care should be taken with patients on a controlled sodium diet.

The flavouring used in this medicinal product contains a small amount of ethanol, less than 0.5mg per 1ml of oral solution.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations

Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics. Amisulpride may oppose the effect of dopamine agonists e.g. bromocriptine, ropinirole.

Combinations not recommended

Amisulpride Oral Solution may enhance the central effects of alcohol.

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;

Co-administration of amisulpride and clozapine may lead to an increase in plasma levels of amisulpride

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).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are only limited data available from the use of amisulpride in pregnant women. The safety of amisulpride during human pregnancy has not been established.

Amisulpride crosses the placenta.

Studies in animals have shown reproductive toxicity (see section 5.3).

The use of amisulpride is not recommended during pregnancy and in women of childbearing potential not using effective contraception, unless the benefits justify the potential risks.

Neonates exposed to antipsychotics (including Amisulpride Oral Solution) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery (see section 4.8). There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breast-feeding
Amisulpride is excreted into breastmilk in rather large amounts above the accepted value of 10% of the maternal weight-adjusted dosage in some cases, but blood concentrations in breastfed infants have not been evaluated. There is insufficient information on the effects of amisulpride in newborns/infants. A decision must be made whether to discontinue breast-feeding or to abstain from amisulpride therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

A decrease in fertility linked to the pharmacological effects of the drug (prolactin-mediated effect) was observed in treated animals.

4.7 Effects on ability to drive and use machines

Even used as recommended, Amisulpride Oral Solution may cause somnolence and blurred vision so that the ability to drive vehicles or operate machinery can be impaired (see Section 4.8).

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); not known (cannot be estimated from the available data).

System organ class	Frequency	Undesirable effects

Blood and lymphatic system disorders	Uncommon	Leukopenia, neutropenia (see Section 4.4).
	Rare	Agranulocytosis (see Section 4.4).
Immune system disorders	Uncommon	Allergic reaction
Endocrine disorders	Common	Galactorrhoea[1], Amenorrhoea[1], Gynaecomastia[1], Breast pain[1], Erectile dysfunction[1]
	Rare	Benign pituitary tumour such as prolactinoma (see sections 4.3 and 4.4)
Metabolism and nutrition disorders	Uncommon	Hyperglycemia (see 4.4), hypertriglyceridemia and hypercholesterolaemia
	Rare	Hyponatraemia, syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Psychiatric disorders	Common	Insomnia, anxiety, agitation, orgasmic dysfunction
	Uncommon	Confusion
Nervous system disorders	Very common	Extrapyramidal symptoms[2] may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia, dyskinesia
	Common	Somnolence, acute dystonia (spasm torticollis, oculogyric crisis, trismus) may appear[3]
	Uncommon	Seizures, tardive dyskinesia characterised by rhythmic, involuntary movements primarily of the tongue and/or face[4]
	Rare	Neuroleptic Malignant Syndrome (see section 4.4), which is a potentially fatal complication
	Not known	Restless legs syndrome
Eye disorders	Common	blurred vision (see section 4.7)
Cardiac disorders	Uncommon:	Bradycardia

	Rare	QT interval prolongation, ventricular arrhythmias such as torsade de pointes, ventricular tachycardia, ventricular fibrillation, cardiac arrest, sudden death (see section 4.4)
Vascular disorders	Common	Hypotension
	Uncommon	increase in blood pressure
	Rare	venous thromboembolism, including pulmonary embolism, sometimes fatal, and deep vein thrombosis (see section 4.4).
Respiratory, thoracic and mediastinal disorders	Uncommon:	nasal congestion, pneumonia aspiration (mainly in association with other antipsychotics and CNS depressants).
Gastrointestinal disorders	Common:	Constipation, nausea, vomiting, dry mouth
Hepatobiliary disorder	Uncommon	hepatocellular injury
Skin and subcutaneous tissue disorders:	Rare:	Angioedema, urticaria
	Not known	photosensitivity reaction
Musculoskeletal and connective tissue disorders	Uncommon	osteopenia, osteoporosis
Renal and urinary disorders	Uncommon:	urinary retention
Pregnancy, puerperium and perinatal conditions:	Not known:	Drug withdrawal syndrome neonatal (see 4.6).
Investigations:	Common:	Weight gain
	Uncommon:	Elevations of hepatic enzymes, mainly transaminases

[1] 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.

[2] 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.

[3] This is reversible without discontinuation of amisulpride upon treatment with an antiparkinsonian agent

[4] These have been reported, usually after long term administration. Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms:

Experience with amisulpride in overdose is limited. Exaggeration of the known pharmacological effects of the drug have been reported. These include drowsiness, sedation, coma, hypotension and extrapyramidal symptoms. Fatal outcomes have been reported mainly in combination with other psychotropic agents.

In cases of acute overdosage, the possibility of multiple drug intake should be considered.

Management:

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 until the patient recovers.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics, ATC Code: N05A L05

Mechanism of action

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,

adrenergic, histamine H_1 and cholinergic receptors. In addition, amisulpride does not bind to sigma sites.

Pharmacodynamic effects

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

Absorption

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.

Distribution

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

Biotransformation

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.

Elimination

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.

6.1 List of excipients

Saccharin sodium,

Sodium gluconate,

Gluconolactone,

Hydrochloric acid, concentrated (pH adjuster),

Methyl parahydroxybenzoate (E218),

Propyl parahydroxybenzoate (E216),

Potassium sorbate,

Toffee Flavour A, (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.,
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8 MARKETING AUTHORISATION NUMBER(S)

PL 20046/0074

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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22/01/2024