SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amisulpride 50 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of amisulpride

Excipient with known effect
Each tablet contains 23.75 mg of lactose (as monohydrate).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, bi-convex, 6 mm in diameter, with a score line. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

This includes patients with predominant negative symptoms.

4.2 Posology and method of administration

Posology

For acute psychotic episodes, oral doses between 400 mg/day and 800 mg/day are recommended. In individual cases, the daily dose may be increased up to 1200 mg. Doses above 1200 mg/day have not been extensively evaluated for safety and therefore should not be used. No specific titration is required when initiating the treatment with amisulpride. Doses should be adjusted according to individual response.

For patients with mixed positive and negative symptoms, doses should be adjusted to obtain optimal control of positive symptoms in example between 400-800mg/day.

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

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

Amisulpride can be administered once daily at oral doses up to 300 mg, higher doses should be administered bid.

The minimum effective dose and appropriate strength tablets should be used.

Special populations

Elderly (over 65 years): The safety of amisulpride has been examined in a limited number of elderly patients. Amisulpride should be used with particular caution because of a possible risk of hypotension and sedation. Reduction in dose may also be required because of renal insufficiency.

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).

Renal impairment: Amisulpride is eliminated by the renal route. In renal insufficiency, the dose should be reduced to half in patients with creatinine clearance (CR_{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 (CR_{CL} < 10 ml/min) particular care is recommended in these patients (see section 4.4).

Hepatic impairment: Since amisulpride is weakly metabolised a dose reduction should not be necessary.

Duration of treatment

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

Method of administration

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

Note

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

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1 concomitant prolactin-dependent tumours, e.g. pituitary gland prolactinomas or breast cancer (see sections 4.4 and 4.8)
- phaeochromocytoma
- children before the onset of puberty
- combination with levodopa (see section 4.5)

4.4 Special warnings and precautions for use

As with other antipsychotics, 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 medicinal products including amisulpride should be discontinued.

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

Amisulpride is eliminated by the renal route. In cases of renal insufficiency, the dose should be decreased or intermittent treatment could be considered (see section 4.2).

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

In elderly patients (over 65 years), amisulpride, like other antipsychotics, should be used with particular caution because of a possible risk of hypotension or sedation. Reduction in dose may also be required because of renal insufficiency.

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

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

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.

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 antipsychotics should be avoided.

Stroke

In randomized clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotics, 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 antipsychotics, or other populations of patients cannot be excluded. Amisulpride should be used with caution in patients with stroke risk factors.

Elderly patients with dementia

Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotics, revealed a risk of death in antipsychotic-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 antipsychotic-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., hearth failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotics, treatment with conventional antipsychotics may increase mortality.

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

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

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. 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.

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 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).

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 contains lactose and sodium

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations

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

Combinations not recommended

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

Combinations to be taken into account

Concomitant use of the following agents can lead to potentiation of the effect:

- CNS depressants including narcotics, anaesthetics, analgesics, sedative H1 antihistamines, barbiturates, benzodiazepines and other anxiolytic medicinal products, clonidine and derivatives
- Antihypertensive medicinal products and other hypotensive medicinal products
- 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 antiarrythmics (e.g., quinidine, disopyramide) and class III antiarrhythmics (e.g. amiodarone, sotalol), some antihistaminics, some other antipsychotics and 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) 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

Limited data suggests amisulpride is excreted into breastmilk and the infant dose can be above 10% of the maternal weight-adjusted dose. 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 amisulpride (prolactin mediated effect) was observed in treated animals.

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 and blurred vision so that the ability to drive vehicles or operate machinery can be impaired (see section 4.8). This effect is enhanced by the consumption of alcohol.

4.8 Undesirable effects

The following frequency estimates are used in assessing adverse effects:

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

The following adverse reactions have been observed in controlled clinical trials and through spontaneous reporting post marketing. It should be noted that in some instances it can be difficult to differentiate adverse reactions from symptoms of the underlying disease.

Adverse Drug Reactions (ADRs) by System Organ Class and Frequency

MedDRA System Organ Class	Frequency	ADRs
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**	Hyperprolactinaemia[1]
	Rare	Benign pituitary tumour such as prolactinoma (see sections 4.3 and 4.4)
Metabolism and nutrition disorders	**Uncommon**	Hyperglycaemia (see section 4.4) hypertriglyceridemia, 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 (tremor, rigidity, hypokinesia, hypersalivation, akathisia, dyskinesia)[2]
	Common	Acute dystonia (spasm torticollis, oculogyric crisis, trismus)[3], somnolence
	Uncommon	Tardive dyskinesia (characterized by rhythmic, involuntary movements primarily of the tongue and/or face)[4], seizures
	Rare	Neuroleptic malignant syndrome (a potentially fatal complication, see section 4.4)
	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	**Uncommon**	Nasal congestion, pneumonia aspiration (mainly in association with other

mediastinal disorders		antipsychotics and CNS depressants)
Gastrointestinal disorders	**Common**	Constipation, nausea, vomiting, dry mouth
Hepatobiliary disorders	**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 section 4.6)
Reproductive system and breast disorders	**Common**	Galactorrhoea, amenorrhoea, gynaecomastia, breast pain and erectile dysfunction
General disorders and administration site conditions	**Very rare**	Acute withdrawal symptoms (including nausea, vomiting and insomnia)[5], 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

[1] Reversible after discontinuation of amisulpride.

[2] These symptoms are generally mild at optimal doses 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] Occurs usually after long term administration of amisulpride. Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms.

[5] After abrupt cessation of high doses of amisulpride.

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 Yellow Card Scheme: 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 amisulpride has been reported. These include drowsiness and sedation, coma, hypotension and extrapyramidal symptoms.

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

Management

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

Since amisulpride is weakly dialysed, haemodialysis is of no use to eliminate it. There is no specific antidote to amisulpride. Appropriate supportive measures should therefore be instituted with close supervision of vital functions including continuous cardiac monitoring due to the risk of prolongation of the QT interval until the patient recovers.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antipsychotics: benzamides
ATC code: N05AL05

Amisulpride binds selectively with a high affinity to human dopaminergic 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 antipsychotics, amisulpride has no affinity for serotonin, alpha-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

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 ng/ml and 54 ± 4 ng/ml after a 50 mg dose.

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

Distribution

The volume of distribution is 5.8 l/kg bodyweight, 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.

Hepatic impairment

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

Renal impairment

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

Amisulpride is very weakly dialysed.

Elderly patients (over 65 years)

Limited pharmacokinetic data in this patient group show that a 10-30% rise occurs in C_{max}, $T_{½}$ 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 dose in man, maximum tolerated doses are 2 and 7 times greater in the rat (200 mg/kg/day) and dog (120 mg/kg/day) respectively in terms of AUC. No carcinogenic risk, relevant to man, was identified in the rat at up to 1.5 to 4.5 times the expected human AUC. A mouse carcinogenicity study (120 mg/kg/day) and reproductive studies (160, 300 and 500 mg/kg/day respectively in rat, rabbit and mouse) were performed. The exposure of the animals to amisulpride during these latter studies was not evaluated. In animal trials, amisulpride elicited an effect on foetal growth and development at doses corresponding to Human Equivalent Dose of 2000 mg/day and upwards for a 50-kg patient. There was no evidence for a teratogenic potential of amisulpride. Studies on the impact of amisulpride on the behavior of the offspring have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Magnesium stearate

Methylcellulose

Cellulose, microcrystalline

Sodium starch glycolate (type A)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The tablets are packed in PVC/aluminium blisters and inserted in a carton.

Pack sizes: 10, 12, 14, 20, 21, 30, 42, 50, 60, 98, 100, 150, 198, 200 (bundled package 2x100) tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Park View, Riverside Way
Watchmoor Park
Camberley, Surrey
GU15 3YL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/1251

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/06/2010

10 DATE OF REVISION OF THE TEXT

08/08/2020