SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sulpiride Grindeks 50 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg sulpiride.

Excipient with known effect:
Each 50 mg tablet contains 5.5 mg lactose (as monohydrate);

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Sulpiride Grindeks 50 mg are white or almost white round tablets with bevelled edges. Dimension of tablet: diameter approximately 6.0 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute and chronic schizophrenia.

4.2 Posology and method of administration

Posology

Adults

A starting dose of 400 mg to 800 mg, given twice daily (morning and early evening) is recommended. Predominantly positive symptoms (formal thought disorder, hallucinations, delusions, incongruity of affect) respond to higher doses, and a starting dose of at least 400 mg twice daily is recommended, increasing if necessary up to a suggested maximum of 1200 mg twice daily. Increasing the dose beyond this level has not been shown to produce further improvement.

Predominantly negative symptoms (flattening of affect, poverty of speech, anergia, apathy, as well as depression) respond to doses below 800 mg daily; therefore, a starting dose of 400 mg twice daily is recommended. Reducing this dose towards 200 mg twice daily will normally increase the alerting effect of Sulpiride Grindeks.
Patients with mixed positive and negative symptoms, with neither predominating, will normally respond to dosage of 400-600 mg twice daily.

Paediatric population
Clinical experience in children under 14 years of age is insufficient to permit specific recommendations.

Elderly
The same dose ranges may be required in the elderly, but should be reduced if there is evidence of renal impairment.

Method of administration
For oral use.
The tablet should be swallowed whole with a sufficient amount of water.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Concomitant prolactin-dependent tumours, for example pituitary gland prolactinomas and breast cancer (see section 4.8).
- Phaeochromocytoma.
- Association with levodopa or antiparkinson drugs (including ropinirole) (see section 4.5).
- Acute porphyria.
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4.4 Special warnings and precautions for use

Increased motor agitation has been reported at high dosage in a small number of patients: in aggressive, agitated or excited phases of the disease process, low doses of Sulpiride Grindeks may aggravate symptoms. Care should be exercised where hypomania is present.

Extrapyramidal reactions, principally akathisia and tremor have been reported in a small number of cases. If warranted, reduction in dosage or anti-parkinsonian medication may be necessary.

Sulpiride Grindeks induces slight electroencephalogram (EEG) modifications. Neuroleptics may lower the epileptogenic threshold and some cases of convulsions, sometimes in patients with no previous history, have been reported with sulpiride (see section 4.8). Therefore caution is advised in prescribing it for patients with unstable epilepsy, and patients with a history of epilepsy should be closely monitored during sulpiride therapy.

In patients requiring Sulpiride Grindeks who are receiving anti-convulsant therapy, the dose of the anti-convulsant should not be changed.

In elderly patients, as with other neuroleptics, sulpiride should be used with particular caution (see section 4.2). Elderly patients are more susceptible to postural hypotension, sedation and extrapyramidal effects.

In children, efficacy and safety of sulpiride have not been thoroughly investigated. Therefore, caution should be exercised when prescribing to children (see section 4.2).

In patients with aggressive behaviour or agitation with impulsiveness, sulpiride could be given with a sedative.

When neuroleptic treatment is absolutely necessary in a patient with Parkinson's disease, sulpiride can be used, although caution is in order.

As with all drugs for which the kidney is the major elimination pathway, the dose should be reduced and titrated in small steps in cases of renal insufficiency.

Initiation of treatment in schizophrenia should only be undertaken by a specialist under whose regular supervision the patients should remain.

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

Sulpiride has an anticholinergic effect and, therefore, should be used with caution in patients with a history of glaucoma, ileus, congenital digestive stenosis, urine retention or hyperplasia of the prostate.

Sulpiride should be used with caution in hypertensive patients, especially in the elderly population, due to the risk of hypertensive crisis. Patients should be adequately monitored.

As hyperglycaemia has been reported in patients treated with atypical antipsychotic agents, patients with diagnosed diabetes mellitus or with risk factors for diabetes who have started treatment with sulpiride, should get appropriate glycaemic monitoring.

Avoid concomitant prescription of other antipsychotics.

QT prolongation
Sulpiride can induce QT prolongation (see section 4.8). It is known that this effect may potentiate the risk of serious ventricular arrhythmias such as *torsade de pointes*.
Before any administration, and if possible taking into account the clinical condition of the patient, it is advisable to monitor the factors that could favour the occurrence of this rhythm disorder, such as:
- bradycardia less than 55 bpm,
- electrolyte imbalance, particularly hypokalaemia,
- congenital QT prolongation,
- ongoing treatment with medicines that may produce pronounced bradycardia (< 55 bpm),
- hypokalaemia,
- decreased intracardiac conduction,
- or QT prolongation (see section 4.5).

Sulpiride should be prescribed with caution in patients presenting with these factors and patients with cardiovascular disorders which may predispose to prolongation of the QT interval.

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 for this increased risk is not known. An increase in the risk with other antipsychotic drugs or in other patient populations cannot be excluded.
Sulpiride should be used with caution in patients with risk factors for stroke.

Increased mortality in elderly patients with dementia
Elderly patients with dementia-related psychosis, who are treated with antipsychotic drugs, are at increased risk of death. Data from two large observational studies showed that elderly patients with dementia who are treated with antipsychotics are at 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. 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. Sulpiride Grindeks is not licensed for the treatment of dementia-related behaviour disturbances.

Venous thromboembolism
There have been reports of venous thromboembolism (VTE), sometimes fatal, 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 Sulpiride Grindeks and preventative measures undertaken.

Breast cancer
Sulpiride 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 sulpiride therapy (see section 4.3).

Neuroleptic Malignant Syndrome
A Neuroleptic Malignant Syndrome (NMS), a potentially fatal complication, reported to occur with antipsychotics is characterised by hyperthermia, muscle rigidity, rhabdomyolysis, elevated serum creatine phosphokinase levels and autonomic dysfunction. Cases with atypical features, such as hyperthermia without muscle rigidity or hypertonia, have been observed. In case of hyperthermia of undiagnosed origin, which may be considered either as an early sign/symptom of NMS or as an atypical NMS, sulpiride and all other antipsychotics should be discontinued promptly under medical supervision.

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

4.5 Interaction with other medicinal products and other forms of interaction

Contraindications of concomitant use
- Levodopa, antiparkinson medicines (including ropinirole): reciprocal antagonism of effects between levodopa or antiparkinsonian medicines (including ropinirole) and neuroleptics (see section 4.3).

Concomitant use not recommended
- Alcohol may potentiate the sedative effects of neuroleptics. Consumption of alcoholic drinks and medicines containing alcohol must be avoided.
- Combination with drugs that may prolong the QT interval or induce *torsade de pointes* (see section 4.4):
  - Bradycardia-inducing medicines such as beta blockers, calcium channel blockers, and bradycardia-inducing medicines such as diltiazem and verapamil, clonidine, guanfacine; digitalis.
  - Drugs that induce electrolyte imbalance, in particular those causing hypokalaemia: hypokalaemic diuretics, stimulant laxatives, amphotericin B IV, glucocorticoids, tetracosactides. Hypokalaemia must be corrected.
  - Class Ia antiarrhythmics such as quinidine and disopyramide.
  - Class III antiarrhythmics such as amiodarone and sotalol.
  - Other drugs such as pimozide, sultopride, haloperidol, thioridazine, methadone, imipramine antidepressants, lithium, bepridil, cisapride, erythromycin IV, vincamine IV, halofantrine, pentamidine and sparfloxacin.

Interactions to be considered

- Antihypertensive agents: antihypertensive effect and the possibility of increasing the occurrence of postural hypotension (additive effect).
- CNS depressants including narcotics, analgesics, sedative H1 antihistamines, barbiturates, benzodiazepines and other anxiolytics, clonidine and derivatives.
- Antacids or sucralfate: the absorption of sulpiride is decreased after coadministration. Therefore, sulpiride must be administered at least two hours before antacids.
- Lithium: lithium increases the risk of extrapyramidal adverse effects. Discontinuation of both medicines at the first sign of neurotoxicity is recommended.
- Sulpiride Grindeks may modify response to metoclopramide therapy.

4.6 Fertility, Pregnancy and lactation

Pregnancy

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

Sulpiride crosses the placenta. Studies in animals are insufficient with respect to reproductive toxicity (see section 5.3).

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

Neonates exposed to antipsychotics, including Sulpiride Grindeks, 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.

Breastfeeding

Sulpiride is excreted into breastmilk in rather large amounts, far 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 sulpiride in newborns/infants. A decision must be made whether to discontinue breast-feeding or to abstain from sulpiride 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

The medicine may cause drowsiness, dizziness, visual disturbances and impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a vehicle. Caution should be used while driving or operating machinery, especially because the particular sensitivity of each patient to the medicine has not been established.

4.8 Undesirable effects

Adverse reactions are presented according to the MedDRA system organ classes and MedDRA frequency convention: 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).

Tabulated summary of adverse reactions

Blood and lymphatic system disorders	Uncommon	Leukopenia[1]
	Not known	Neutropenia, agranulocytosis[1]
Immune system disorders	Not known	Anaphylactic reactions: urticaria, dyspnoea, hypotension, anaphylactic shock
Metabolism and nutrition disorders	Not known	Hyponatremia
		Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Endocrine disorders	Common	Hyperprolactinaemia
Psychiatric disorders	Common	Insomnia
	Not known	Confusion
Nervous system disorders	Common	Sedation or somnolence
		Extrapyramidal symptoms
		Parkinsonism
		Tremor
		Akathisia
	Uncommon	Hypertonia
		Dyskinesia
		Dystonia
	Rare	Oculogyric crises
	Not known	Neuroleptic malignant syndrome
		Hypokinesia
		Tardive dyskinesia[2]
		Convulsion
Cardiac disorders[1]	Rare	Ventricular arrhythmia
		Ventricular tachycardia
		Ventricular fibrillation
	Not known	QT prolongation on electrocardiogram
		Cardiac arrest
		Torsades de pointes

		Sudden death
Vascular disorders[1]	Uncommon	Orthostatic hypotension
	Not known	Venous thromboembolism
		Pulmonary embolism
		Deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	Not known	Pneumonia aspiration (mainly in association with other CNS depresants)
Gastrointestinal disorders	Common	Constipation
	Uncommon	Salivary hypersecretion
Hepatobiliary disorders	Common	Increase in liver enzymes
	Not known	Hepatocellular, cholestatic or mixed liver injury
Skin and subcutaneous tissue disorders	Common	Maculopapular rash
Musculoskeletal and connective tissue disorders	Not known	Torticollis
		Trismus
		Rhabdomyolysis
Pregnancy, puerperium and perinatal conditions[3]	Not known	Extrapyramidal symptoms
		Withdrawal syndrome in neonates
Reproductive system and breast disorders	Common	Breast pain
		Galactorrhoea
	Uncommon	Breast enlargement
		Amenorrhea
		Abnormal orgasm
		Erectile dysfunction
	Not known	Gynecomastia
General disorders and alterations at the site of administration	Common	Weight gain
	Not known	Hyperthermia[1]
Investigations	Not known	Blood creatine phosphokinase increased

[1] See section 4.4.
[2] Characterized by rhythmic and involuntary movements mainly of the tongue and/or face, has been reported, as with all neuroleptics, after a neuroleptic administration of more than 3 months. Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms.
As with all neuroleptics, the neuroleptic malignant syndrome (see section 4.4) is a life-threatening complication.
[3] See section 4.6.

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 national reporting system listed in via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs and symptoms
Experience with sulpiride overdose is limited.
In case of overdose, signs of dyskinetic type may occur with spasmodic torticollis, protrusion of the tongue and trismus may occur. Some patients may develop life-threatening parkinsonian manifestations and coma.
Cases of fatal outcomes have been reported mainly in combination with other psychotropic agents.
Sulpiride is partially removed by hemodialysis.
Treatment
There is no specific antidote for sulpiride. The treatment is strictly symptomatic. Nevertheless, appropriate supportive measures must be instituted, with close monitoring of vital functions; monitoring of cardiac function is recommended until the patient recovers (risk of QT prolongation and subsequent ventricular arrhythmias).
In case of severe extrapyramidal symptoms, anticholinergic agents should be administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics, benzamides, ATC code: N05AL01

Sulpiride Grindeks is a member of the group of substituted benzamides, which are structurally distinct from the phenothiazines, butyrophenones and thioxanthenes. Current evidence suggests that the actions of Sulpiride Grindeks hint at an important distinction between different types of dopamine receptors or receptor mechanisms in the brain.

Behaviourally and biochemically, Sulpiride Grindeks shares with these classical neuroleptics a number of properties indicative of cerebral dopamine receptor antagonism. Essential and intriguing differences include lack of catalepsy at doses active in other behavioural tests, lack of effect in the dopamine sensitive adenylate cyclase systems, lack of effect upon noradrenaline or 5HT turnover, negligible anticholinesterase activity, no effect on muscarinic or GABA receptor binding, and a radical difference in the binding of tritiated sulpiride to striatal preparations in-vitro, compared to ^{3}H-spiperone or ^{3}H-haloperidol. These findings indicate a major differentiation between Sulpiride Grindeks and classical neuroleptics which lack such specificity.

One of the characteristics of Sulpiride Grindeks its bimodal activity, as it has both antidepressant and neuroleptic properties. Schizophrenia characterised by a lack of social contact can benefit strikingly. Mood elevation is observed after a few days treatment, followed by disappearance of the florid schizophrenic symptoms. The sedation and lack of affect characteristically associated with classical neuroleptics of the phenothiazine or butyrophenone type are not features of Sulpiride Grindeks therapy.

5.2 Pharmacokinetic properties

Peak sulpiride serum levels are reached 3 - 6 hours after an oral dose. The plasma half-life in man is approximately 8 hours. Approximately 40 % sulpiride is bound to plasma proteins. 95 % of the compound is excreted in the urine and faeces as unchanged sulpiride.

5.3 Preclinical safety data

In long-term animal studies with neuroleptic drugs, including sulpiride, an increased incidence of various endocrine tumours (some of which have occasionally been malignant) has been seen in some but not all strains of rats and mice studied. The significance of these findings to man is not known; there is no current evidence of any association between neuroleptic use and tumour risk in man.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Methylcellulose
Potato starch
Potato starch, dried
Silica, colloidal anhydrous
Magnesium stearate
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Alu blisters containing 30 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

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18/05/2022

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