SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sulpiride 400mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400mg of the active substance sulpiride.

Also contains 256mg of Lactose Monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated Tablet.

White, oval, film coated tablets marked S400 and break line on one face and plain on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for the treatment of acute and chronic schizophrenia.

4.2 Posology and method of administration

Adults:
The initial dose depends on the nature of the symptoms.

In patients with predominantly negative symptoms (flattening of affect, poverty of speech, anergia, apathy, as well as depression) the usual starting dose is 400 mg twice

daily. This can be reduced to 200mg twice daily as a response occurs, increasing the alerting effect of sulpiride that occurs at lower doses.

In patients with predominantly positive symptoms (formal thought disorder, hallucinations, delusions, incongruity of affect) the usual starting dose is 400mg twice daily increasing if necessary to a suggested maximum of 1200mg twice daily.

In patients with positive and negative symptoms, with neither predominating, a dose of 400mg-600mg twice daily is recommended.

Elderly:
Initially one quarter to one half of the adult dose.

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

Renal impairment:
The dosage should be reduced or the dosage interval increased.

4.3 Contraindications

Phaeochromocytoma

Acute porphyria

Hypersensitivity to sulpiride or to any of the excipients listed in section 6.1.

Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer (See section 4.8 Undesirable effects).

Association with levodopa or antiparkinsonian drugs (including ropinirole) (See section 4.5 Interactions with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

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

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

As with other neuroleptics, neuroleptic malignant syndrome, a potentially fatal complication, which is characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels, has been reported. In such an event, or in the event of hyperthermia of undiagnosed origin, all antipsychotic drugs, including sulpiride, should be discontinued.

Elderly patients are more susceptible to postural hypotension, sedation and extrapyramidal effects.
In patients with aggressive behaviour or agitation with impulsiveness, sulpiride could be given with a sedative.

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

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 Sulpiride and preventive measures undertaken.

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.

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

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.

Precautions:

In elderly patients, as with other neuroleptics, sulpiride should be used with particular caution (see section 4.2).

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).

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

Neuroleptics may lower the epileptogenic threshold. Cases of convulsions, sometimes in patients with no previous history, have been reported with sulpiride. Caution is advised in prescribing it for patients with unstable epilepsy, and patients with a history of epilepsy should be closely monitored during therapy with sulpiride.

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

Cases of convulsions, sometimes in patients with no previous history, have been reported.

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. 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.

Prolongation of the QT interval:

Sulpiride induces a prolongation of the QT interval (see section 4.8). This effect is known to potentiate the risk of serious ventricular arrhythmias such as torsade de pointes.

Before any administration, and if possible according to the patient's clinical status, it is recommended to monitor factors which could favour the occurrence of this rhythm disorder, for example:

- Bradycardia less than 55 bpm

- Electrolyte imbalance in particular hypokalaemia

- Congenital prolongation of the QT interval

- On-going treatment with a medication likely to produce pronounced bradycardia (< 55 bpm), hypokalaemia, decreased intracardiac conduction, or prolongation of the QTc interval (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.

Avoid concomitant treatment with other neuroleptics (see section 4.5).

Stroke:

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

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

Sulpiridel 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.

4.5 Interaction with other medicinal products and other forms of interaction

Associations contra-indicated

Levodopa, antiparkinsonian drugs (including ropinirole): reciprocal antagonism of effects between levopoda or antiparkinsonian drugs (including ropinirole) and neuroleptics.

Associations not recommended.

Alcohol: alcohol enhances the sedative effects of neuroleptics.

Avoid the consumption of alcoholic beverages and drugs containing alcohol.

Combination with the following medications which could induce torsades de pointes or prolong the QT interval (see section 4.4):

− Bradycardia-inducing medications such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine; digitalis.

− Medications which induce electrolyte imbalance, in particular those causing hypokalaemia: hypokalaemic diuretics, stimulant laxatives, IV amphotericin B, glucocorticoids, tetracosactides.

Electrolyte imbalance should be corrected

− Class Ia antiarrhythmic agents such as quinidine, disopyramide.

− Class III antiarrhythmic agents such as amiodarone, sotalol.

− Other medications such as pimozide, haloperidol; methadone, imipramine antidepressants; lithium, cisapride, thioridazine, IV erythromycin, halofantrine, pentamidine.

Associations to be taken into account.

Antihypertensive agents: antihypertensive effect and possibility of enhanced 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 co-administration. Therefore, sulpiride should be administered two hours before these drugs.

Lithium: lithium increases the risk of extrapyramidal side effects. Discontinuation of both drugs is recommended at first signs of neurotoxicity.

4.6 Fertility, pregnancy and lactation

Pregnancy:

A decrease in fertility linked to the pharmacological effects of the drug (prolactin mediated effect) was observed in treated animals. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development and/or postnatal development. In humans, very limited clinical data on exposed pregnancies are available. In almost all cases of foetal or neonatal disorders reported in the context of sulpiride use during pregnancy, alternative explanations can be suggested and seem more likely. Therefore the use of sulpiride is not recommended during pregnancy because of the limited experience.

Neonates exposed to antipsychotics (including Sulpiride) 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. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Lactation:
Sulpiride is excreted into breast milk and its use should be avoided in mothers wishing to breast feed.

4.7 Effects on ability to drive and use machines

Even used as recommended, sulpiride may cause sedation so that the ability to drive vehicles or operate machinery can be impaired. (See section 4.8)

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:

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).

Blood and lymphatic system disorders (see section 4.4)

Uncommon: leukopenia

Not known: neutropenia, agranulocytosis

Immune system disorders

Not known: anaphylactic reactions; urticaria, dyspnoea, hypotension and anaphylactic shock

Endocrine disorders

Common: hyperprolactinaemia

Psychiatric disorders

Common: insomnia

Not known: confusion

Nervous system disorders

Common: sedation or drowsiness, extrapyramidal disorder (these symptoms are generally reversible upon administration of antiparkinsonian medication), Parkinsonism, tremor, akathisia

Uncommon: hypertonia, dyskinesia, dystonia

Rare: oculogyric crisis

Not known: neuroleptic malignant syndrome, hypokinesia, tardive dyskinesia (have 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), convulsion

Cardiac disorders

Rare: ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia

Not known: electrocardiogram QT prolonged, cardiac arrest, torsade de pointes, sudden death (see section 4.4).

Vascular disorders

Uncommon: orthostatic hypotension

Not known: venous embolism, pulmonary embolism, deep vein thrombosis, increase in blood pressure (see section 4.4)

Gastrointestinal disorders

Uncommon: salivary hypersecretion

Hepatobiliary disorders

Common: hepatic enzyme increased

Skin and subcutaneous tissue disorders

Common: maculo-papular rash

Musculoskeletal and connective tissue disorders

Not known: torticollis, trismus

Pregnancy, puerperium and perinatal conditions

Not known: extrapyramidal symptoms, drug withdrawal syndrome neonatal (see section 4.6)

Reproductive system and breast disorders

Common: breast pain, galactorrhoea

Uncommon: breast enlargement, amenorrhoea, orgasm abnormal, erectile dysfunction.

Not known: gynaecomastia

General disorders and administration site conditions

Common: weight gain

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.

4.9 Overdose

Experience with sulpiride in overdosage is limited.

The range of single toxic doses is 1 to 16g but no deaths have occurred even at a dose of 20g.

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

Symptoms

The clinical manifestations of poisoning vary depending upon the size of the dose taken.

After single doses of 1g to 3g restlessness and clouding of consciousness have been reported and (rarely) extrapyramidal symptoms. Doses of 3g to 7g may produce a degree of agitation, confusion and extrapyramidal symptoms; more than 7g can cause, in addition, coma and low blood pressure.

The duration of intoxication is generally short, the symptoms disappearing within a few hours. Comas which have occurred after large doses have lasted up to four days.

There are no specific complications from overdose. In particular no haematological or hepatic toxicity has been reported.

Treatment

Sulpiride is partly removed by haemodialysis.

There is no specific antidote to sulpiride. Treatment is only symptomatic. Appropriate supportive measures should therefore be instituted, close supervision of vital functions and cardiac monitoring (risk of QT interval prolongation and subsequent ventricular arrhythmias) is recommended until the patient recovers.

If severe extrapyramidal symptoms occur anticholinergics should be administrated.

Overdose may be treated with alkaline osmotic diuresis and, If necessary, antiparkinsonian drugs. Emetic drugs are unlikely to be effective. Coma needs appropriate nursing.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics; Benzamides, ATC code: N05AL01

Sulpiride 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 hint at an important distinction between different types of dopamine receptors or receptor mechanisms in the brain.

Behaviourally and biochemically, sulpiride shares with 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 and classical neuroleptics, which lack such specificity.

One of the characteristics of sulpiride is its bimodal activity, as it has both antidepressant and antipsychotic 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 sedative, anti-muscarinic, alpha-blocking and extrapyramidal effects of sulpiride are less pronounced than those characteristically associated with classical neuroleptics of the phenothiazine type.

5.2 Pharmacokinetic properties

The bioavailability of the oral form ranges from 25-40%. Peak sulpiride serum levels are reached 3-6 hours after an oral dose. The plasma half-life in man is 8 hours. Sulpiride is less than 40% bound to plasma proteins. Sulpiride crosses the blood-brain barrier. 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 an association between neuroleptic use and tumour risk in man.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Povidone K30
Microcrystalline cellulose
Sodium starch glycollate
Magnesium stearate
Tablet coating: Titanium dioxide, Hypromellose, Polyethylene Glycol/Macrogol

6.2 Incompatibilities

None known

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25^{o}C

6.5 Nature and contents of container

Blister strip consisting of hard tempered aluminium foil (20 micron) and PVC

film (250 micron) containing 10,20,30,40,50,60,70,80,90,100,500,1000,28,56,84,112 tablets.
Polypropylene tablet containers with polyethylene tamper evident lids containing 10, 20, 30,40,50,60,70,80,90,100,500,1000,28,56,84,112 tablets

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Limited
11 Boumpoulinas, 3rd Floor,
P.C. 1060
Nicosia.
Cyprus

8 MARKETING AUTHORISATION NUMBER(S)

PL 28444/0267

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