SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sulpiride Tablets 400 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg of sulpiride.

Sulpiride is a benzamide derivative

For full list of excipients, see section 6.1. List of Excipients.

3 PHARMACEUTICAL FORM

Tablet

White, oblong tablet debossed “SD/400” on one side and “G” on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute and chronic schizophrenia

4.2 Posology and method of administration

Sulpiride has bimodal dose-dependent therapeutic activity; its actions at low dose levels are therefore qualitatively different to those at high dose levels.

Adults

A starting dose of 400 mg to 800 mg per day, given as two divided doses (morning and early evening), is recommended.

Where positive symptoms predominate (hallucinations, delusions, formal thought disorder, incongruity of affect) these symptoms respond to higher doses and a starting dose of at least 400 mg twice daily is recommended. This can then be increased if necessary up to a maximum daily dose of 2400 mg, taken as two divided doses. Increasing the dose beyond 1200mg twice daily has not shown to produce further improvement.

Where negative symptoms predominate, (anergia, apathy, flattening of affect, poverty of speech) and for depression, doses below 800mg are most effective. A starting dose of 400 mg twice daily is therefore recommended. Reducing this dose towards 200 mg twice daily will normally increase the alerting effect of sulpiride.

Where neither negative or positive symptoms predominate a response is usually seen to a dose of 400 mg to 600 mg twice daily.

Elderly and patients with renal impairment

The same maintenance dose ranges may be required in the elderly but should be reduced in cases of renal impairment according to the following guidelines:

Creatinine clearance 30-60ml/min: 2/3 of normal dose

Creatinine clearance 10-30ml/min: 1/2 of normal dose

Creatinine clearance <10ml/min: 1/3 of normal dose

Alternatively the dosage interval can be prolonged by a factor of 1.5, 2 and 3 respectively.

Children under 14 years of age

Sulpiride tablets are not recommended for use in children as there is insufficient clinical experience in this age group.

4.3 Contraindications

Known hypersensitivity to the active ingredient or to any of the excipients.

Phaeochromocytoma.

Porphyria.

CNS depression

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

Association with levodopa (See 4.5 Interactions with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

Where hypomania is present care should be taken. Increased motor agitation has been reported at high doses. Symptoms may be aggravated in aggressive, agitated or excited phases of the disease process by low doses. Higher doses may also produce a motor agitation (excitability, irritability anxiety and mood inversion) in a small number of patients.

Extrapyramidal reactions, namely tremor and akathisia, have been reported; a reduction in dose or anti-parkinsonian medication may be necessary.

As with other neuroleptic drugs, unexplained hyperthermia, muscle rigidity, autonomic instability, altered consciousness, and elevated CPK levels, could indicate neuroleptic malignant syndrome (NMS). In such cases sulpiride tablets, and any other neuroleptics, should be discontinued. Avoid concomitant neuroleptics.

Elderly patients are more susceptible to sedation, postural hypotension and extrapyramidal effects.

An abrupt cessation of treatment in some patients may produce a withdrawal response including nausea, vomiting, insomnia and sweating. Recurrence of psychotic symptoms can also occur, as can the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia). Therefore gradual withdrawal is advised.

Precautions:

In elderly patients, sulpiride (as with other neuroleptics) should be used with particular caution (see 4.2 Posology and method of administration).

<u>Increased Mortality in Elderly people with Dementia</u>

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.

In children, sulpiride has not been thoroughly investigated hence caution should be exercised when prescribing (see 4.2 Posology and method of administration).

Caution should be taken in patients with respiratory disease, myasthenia gravis, prostatic hypertrophy and glaucoma.

In patients with Parkinson's disease, sulpiride can be used when neuroleptic treatment is absolutely necessary, but caution is advisable.

Patients with unstable epilepsy and those with a history of epilepsy should be more frequently monitored during therapy with sulpiride. Sulpiride is known to induce slight EEG modifications.

When patients receiving anti-convulsant therapy require sulpiride treatment, the dose of the anti-convulsant should not be changed.

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

Caution should be exercised in patients with a history of jaundice.

In cases of renal insufficiency, the dose should be reduced and titrated in small steps (as with all drugs for which the kidney is a major elimination pathway). Sulpiride has no significant anticholinergic effect.

Caution should be exercised in patients with cardiovascular disease or family history of QT prolongation.

Sulpiride may induce a prolongation of the QT interval, which is known to potentiate the risk of serious ventricular arrhythmias such as torsade de pointes. This effect is enhanced by the pre-existence of bradycardia, hypokalaemia, congenital or acquired long QT interval.

It is recommended that factors that could favour the occurrence of this rhythm disorder should be monitored before any administration, if possible according to the patient's clinical status. Such factors are:

- Bradycardia less than 55 bpm
- Hypokalaemia (which should be corrected)
- 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 4.5 Interaction with other medicinal products and other forms of interactions).

An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics or other patient populations.

Sulpiride should be used with caution in patients with risk factors for stroke.

Due to the findings of increased incidence of endocrine tumours in animal studies (see section 5.3 for further information) a benefit/risk assessment should be undertaken when prescribing neuroleptics to patients with a history of, or with existing mammary neoplasia.

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk for VTE, all possible risk factors for VTE should be identified before and during treatment with Sulpiride and preventive measures undertaken.

4.5 Interaction with other medicinal products and other forms of interaction

Associations contra-indicated

Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics.

Associations not recommended

Alcohol: alcohol enhances the sedative effects of neuroleptics.

Avoid the consumption of alcoholic beverages and dugs containing alcohol.

Combination with the following medications which could induce torsades de pointes:

- Bradycardia-inducing medications such as beta-blockers, Bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine; digitalics.
- Medications which induce hypokalaemia: hypokalaemic diuretics, stimulant laxatives, IV amphotericin B, glucocorticoids, tetracosactides.
- Class Ia antiarrhythmic agents such as quinidine and disopyramide.
- Class III antiarrhythmic agents such as amiodarone and sotalol.
- Other medications such as pimozide, haloperidol, imipramine antidepressants, cisapride, thioridazine, IV erythromycin, pentamide.

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 bioavailability of sulpiride is reduced by concomitant administration with sucralfate and antacids. Sulpiride should therefore be taken before rather than with or following these drugs.

Lithium increases the risk of extrapyramidal side effects.

Sulpiride may reduce the effectiveness of ropinirole.

4.6 Fertility, pregnancy and lactation

Pregnancy:

No teratogenicity has been reported either in animal studies, or during clinical practice. However use during pregnancy, particularly in the first 16 weeks, should be avoided unless considered essential by the physician.

In humans, no increase in the risk of birth defects was seen in a small sample of women given low-dose sulpiride (approximately 200 mg/d). No data are available on the effects of higher dosages.

There are no data on the potential effects of neuroleptic agents given throughout pregnancy.

These data suggest that sulpiride has little or no potential for inducing congenital defects. However it seems reasonable to reduce the duration of the treatment during pregnancy if possible.

A few cases of extrapyramidal syndrome have been reported in neonates born to mothers under long-term, high-dose neuroleptic therapy.

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.

It seems warranted to monitor neurological function for some time after birth.

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

Lactation:

Sulpiride has been found in low concentrations in breast milk and therefore it is recommended that the use of sulpiride be avoided in patients who are breast-feeding.

4.7 Effects on ability to drive and use machines

Even used as recommended, sulpiride may affect reaction time so that the ability to drive vehicles or operate machinery can be impaired.

4.8 Undesirable effects

Neuroleptic malignant syndrome:

As with other neuroleptics, rare cases of neuroleptic malignant syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels, have been reported. In such an event, all antipsychotic drugs, including sulpiride, should be discontinued (see 4.4 Special warnings and precautions for use).

Neurological events: Sedation or drowsiness. Insomnia has been reported.

Very rare cases of convulsions have been reported, in particular in epileptic patients (see 4.4 Special warnings and precautions for use).

Extrapyramidal symptoms and related disorders:

- parkinsonism and related symptoms: tremor, hypertonia, hypokinesia, hypersalivation
- acute dyskinesia and dystonia (spasm torticollis, oculogyric crisis, trismus)
- akathisia

These symptoms are generally reversible upon administration of antiparkinsonian medication.

- Tardive dyskinesia has been reported (characterised by rhythmic, involuntary movements primarily of the tongue and/or the face), as with all neuroleptics, after a neuroleptic administration of more than 3 months. Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms.

Autonomic events: postural hypotension.

Pregnancy, puerperium and perinatal conditions
Drug withdrawal syndrome neonatal (see 4.6) / not known

Very rare cases of QT prolongation and very rare cases of torsades de pointes have been reported.

Hyperprolactinaemia and related disorders: galactorrhoea, amenorrhoea, gynaecomastia, breast enlargement and breast pain, orgasmic dysfunction and impotence.

Hepatic reactions have been reported.

Bodyweight gain, potentially significant in very rare cases.

Very rare cases of hypersensitivity reactions such as skin reactions have been reported.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs. – Frequency unknown.

4.9 Overdose

Experience with sulpiride in overdosage is limited

Single toxic doses ranging from 1 g to 16 g have been recorded, but no deaths have resulted. The duration of intoxication is typically short with symptoms disappearing within a few hours. Comas resulting from large doses have lasted up to four days.

After doses of 1-3 g restlessness and clouding of consciousness have been reported and extrapyramidal symptoms rarely. Doses of 3 to 7 g may produce a degree of agitation, confusion and extrapyramidal symptoms. Doses of greater than 7 g can additionally cause coma and low blood pressure.

Overdose can be treated with alkaline osmotic diuresis and anti-parkinsonian drugs, if necessary. Appropriate nursing is required where coma results. Emetic drugs are unlikely to be of use in treatment of overdosage of sulpiride.

No hepatic or haematological toxicity has been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Sulpiride is a substituted benzamide and has bimodal activity, having both anti-depressant and antipsychotic properties. (ATC code = N05A L01)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 classic 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.

Schizophrenia, characterized by a lack of social content, can benefit remarkably by the bimodal activity of sulpiride. Mood elevation is observed after a few days of treatment, followed by disappearance of the florid schizophrenia symptoms. The sedation and lack of affect characteristically associated with classical neuroleptics of the phenothiazine or butyrophenone type are not features of treatment with sulpiride.

5.2 Pharmacokinetic properties

Sulpiride is moderately well absorbed from the gastrointestinal tract, with oral bioavailability of 25%-40%. Sulpiride does not undergo presystemic metabolism.

Peak serum levels are seen after 3-6 hours following oral dosing. Approximately 14% is bound to plasma proteins, although this figure has been reported to be as high as 40% in patients with schizophrenia. Plasma half-life in humans has been reported as between 3 and 10 hours.

95% of the compound is excreted in the urine and faeces as unchanged sulpiride.

5% is converted to a pharmacologically inactive metabolite, 5-oxypyrrolidinyl sulpiride, which is eliminated in the urine.

5.3 Preclinical safety data

Animal studies have indicated that sub-chronic and chronic dosing with sulpiride does not cause significant toxicity, nor is there any evidence of any major effect on reproduction. Adverse effects of higher doses of sulpiride have been restricted to neurological disturbances typical of neuroleptics together with the endocrine disturbances associated with dopamine antagonism.

Neuroleptics such as sulpiride dosed long-term have been associated with an increased incidence of endocrine tumours, though such findings have not been common to all strains of rats and mice studied and the significance of such findings to man is uncertain. Long-term sulpiride treatment does not appear to be associated with any consistent carcinogenic potential. There is no evidence that sulpiride exerts any mutagenic effect.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch

Colloidal anhydrous silica

Sodium starch glycollate

Magnesium stearate

Microcrystalline cellulose

Hydroxypropylcellulose

6.2 Incompatibilities

None known

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Polyvinylidene chloride coated polyvinyl chloride/aluminium foil blister packs containing 10, 12, 15, 20, 24, 28, 30, 50, 56, 60, 84, 96, 100, 112 or 150 tablets.

Polypropylene containers with polyethylene caps (with optional polyethylene ullage filler) containing 10, 12, 15, 20, 24, 28, 30, 50, 56, 60, 84, 96, 100, 112 or 150 tablets.

High density polyethylene bottles with polyethylene snap closures containing 10, 12, 15, 20, 24, 28, 30, 50, 56, 60, 84, 96, 100, 112 or 150 tablets.

6.6 Special precautions for disposal

No special instructions are required.

7 MARKETING AUTHORISATION HOLDER

Generics (U.K.) Limited T/A Viatris,
Station Close,
Potters Bar,
EN6 1TL,
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/0448

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/11/2000 / 3/05/2006

10 DATE OF REVISION OF THE TEXT

08/05/2026