SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sulpiride 200 mg/5 ml Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains 200 milligrams sulpiride.

Excipient(s) with known effect:
Each 5 ml of oral solution contains 3073.5 mg liquid maltitol (E965).
Each 5 ml of oral solution contains 6 mg methyl hydroxybenzoate (E218).
Each 5 ml of oral solution contains 1.5 mg propyl hydroxybenzoate (E216).
Each 5 ml of oral solution contains 109 mg propylene glycol (E1520).
Each 5 ml of oral solution contains 0.19 mg glycerine.
Each 5 ml of oral solution contains 0.002 mg benzyl alcohol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A colourless to slightly yellow oral solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sulpiride is indicated in acute and chronic schizophrenia.

4.2 Posology and method of administration

Posology

Adults

A starting dose of 400 mg to 800 mg daily, given in two divided doses (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.

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 administration only.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Phaeochromocytoma.
- Acute porphyria.
- Severe renal, haematological or hepatic disease.
- Alcoholic intoxication and other disorders which depress CNS function.
- Concomitant prolactin-dependant tumours e.g. pituitary gland prolactinomas and breast cancer (see section 4.8 Undesirable effects).
- Association with levodopa or antiparkinsonian drugs (including ropinirole) (See 4.5 Interactions with other medicinal products and other forms of interaction).
- Bone marrow suppression.

4.4 Special warnings and precautions for use

Warnings:

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 may aggravate symptoms. Care should be exercised where hypomania is present. If extrapyramidal reactions occur, principally akathisia have been reported in a small number of cases, a reduction in dosage of sulpiride or initiation of antiparkinsonian medication may be necessary.

As with other neuroleptics, neuroleptic malignant syndrome (NMS), a potentially fatal complication, which is characterised by hyperthermia, muscle rigidity, autonomic instability, rhabdomyolisis, altered consciousness and elevated CPK levels, has been reported. In such an event, or in the event of hyperthermia of undiagnosed origin, which may be considered either as an early sign/symptom of NMS or as an atypical NMS (cases with atypical features, such as hyperthermia without muscle rigidity or hypertonia, have been observed), all antipsychotic drugs, including sulpiride, should be discontinued promptly under medical supervision.

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) has been reported. Therefore, gradual withdrawal is advisable.

Increased Mortality in Elderly people with Dementia
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an 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 trialsvwith 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 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 Sulpiride and preventive measures undertaken.

Patients should be warned against taking alcohol with sulpiride as reaction capacity may be impaired.

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.

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

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.

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 dosage should be reduced and titrated in small steps in cases of renal insufficiency.

Prolongation of the QT interval
Sulpiride may induce a prolongation of the QT interval (see section 4.8). This effect, known to potentiate the risk of serious ventricular arrhythmias such as torsade de pointes is enhanced by the pre-existence of bradycardia or cardiovascular disease, hypokalaemia, congenital or acquired long QT interval, concomitant neuroleptic treatment, or a family history of QT prolongation (see section 4.5).

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).

Sulpiride Oral Solution induces slight EEG modifications. Neuroleptics may lower the epileptogenic threshold and some cases of convulsions have been reported with sulpiride (see section 4.8). Therefore, patients with a history of epilepsy should be closely monitored during sulpiride therapy.

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.

Diabetes mellitus
As hyperglycaemia has been reported in patients treated with atypical antipsychotic agents, patients with an established diagnosis of diabetes mellitus or with risk factors for diabetes who are started on sulpiride, should get appropriate glycaemic monitoring.

Sulpiride should be given with caution to patients suffering from extrapyramidal disturbances as these may be aggravated by sulpiride. Patients on concomitant dopaminergics should be monitored for deterioration in

parkinsonism and mental state (see 4.5 Interactions with other medicaments and other forms of interaction).

Sulpiride should be used with caution in patients with a history of jaundice or with hepatic impairment as it may precipitate coma.

Sulpiride should be used with caution in patients with hypertension, severe respiratory disease and myasthenia gravis.

As photosensitisation may occur with higher doses, avoidance of undue exposure to direct sunlight is recommended.

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

Excipient Warnings:

The product contains liquid maltitol (E965). Patients with rare hereditary problems of fructose intolerance should not take this medicine. May have a mild laxative effect. Calorific value 2.3kcal/g maltitol.

This product also contains parahydroxybenzoates (E216 & E218) (preservatives) which may cause allergic reactions (possibly delayed).

This product contains 109 mg propylene glycol (E1520) in each 5 ml dose. This product contains 654 mg propylene glycol in each 30 ml dose.

This product contains 0.19 mg glycerine in each 5 ml dose.

This product contains 0.002 mg benzyl alcohol in each 5 ml dose. Benzyl alcohol may cause allergic reactions. High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

4.5 Interaction with other medicinal products and other forms of interaction

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

Associations not recommended:
Alcohol: Enhances the sedative effect of neuroleptics. Avoid the consumption of alcoholic beverages and drugs containing alcohol.

Use with concomitant QT prolonging drugs and with drugs causing electrolyte imbalance is not recommended. If the benefit is considered to outweigh the risk in the individual patient, coadministration should be undertaken with caution and ECG monitoring should be considered (see section 4.4).

Dopaminergics: Antagonism of the effects of dopaminergic agents such as amantidine, bromocriptine, cabergoline, and lisuride. Pramipexole and ropinirole should be avoided. Concomitant use of dopaminergic agents may also lead to exacerbation of psychotic symptoms. The patient should be monitored for the deterioration in Parkinsonism and mental state (see section 4.4).

Combination with the following medications could induce *torsade 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. Hypokalaemia should be corrected. 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, sultopride, haloperidol; methadone, imipramine antidepressants; lithium, bepridil, cisapride, thioridazine, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin.

<u>Associations to be taken into account:</u>
Anaesthetics: The hypotensive effect of anaesthetics may be enhanced by concomitant use.

Analgesics: Enhanced sedative and hypotensive effect with opioid analgesics

Antidepressants: Possibility of extrapyramidal symptoms, including Parkinson-like symptoms or dystonia, in patients taking sulpiride and fluoxetine concurrently. Possibly increased risk of ventricular arrhythmias with tricyclic antidepressants.

Antiepileptics: The convulsive threshold may be lowered by sulpiride.

Unnecessary polypharmacy should be avoided. As with other psychotropic compounds, sulpiride may increase the effect of antihypertensives and CNS depressants or stimulants such as sedative H1 antihistamines, barbiturates, benzodiazepines and other anxiolytics, clonidine and derivatives.

The bioavailability of sulpiride is reduced by concomitant administration with sucralfate and antacids, therefore, sulpiride should be taken two hours before these drugs.

Also concurrent use with lithium may cause extrapyramidal symptoms to develop. Discontinuation of both drugs is recommended at first signs of neurotoxicity.

Sympathomimetics: The pressor effects of sympathomimetics may be antagonised when taken concomitantly with sulpiride, resulting in severe hypotension.

Sulpiride Oral Solution 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) 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.

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

Patients should be advised not to drive or operate machinery if they experience symptoms of slowing of reaction time, drowsiness or loss of concentration (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, haemolytic anaemia, thrombocytopenic purpura

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

Endocrine disorders
Common: hyperprolactinaemia

Eye disorders
Not known: blurred vision, corneal and lens opacities, deposition of pigment in the eyes

Psychiatric disorders
Common: insomnia
Not known: confusion, depression, agitation

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

Metabolism and nutrition disorders
Not known: hyponatraemia, syndrome of inappropriate antidiuretic hormone secretion (SIADH), hyperglycaemia, hypothermia

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

(see section 4.4)

Respiratory, thoracic and mediastinal disorders
Not known: pneumonia aspiration (mainly in association with other CNS depressants), nasal congestion

Gastrointestinal disorders
Common: constipation
Uncommon: salivary hypersecretion
Not known: dry mouth

Hepatobiliary disorders
Common: hepatic enzyme increased
Not known: jaundice, hepatitis, cholestatic or mixed liver injury

Skin and subcutaneous tissue disorders
Common: maculo-papular rash
Not known: contact sensitivity, exfoliative dermatitis, pigmentation of the skin, photosensitivity and skin rashes

Musculoskeletal and connective tissue disorders
Not known: torticollis, trismus, rhabdomylosis

Pregnancy, puerperium and perinatal conditions
Not known: extrapyramidal symptoms, drug withdrawal syndrome neonatal (see section 4.6)

Renal and urinary disorders
Not known: difficulties with micturition

Reproductive system and breast disorders
Common: breast pain, galactorrhoea
Uncommon: breast enlargement, amenorrhoea, orgasm abnormal, erectile dysfunction.
Not known: gynaecomastia, ejaculatory dysfunction

General disorders and administration site conditions
Common: weight gain
Not known: hyperthermia (see section 4.4)

Investigations
Not known: blood creatine phosphokinase increased

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

Experience with sulpiride in overdosage is limited.

The range of single toxic doses is 1 to 16 g but no death has occurred even at the 16 g dose.

The clinical manifestations of poisoning vary depending upon the size of the dose taken.
After single doses of 1 to 3 g restlessness and clouding of consciousness have been reported and (rarely) extrapyramidal symptoms.
Dyskinetic manifestations with spasmodic torticollis, protrusion of the tongue, and trismus may occur.
Doses of 3 to 7 g may produce a degree of agitation, confusion and extrapyramidal symptoms (see section 4.8); more than 7 g 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.

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

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 administered.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics; Benzamides
ATC code: N05AL01

One of the characteristics of sulpiride is 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 effect characteristically associated with classical neuroleptics of the phenothiazine or butyrophenone type are not features of sulpiride therapy.

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 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 3Hspiperone and 3H-haloperidol. These findings indicate a major differentiation between sulpiride and classical neuroleptics which lack such specificity.

5.2 Pharmacokinetic properties

Peak sulpiride serum levels are reached 3-6 hours after an oral dose. The plasma halflife 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. However, when prescribing neuroleptics to patients with existing mammary neoplasia or a history of this disease, possible risks should be weighed against benefits of therapy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), propylene glycol (E1520), citric acid monohydrate (E330), liquid maltitol (E965), lemon flavour (containing propylene glycol (E1520), glycerine, and benzyl alcohol), aniseed flavour (containing propylene glycol (E1520)) and purified water.

6.2 Incompatibilities

None known

6.3 Shelf life

36 months - unopened
3 months - opened

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Bottle: 150 ml amber (Type III) glass.
Closure: HDPE, EPE wadded, tamper evident, child resistant closure.

6.6 Special precautions for disposal

The date of opening should be entered on the label next to the “use within 3 months of opening” statement.

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

7 MARKETING AUTHORISATION HOLDER

Essential Pharma Limited
8a Crabtree Road, Egham,

Surrey, TW20 8RN,
UK.

8 MARKETING AUTHORISATION NUMBER(S)

PL 41871/0020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 August 2001

Date of latest renewal: 07 April 2009

10 DATE OF REVISION OF THE TEXT

19/06/2025