1 NAME OF THE MEDICINAL PRODUCT
Sulpiride Rosemont 200mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5ml contains 200 milligrams Sulpiride

Excipient(s) with known effect:
Each 5ml of oral solution contains 3073.5 mg liquid maltitol.
Each 5ml of oral solution contains 6 mg methyl hydroxybenzoate
Each 5ml of oral solution contains 1.5 mg propyl hydroxybenzoate
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 400mg to 800mg 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 400mg twice daily is recommended, increasing if necessary up to a suggested maximum of 1200mg 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 800mg daily; therefore, a starting dose of 400mg twice daily is recommended. Reducing this dose towards 200mg 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 400-600mg twice daily.

*Paediatric population*

Clinical experience in children under the age of 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

- Phaeochromocytoma. Acute porphyria.
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- 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
- Association with levodopa (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, a reduction in dosage of sulpiride or initiation of antiparkinsonian 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) has been reported. Therefore, gradual withdrawal is advisable.

**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 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.

**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 no significant anticholinergic activity. 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. 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).

**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.
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, myasthenia gravis and prostatic hypertrophy.

Sulpiride should be used with caution in patients with a personal or family history of angle-closure glaucoma.

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. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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

### 4.5 Interaction with other medicinal products and other forms of interaction

**Associations contraindicated:**
Levodopa: reciprocal antagonism of effects between levodopa 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:
- 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.
- 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:
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, benzodiazepines and other anxiolytics.

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.

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

Pregnancy:
Despite the negative results of teratogenicity studies in animals and the lack of teratogenic effects during widespread clinical use in other countries, sulpiride should not be considered an exception to the general principle of avoiding drug treatment in pregnancy, particularly during the first 16 weeks, with potential benefits being weighed against possible hazards.

In humans, very limited clinical data on exposed pregnancies are available. If sulpiride is used during pregnancy, appropriate monitoring of the neonate should be considered in view of sulpiride safety profile.

The use of sulpiride in the third trimester of pregnancy may result in extrapyramidal effects, lethargy and hypotonia in the neonate.

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 has been found in low concentrations in breast milk. It is, therefore, recommended that the use of sulpiride be avoided in patients who are breast feeding.

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.

4.8 Undesirable effects

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Agranulocytosis, haemolytic anaemia, thrombocytopenic purpura and leucopenia.</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Hyperprolactinaemia</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyperglycaemia, hypothermia, hyperthermia.</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Delirium/confusion, catatonia, depression and somnolence. Sleep disturbances, overstimulation and agitation may occur.</td>
</tr>
</tbody>
</table>
### Nervous system disorders
- **Extrapyramidal symptoms and related disorders:**
  - parkinsonism and related symptoms (tremor, hypertonia, hypokinesia, hypersalivation)
  - acute dyskinesia and dystonia (spasm torticollis, oculogyric crisis, trismus)
  - akinesia.
  
  These symptoms are generally reversible upon administration of antiparkinsonian medication.
  - tardive dyskinesia (characterised by rhythmic, involuntary movements primarily of the tongue and/or the face) 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
  
  Very rare cases of convulsions have been reported, in particular in epileptic patients (see section 4.4 Special warnings and precautions for use).

- **Sedation or drowsiness.** Insomnia has been reported

### Eye disorders
- Blurred vision, corneal and lens opacities, deposition of pigment in the eyes

### Cardiac disorders
- Very rare cases of QT prolongation and very rare cases of torsade de pointes have been reported.
  - Ventricular arrhythmias such as VF, VT (rare), sudden unexplained death, cardiac arrest are class effects of neuroleptics.
  - Postural hypotension.

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

### Respiratory, thoracic and mediastinal disorder
- Nasal congestion.

### Gastrointestinal disorders
- Dry mouth and constipation.
  - A mild laxative effect or diarrhoea may be caused by the liquid maltitol in the formulation.

### Hepatobiliary disorders
- Jaundice, elevation in hepatic enzymes and hepatitis have been reported

### Skin and subcutaneous tissue disorders
- Contact sensitivity, exfoliative dermatitis and urticaria.
  - Maculopapular rash.
  - Pigmentation of the skin, photosensitivity and skin rashes.

### Renal and urinary disorders
- Difficulties with micturition.

### Reproductive system and breast
- Hyperprolactinaemia which may be associated with...
### disorders

- galactorrhoea, oligomenorrhoea, and amenorrhoea, gynaecomastia, breast enlargement and pain.
- Male sexual dysfunction: Ejaculatory dysfunction, impotence, increased and decreased libido has been reported.

### General disorders and administration site conditions

- 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 Rosemont 200mg/5ml Oral Solution, should be discontinued (section 4.4 Special warnings and precautions for use).

- Lassitude.
- Weight gain.

### Pregnancy, puerperium and perinatal conditions.

- **Not known**: Drug withdrawal syndrome neonatal (see 4.6)

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**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](http://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 death has occurred even at the 16g dose.

The clinical manifestations of poisoning vary depending upon the size of the dose taken. After single doses of 1 to 3g restlessness and clouding of consciousness have been reported and (rarely) extrapyramidal symptoms.

Doses of 3 to 7g may produce a degree of agitation, confusion and extrapyramidal symptoms (see section 4.8 Undesirable Effects); 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.
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, anti-parkinsonian 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 3H-spiperone 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 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. 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, propyl parahydroxybenzoate, propylene glycol, citric acid monohydrate, liquid maltitol, lemon flavour, aniseed flavour and purified water.

6.2 Incompatibilities

None known

6.3 Shelf Life

36 months - unopened
3 months - opened

6.4 Special Precautions for Storage
6.5 **Nature and contents of container**

Bottle: 150ml 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**

Rosemont Pharmaceuticals Ltd
Rosemont House
Yorkdale Industrial Park
Braithwaite Street
Leeds, LS11 9XE
United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 00427/0129

**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

03/02/2016