SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Sulpiride 200mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 200mg Sulpiride BP.
For the full list of excipients see section 6.1

3 PHARMACEUTICAL FORM
White circular flat bevel-edged tablets with a breakline and coded "SPD 200" on one side, and plain on the reverse.
The breakline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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 daily, given as one or two tablets 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 the 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 dosages of 400-600 mg twice daily.

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

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

**Method of Administration:**
For oral use.

### 4.3 Contraindications
Phaeochromocytoma and acute porphyria.
Hypersensitivity to sulpiride or to any of the excipients.
Concomitant prolactin-dependant tumours e.g. pituitary gland prolactinomas and breast cancer (see section 4.8).
Association with levodopa (see section 4.5).

### 4.4 Special warnings and precautions for use
Avoid concomitant treatment with other neuroleptics (see section 4.5).

The drug may interfere with tests for estimating glucose and cholesterol concentration in serum.

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 failure.

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

_Neuroleptic malignant syndrome_
As with all other neuroleptic drugs, neuroleptic malignant syndrome, a potentially fatal complication, which is characterised by unexplained hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels, has been reported. In this event, or in the event of hyperthermia of undiagnosed origin, all antipsychotic drugs, including sulpiride, and any associated neuroleptic treatment should be discontinued until the origin of the fever has been determined.

Withdrawal
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.

Use in the elderly
Elderly patients are more susceptible to postural hypotension, sedation and extrapyramidal effects.
In elderly patients, as with other neuroleptics, sulpiride should be used with particular caution.
Sulpiride is not licensed for the treatment of dementia-related behavioural disturbances.

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.

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.

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

Parkinson’s
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.
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.

**Epilepsy**
Although sulpiride only induces slight EEG modifications, caution is advised in prescribing it for patients with unstable epilepsy. Patients requiring sulpiride who are receiving anti-convulsant therapy should continue unchanged on the latter medication. Patients with a history of epilepsy should be closely monitored during therapy with sulpiride.

**Prolongation of QT interval**
Sulpiride induces a prolongation of QT interval (see section 4.8). This effect is known to potentiate the risk of serious ventricular arrhythmias such as torsade de pointes.
Therefore, Sulpiride should be used with caution in patients with cardiovascular disease or a family history of QT prolongation.

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

**Stroke**
An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Sulpiride should be used with caution in patients with risk factors for stroke.

**Cancer**
Although there is no evidence of an association between sulpiride use and tumour risk in man, the possible risks should be weighed against benefits of therapy when prescribing neuroleptics to patients with existing mammary neoplasia or a history of this disease.

**Alcohol**
Alcohol enhances the sedative effects of neuroleptics. Patients should avoid consuming alcoholic beverages and drugs containing alcohol throughout treatment (see Section 4.5).
Lactose
With reference to the presence of lactose monohydrate in the formulation, patients with the rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Unnecessary polypharmacy should be avoided. As with other compounds in the therapeutic class, precautions include use with tranquillisers, neuroleptics, anaesthetics and analgesics.

Interactions may occur with concomitant QT prolonging drugs, drugs causing electrolyte imbalance and metabolic inhibitors.

4.5.1 Associations contra-indicated
Levodopa: reciprocal antagonism of effects between levopoda and neuroleptics.

4.5.2 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 β-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 balance 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.

4.5.3 Associations to be taken into account
Antihypertensive agents: antihypertensive effect and possibility of enhanced postural hypotension (additive effect).

Symptoms of CNS depression may be enhanced by drugs with CNS-depressant properties, such as narcotics; analgesics; sedative H₁
antihistamines; barbiturates; benzodiazepines and other anxiolytics or hypnotics; clonidine and derivatives; baclofen and thalidomide. Antacids or sucralfate: The absorption of sulpiride is decreased after co-administration. Therefore, sulpiride should be administered two hours before these drugs.

Lithium increases the risk of extrapyramidal side effects.

Sulpiride may reduce the effectiveness of ropinirole.

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/foetal 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.

Breastfeeding:
Sulpiride is secreted in breast milk and therefore breast-feeding is not recommended during treatment. Potential benefits of treatment must be balanced against possible ill effects on the infant when considering use of the drug.

4.7 Effects on ability to drive and use machines

Although the sedative effects normally associated with neuroleptic therapy rarely occurs with sulpiride, patients who normally experience such an effect should be advised not to drive or operate machinery. Paralysis of accommodation may occur, resulting in blurred or distorted vision. Patients should be advised to avoid driving or using machinery should this occur.
4.8 Undesirable effects

List of adverse reactions

The frequencies of adverse events are ranked according to the following: 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 (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 overdose is limited. Sulpiride is very well tolerated and only minor side effects occur, if at all, at the recommended doses.
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 to 1 to 3 g, restlessness and clouding of consciousness have been reported and (rarely) extrapyramidal symptoms. Doses of 3 to 7 g may produce a degree of agitation, confusion and extrapyramidal symptoms; 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 overdosage. 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.
Overdosage may be treated with alkaline osmotic diuresis and, if necessary, anti-parkinsonian drugs. Coma needs appropriate nursing, and cardiac monitoring if recommended until the patient recovers. Emetic drugs are unlikely to be effective in sulpiride overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antipsychotics
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. It is claimed that sulpiride exerts its
antipsychotic action by a selective blockade of central dopamine D2 receptors. It is also claimed to have mood elevating properties, and has anti-emetic actions and an effect on gastric secretion.

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 $^3$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 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 therapy.

5.2 Pharmacokinetic properties
Sulpiride is absorbed from the gastro-intestinal tract. 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% of 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
As this product is a generic, no preclinical studies were performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose BP  
Pregelatinised Maize Starch BP  
Magnesium Stearate BP  
Povidone BP  
Sodium Starch Glycollate BP  
Water BP
6.2 Incompatibilities
None known.

6.3 Shelf life
36 months from the date of manufacture.

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
Sulpiride Tablets 200 mg may be supplied in either or both of the following containers in the pack sizes indicated:

- Polypropylene tubular containers with an open end equipped to accept a low density polyethylene closure.

- Blister packs of 250 micron white PVC backed by 20 micron hard tempered aluminium foil, bearing a 6-8 gm$^{-2}$ lacquer on the dull side and printed on the bright side, or PVdC coated PVC/Aluminium blisters (60g/m$^2$ PVdC on 250µm PVC/20µm Al)

The packs are available with 7, 14, 21, 28, 30, 50, 56, 60, 84, 90, 100, 112 or 120 tablets.

6.6 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORISATION HOLDER
Teva UK Limited
Brampton Road
Hampden Park
Eastbourne
8  MARKETING AUTHORISATION NUMBER(S)
   PL 00289/1532

9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   08\textsuperscript{th} February 1995

10 DATE OF REVISION OF THE TEXT
    27/06/2016