SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

BIO-SULPIRIDE 200 Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg sulpiride.

Contains sugar (lactose monohydrate 67,0 mg per tablet).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

White circular flat bevelled edged tablet with a breakline on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Schizophrenia.

The management of acute episodes and the prevention of acute relapses in chronic cases.

4.2 Posology and method of administration

Posology

Initial Treatment

200 to 800 mg orally in divided doses 8 or 12 hourly over 24 hours. Duration one to six weeks.

Maintenance treatment

600 to 800 mg per day (three to four BIO-SULPIRIDE 200 tablets) in divided doses.

Duration as long as necessary.

Plasma concentrations may be increased in elderly patients due to renal insufficiency (see section 4.4) for dosage adaption).

There is a progressive reduction in the rate of elimination and an increase in half-life with decreasing renal function (see section 4.4).

Patients with renal impairment or the elderly, with creatinine clearance of 30 to 60 ml/minute require a reduction of 70 % of normal dose, 10 to 30 ml/minute require a reduction of 50 % of normal dose and creatinine clearance of less than 10 ml/minute require a reduction of 35 % of normal dose. Alternatively, increase the dosage interval between doses by a factor of 1,5; 2 and 3, respectively.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to sulpiride or to any of the excipients of BIO-SULPIRIDE 200, listed in section 6.1.
- BIO-SULPIRIDE 200 is contraindicated in patients with known or suspected phaeochromocytoma.
- Pregnancy and Lactation (see section 4.6).
- BIO-SULPIRIDE 200 should be avoided in patients with bone marrow depression.
- BIO-SULPIRIDE 200 should not be given with other medicines that may induce leucopenia and blood dyscrasias.
- Porphyria.
- Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer.

- Congenital QT prolongation.
- Concomitant use with anti-Parkinson dopaminergic medicines (see section 4.5).

4.4 Special warnings and precautions for use

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

Neuroleptic malignant syndrome:

In case of unexplained hyperthermia, it is essential to discontinue BIO-SULPIRIDE 200 since this may be indicative of the malignant syndrome described with neuroleptic medicines such as BIO-SULPIRIDE 200 (pallor, hyperthermia, vegetative disturbances, alteration of consciousness and muscle rigidity). Neuroleptic malignant syndrome may occur more frequently in catatonic schizophrenia. Symptoms of vegetative dysfunction such as sweating and unstable blood pressure can occur prior to the occurrence of hyperthermia and consequently represent early onset warning signs. Even though this neuroleptic-related adverse event can result from an individual idiosyncrasy to BIO-SULPIRIDE 200, certain risk factors appear to predispose to it such as dehydration or organic brain disease.

Prolongation of the QT interval:

BIO-SULPIRIDE 200 produces a dose-dependent prolongation of the QT interval. This effect, known to potentiate the risk of serious ventricular dysrhythmias such as Torsades de Pointes, is enhanced by the presence of bradycardia, hypokalaemia, or congenital or acquired long QT interval as in combination with other medicines that increase the QT interval.

Refer to section 4.5 for combinations of medicines with BIO-SULPIRIDE 200 which could induce “Torsades de Pointes”.

Before administering BIO-SULPIRIDE 200, the absence of factors which can promote the occurrence of this dysrhythmias should be verified:

- Bradycardia less than 55 bpm
- Hypokalaemia
- Congenital prolongation of the QT interval
- Ongoing treatment with a medication which can cause marked bradycardia (< 55 bpm), hypokalaemia, slowing of intracardiac conduction or prolongation of the QT interval.

It is recommended to perform an ECG in the initial evaluation of patients who are to be treated with BIO-SULPIRIDE 200.

Stroke:

BIO-SULPIRIDE 200 should be used with caution in patients with stroke risk factors.

BIO-SULPIRIDE 200 is not recommended in hypomanic patients, in the manic or pre-manic phase of manic-depressive psychosis, or in patients with acute mania, as BIO-SULPIRIDE 200 may precipitate manic states, which can last up to two days in certain patients prone to these conditions. If this should occur, BIO-SULPIRIDE 200 may either be discontinued or, if the therapeutic effect is required notwithstanding, BIO-SULPIRIDE 200 must be combined with sedative neuroleptics or other psychotropic medicines.

Psychotic suicidal cases:

BIO-SULPIRIDE 200, because of its disinhibitory effect, should be administered with care and combined with psychotherapy.

Parkinson's disease:

BIO-SULPIRIDE 200 should not be used in patients with Parkinson's disease (see section 4.5). BIO-SULPIRIDE 200 inhibits the action of levodopa and may potentiate the adverse effects of other antimuscarinics, including antimuscarinic anti-parkinsonian medicines.

Renal impairment:

Patients with renal impairment, with creatinine clearance of 30 to 60 ml/minute require a reduction of 70 % of normal dose, 10 to 30 ml/minute require a reduction of 50 % of normal dose and creatinine clearance of less than 10 ml/minute require a reduction of 35 % of normal dose. Alternatively, increase the dosage interval between doses by a factor of 1,5; 2 and 3, respectively.

Caution is required in patients with impaired liver, kidney or respiratory function, and in patients receiving other central nervous system depressant medicines, in whom central nervous system depression may be potentiated.

Elderly patients:

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

There is an increased mortality in elderly people with dementia who are treated with BIO-SULPIRIDE 200. BIO-SULPIRIDE 200 is not indicated for the treatment of dementia-related behavioural disturbances.

In patients with aggressive behaviour or agitation with impulsiveness, BIO-SULPIRIDE 200 could be given with a sedative.

BIO-SULPIRIDE 200 should only be administered with caution to patients with hypertension, especially in the elderly population, due to the risk of hypertensive crisis. Patients should be adequately monitored.

BIO-SULPIRIDE 200 should be given with caution to patients in whom a sudden drop in blood pressure would be undesirable, and cardiovascular disorders. Concomitant use with medicines that produce postural hypotension may require dosage adjustments. The antihypertensive action of adrenergic neurone blockers is reduced by BIO-SULPIRIDE 200.

BIO-SULPIRIDE 200 effects on the vomiting centre may mask the symptoms of overdosage of other medicines, or of disorders such as gastrointestinal obstruction or congenital digestive stenosis.

BIO-SULPIRIDE 200 should be given with care in patients with diabetes. Patients with an established diagnosis of diabetes mellitus or with risk factors for diabetes who are started on BIO-SULPIRIDE 200, should get appropriate glycaemic monitoring.

BIO-SULPIRIDE 200 induces slight EEG modifications. Neuroleptics may lower the epileptogenic threshold and some cases of convulsions have been reported with BIO-SULPIRIDE 200 (see section 4.8 Undesirable Effects). Therefore, patients with a history of epilepsy should be closely monitored during BIO-SULPIRIDE 200 therapy. Care is required in epileptic patients receiving anticonvulsant therapy as BIO-SULPIRIDE 200 may lower the seizure threshold.

In patients requiring BIO-SULPIRIDE 200 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.

Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics, including BIO-SULPIRIDE 200. Unexplained sore throat, lymphadenopathy, infections or fever may be evidence of blood dyscrasia (see section 4.8) and requires immediate haematological investigation.

Patients receiving BIO-SULPIRIDE 200 therapy should receive regular examinations for abnormal ocular pigmentation or ocular changes.
BIO-SULPIRIDE 200 has an anticholinergic effect and, therefore, should be used with caution in patients with a history of glaucoma, urine retention or hyperplasia of the prostate.

Venous thromboembolism:

Cases of venous thromboembolism (VTE), sometimes fatal, have been reported with antipsychotic medicines. 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 BIO-SULPIRIDE 200 and preventative measures undertaken.

Breast cancer

Sulpiride as contained in BIO-SULPIRIDE 200 may increase prolactin levels. Therefore, BIO-SULPIRIDE 200 should not be used in patients with a history or a family history of breast cancer or tumour of the pituitary gland (see section 4.3).

Avoid concomitant prescription of other antipsychotics.

In children, under the age of 18 years, efficacy and safety of BIO-SULPIRIDE 200 has not been established.

Ingestion of alcohol as well as ingestion of any medication containing alcohol are strongly discouraged throughout duration of treatment with BIO-SULPIRIDE 200 (see section 4.5).

BIO-SULPIRIDE 200 contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take BIO-SULPIRIDE 200.

4.5 Interaction with other medicines and other forms of interaction

Co-administration of BIO-SULPIRIDE 200 and the following combinations are contraindicated (see section 4.3):

Dopaminergic anti-Parkinson medicines:

Amantadine, bromocriptine, cabergoline, levodopa, lisuride, pergolide, piribedil, ropinirole.

Due to the reciprocal antagonism between these anti-Parkinson medicines and neuroleptics such as BIO-SULPIRIDE 200, concomitant use is contraindicated.

- In case of an extrapyramidal syndrome induced by BIO-SULPIRIDE 200, do not administer an anti-Parkinson dopaminergic medicine (blockade of dopaminergic receptors by neuroleptic medicines) to patients, but rather use an anticholinergic medicine (see section 4.4).

The following combination with BIO-SULPIRIDE 200 is not recommended:

Alcohol:

The sedative effect of BIO-SULPIRIDE 200 can be enhanced by alcohol. Alteration of concentration can be dangerous when driving and/or operating machinery. The intake of alcohol and medications containing alcohol should be avoided.

Careful consideration should be given before administration of the following combinations:

Antihypertensive medicines:

The antihypertensive effect and risk of postural hypotension are enhanced (additive effect).

Other central nervous system depressants:

Morphine-related compounds; barbiturates; benzodiazepines; carbamates, etifoxine; hypnotic medicines; sedative antidepressants; sedative H_1 histamine antagonists; central antihypertensive medicines; baclofen, thalidomide, other anxiolytics, clonidine and derivatives.

Antacids or sucralfate: The absorption of BIO-SULPIRIDE 200 is decreased after coadministration. Therefore, BIO-SULPIRIDE 200 should be administered two hours before these medicines.

Lithium: lithium increases the risk of extrapyramidal adverse reactions.

Discontinuation of both medicines is recommended at first signs of neurotoxicity.

BIO-SULPIRIDE 200 may modify response to metoclopramide therapy.

Concomitant administration of BIO-SULPIRIDE 200 with the following medication could induce Torsades de Pointes or prolong the QT interval:

- Medicines that induce electrolyte imbalance e.g. stimulant laxatives, tetracosactides, hypokalaemic diuretics, glucocorticoids and IV amphotericin B. The electrolyte balance of the patients should be corrected.
- Class Ia antidysrhythmic medicines such as quinidine, disopyramide.
- Class III antidysrhythmic medicines such as amiodarone, sotalol.
- Bradycardia-inducing medications such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine, digoxin, guanfacine.
- Methadone, pimozide, imipramine, haloperidol, antidepressants, pentamidine, halofantrine, lithium, cisapride, thioridazine, IV erythromycin, sultopride, bepridil, IV vincamine, sparfloxacin.

The use of alcoholic beverages and medicines containing alcohol should be avoided as alcohol enhances the sedative effects of BIO-SULPIRIDE 200.

4.6 Fertility, pregnancy and lactation

The safety and/or efficacy of BIO-SULPIRIDE 200 during pregnancy and lactation has not been established.

Pregnancy

BIO-SULPIRIDE 200 is contraindicated during pregnancy (see section 4.3).

Breastfeeding

BIO-SULPIRIDE 200 is contraindicated during lactation (see section 4.3).

BIO-SULPIRIDE 200 is excreted in breastmilk. Mothers on BIO-SULPIRIDE 200 should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

Because of the drowsiness and impaired concentration that may ensue, affected patients should not drive or operate machines where loss of attention might be hazardous. Alteration of vigilance when using alcohol, and enhancement of central nervous system depression, is observed. Alteration of vigilance can occur when driving and using machines.

The sedative effect must be fully assessed on the individual before driving or operating heavy machinery is allowed.

4.8 Undesirable effects

Tabulated list of adverse reactions

MedDRA System Organ Class	
Immune system disorders	
Frequency unknown:	Anaphylactic reactions: urticaria, exfoliative dermatitis, and contact sensitivity, dyspnoea, hypotension, and anaphylactic shock
Blood and lymphatic system disorders	
Less frequent:	Leukopenia
Frequency unknown:	Haematological disorders, including haemolytic anaemia, aplastic anaemia, thrombocytopenic purpura, eosinophilia, neutropenia and a potentially fatal agranulocytosis have been reported (see section 4.4).
Endocrine disorders	
Frequent:	Hyperprolactinaemia
Psychiatric disorders	
Frequent:	Insomnia
Frequency unknown:	Confusion

Nervous system disorders	
Frequent:	Sedation or drowsiness, extrapyramidal symptoms, parkinsonism, tremor, akathisia
Less frequent:	Hypertonia, dyskinesia, dystonia such as spastic oculogyric crisis
Frequency unknown:	Malignant neuroleptic syndrome, hypokinesia, tardive dyskinesia, convulsion
Cardiac disorders	
Less frequent:	Ventricular dysrhythmias, ventricular fibrillation, ventricular tachycardia
Frequency unknown:	Electrocardiogram QT prolonged, cardiac arrest, torsade de pointes, and sudden death (see section 4.4), tachycardia, electrocardiographic changes
Vascular disorders	
Less frequent:	Orthostatic hypotension
Frequency unknown:	Hypertension, venous embolism, pulmonary embolism, deep vein thrombosis (see section 4.4)
Eye disorders	
Frequency unknown:	Mydriasis, miosis, blurred vision, pigmentary retinopathy, corneal and lens opacities
Respiratory, thoracic and mediastinal disorders	
Frequency unknown:	Pneumonia aspiration (mainly in association with other CNS depressants)
Reproductive system and breast disorders	
Frequent:	Breast pain, galactorrhoea
Less frequent:	Breast enlargement, amenorrhoea, orgasm abnormal, erectile dysfunction
Frequency unknown:	Impotence or frigidity, priapism, breast congestion, menstrual irregularities, gynecomastia
Metabolism and nutrition disorders	

Frequency unknown:	Hyperglycaemia, altered glucose tolerance and increased serum cholesterol concentrations, hyponatraemia, syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Renal and urinary disorders	
Frequency unknown:	Urinary retention
Gastrointestinal disorders	
Frequent:	Constipation
Less frequent:	Salivary hypersecretion
Hepato-biliary disorders	
Frequent:	Hepatic enzyme increased
Frequency unknown:	Abnormalities in liver function tests and jaundice, hepatocellular, cholestatic or mixed liver injury
Skin and subcutaneous tissue disorders	
Frequent:	Maculo-papular rash
Frequency unknown:	Photosensitivity reactions
Musculoskeletal and connective tissue disorders	
Frequency unknown:	Torticollis, trismus, rhabdomyolysis
Pregnancy, puerperium and perinatal conditions	
Frequency unknown:	Extrapyramidal symptoms, drug withdrawal syndrome neonatal
General disorders and administration site conditions	
Frequent:	Weight gain
Frequency unknown:	Hypo- and hyperthermia (see section 4.4), fatigue
Investigations	
Frequency unknown:	Blood creatine phosphokinase increased

Description of selected adverse reactions

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).

Extrapyramidal symptoms and related disorders:

Akinesia with or without hypertonia, and partially responsive to anticholinergic medicines, hyperkinetic-hypertonic syndrome, excitomotor syndrome, sleep disturbances, overstimulation and agitation, dry mouth and depression.

The neuroleptic malignant syndrome (see section 4.4) is a life-threatening complication.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

In overdose, side effects will be exacerbated and exaggerated (see section 4.8). Dyskinetic manifestations with spasmodic torticollis, protrusion of the tongue and trismus may occur.

Manifestations may vary depending on dose, and range from restlessness, clouding of consciousness, agitation, confusion. Some patients may develop life-threatening QT prolongation, Parkinsonian manifestations and coma.

There is no specific antidote to BIO-SULPIRIDE 200.

Administer symptomatic therapy, intensive care, under close and continuous monitoring of respiratory and cardiac functions (risk of prolongation of QT interval), which will be continued until the patient's recovery. In cases of severe extrapyramidal symptoms, anticholinergics should be administered.

BIO-SULPIRIDE 200 is partly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.6.5 Tranquillisers: Miscellaneous structures

Pharmacotherapeutic group: Antipsychotics, benzamides, ATC code: N05AL01

Sulpiride has antipsychotic actions. It is a substituted benzamide with both anti-depressant and neuroleptic properties. Antipsychotic actions are believed to be due to a selective blockade of central dopamine D2 receptors.

5.2 Pharmacokinetic properties

Absorption

Sulpiride is absorbed from the gastrointestinal tract; bioavailability (30 – 40 %) is low and is subject to individual variation.

Plasma concentrations may be increased in elderly patients due to renal insufficiency (see section 4.4 for dosage adaption.)

Peak sulpiride serum levels are reached 3 – 6 hours after an oral dose.

Distribution

Sulpiride is rapidly distributed to the tissues but passage across the blood-brain barrier is poor.

Sulpiride is distributed into breast milk.

Biotransformation

Sulpiride is less than 40 % bound to plasma proteins and is reported to have a plasma half-life of about 6 – 9 hours.

Elimination

95 % of the parent compound is excreted in the urine and faeces, mainly as unchanged sulpiride. Hepatic metabolism does not appear to be significant, although traces of metabolites can be found in the urine.

Characteristics in specific groups of subjects or patients

As sulpiride is eliminated mainly unchanged in the urine, the pharmacokinetic parameters are altered in patients with impaired renal function. There is a progressive diminution in the rate of elimination and an increase in half-life with decreasing renal function (see section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Magnesium stearate

Maize starch, pregelatinised

Povidone K30

Sodium starch glycollate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 ˚C.

6.5 Nature and contents of container

50 tablets in either a polypropylene securitainer, HDPE container with screw cap and induction sealing wad or a Patient-Ready-Pack (LDPE bag).

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd.

Block K West, Central Park,

400 16th Road,

Halfway house,

Midrand 1685

8. REGISTRATION NUMBER

30/2.6.5/0511

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 09 June 1997

10. DATE OF REVISION OF THE TEXT

To be allocated