APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

PROPRIETARY NAME (AND DOSAGE FORM):

BISBETA 2.5 mg TABLETS (Tablet)

BISBETA 5 mg TABLETS (Tablet)

BISBETA 10 mg TABLETS (Tablet)

COMPOSITION:

BISBETA 2.5 mg TABLETS: Each film-coated tablet contains bisoprolol fumarate (2:1)

2,5 mg. Sugar free.

BISBETA 5 mg TABLETS: Each film-coated tablet contains bisoprolol fumarate (2:1)

5 mg. Sugar free.

BISBETA 10 mg TABLETS: Each film-coated tablet contains bisoprolol fumarate (2:1)

10 mg. Sugar free.

Each film-coated tablet contains bisoprolol fumarate (2:1) 10 mg. Sugar free.

The other ingredients of BISBETA TABLETS are calcium hydrogen phosphate; cellulose microcrystalline; crospovidone; magnesium stearate and silica colloidal anhydrous.

The coating material of BISBETA TABLETS contains hypromellose; macrogol / PEG 400 and titanium dioxide (C.I. No: 77891).

PHARMACOLOGICAL CLASSIFICATION:

A 5.2 Adrenolytics (sympathicolytics).

PHARMACOLOGICAL ACTION:

Pharmacodynamics

Bisoprolol is a selective β_1-adrenoceptor antagonist with low β_2 receptor affinity. It is devoid of intrinsic sympathomimetic and membrane-stabilising activity.

*It reduces blood pressure, and by blockade of the cardiac β_1-receptors, it reduces cardiac action, and hence myocardial oxygen demand.

Pharmacokinetics:

Bisoprolol is well absorbed following oral administration with a resultant bioavailability of about 90 %, Tmax is at 3 hours. About 50 % of a dose is metabolised in the liver and the remainder is excreted unchanged via the kidneys.The plasma elimination half-life is approximately 10 to 12 hours in healthy volunteers and the duration of action is about 24 hours.

*The kinetics of bisoprolol are linear.

*In patients with chronic heart failure, patients with renal impairment and in patients with liver cirrhosis, the plasma levels of bisoprolol are about one third higher and the half-life is prolonged. In the elderly with hypertension, the elimination is delayed and plasma levels are higher.

INDICATIONS:

BISBETA TABLETS are indicated for the treatment of stable chronic moderate to severe heart failure with reduced systolic ventricular function (ejection fraction $\leq$ 35 %, based on echocardiography) in addition to ACE inhibitors, and diuretics, and optionally digoxin, prior to the administration of **BISBETA TABLET**. The patients should have stable chronic heart failure without acute failure during the previous six weeks and an unchanged basic therapy during the previous two weeks. They should be treated at optimal dose with an ACE inhibitor (or other vasodilator in case of intolerance to ACE inhibitors) and a diuretic, and optionally digoxin, prior to the administration of **BISBETA TABLETS**. It is recommended that the treating medical practitioner should be experienced in the management of chronic heart failure.

CONTRA-INDICATIONS:

BISBETA TABLETS are contra-indicated in chronic heart failure patients with:

- hypersensitivity to bisoprolol or to any of the ingredients
- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock
- AV block of second or third degree (without a pacemaker)
- sick sinus syndrome
- sinoatrial block
- bradycardia with less than 50 beats/min before the start of therapy
- hypotension (systolic blood pressure less than 100 mm Hg)
- bronchial asthma, bronchitis and severe chronic obstructive pulmonary disease
- peripheral arterial occlusive disease
- Raynaud's syndrome
- phaeochromocytoma
- metabolic acidosis
- pregnancy and lactation **(see Pregnancy and Lactation)**
- hyperthyroidism, as clinical manifestations may be masked
- peripheral vascular disease
- sinus bradycardia

The normal dose should be reduced in elderly patients, or in patients suffering from renal dysfunction. In the peri-operative period, it is generally unwise to reduce the dosage to which the patient is accustomed, as there may be danger of aggravation of angina pectoris or hypertension. A patient's normal tachycardic response to hypovolaemia or blood loss may be obscured during or after surgery. Particular caution should be taken in this regard. Safety and efficacy in children have not been established.

WARNINGS and SPECIAL PRECAUTIONS:

BISBETA TABLETS must be used with caution in:

- concomitant treatment with inhalation anaesthetics
- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia can be masked, *and as responses to hypoglycaemia are diminished
- strict fasting
- ongoing desensitisation therapy
- AV block of first degree
- Prinzmetal's angina
- peripheral arterial occlusive disease (intensification of complaints might happen especially during the start of therapy)

There is no therapeutic experience of **BISBETA TABLETS** treatment in heart failure in patients with the following diseases and conditions:

- NYHA class II heart failure
- insulin dependent diabetes mellitus (type I)
- impaired renal function (serum creatinine <80 ml/min)
- impaired liver function
- patients older than 80 years
- restrictive cardiomyopathy
- congenital heart disease
- haemodynamically significant organic valvular disease
- myocardial infarction within 3 months

β- blockers, such as **BISBETA TABLETS**, may cause bronchospasm in patients with asthma

(see **CONTRAINDICATIONS)**

Bbisoprolol may increase both the sensitivity towards allergens

and the severity of anaphylactic reactions. Epinephrine adrenaline treatment does not

always give the expected therapeutic effect.

Psoriasis may be aggravated by **BISBETA TABLETS**.

The symptoms of a thyrotoxicosis may be masked under treatment with **BISBETA TABLETS**.

Initiation of treatment with **BISBETA TABLETS** necessitates regular monitoring.

The cessation of therapy with **BISBETA TABLETS** should not be done abruptly unless

clearly indicated. Patients should be advised to limit the extent of their physical activity during

the period in which **BISBETA TABLETS** is being discontinued.

A patient's normal tachycardiac response to hypovolaemia or blood loss may be obscured

during or after surgery. Particular caution should be taken in this regard.

In the event of surgery, the anaesthetist should be informed of therapy with

BISBETA TABLETS prior to any operation.

If the decision is made to withdraw **BISBETA TABLETS** before anaesthesia, at least 48 hours

should be allowed to elapse between the last dose and surgery. If the medicine is to be

continued, care should be taken when using halogenated anaesthetics.

Atropine (1 – 2 mg I.V.) may be used to correct vagal dominance.

The patient must be maintained on their usual dosage perioperatively. In the perioperative period

it is generally unwise to reduce the dosage to which the patient is accustomed, as there may

be danger of aggravation of angina pectoris or hypertension.

In patients suffering from ischaemic heart disease, treatment should not be discontinued

abruptly.

The dosage of **BISBETA TABLETS** should be adjusted in severe renal impairment.

Care should be taken in prescribing **BISBETA TABLETS** together with Class 1 antidysrhythmic agents such as disopyramide, myocardial depressants and inhibitors of AV conduction such as calcium antagonists. Caution should be exercised when transferring a patient from clonidine, as the withdrawal of clonidine may result in the release of large amounts of catecholamines that may give rise to a hypertensive crisis. If **BISBETA TABLETS** are administered in these circumstances, the unopposed alpha receptor stimulation may potentiate this effect. If **BISBETA TABLETS** and clonidine are given concurrently, the clonidine should not be discontinued until several days after the withdrawal of **BISBETA TABLETS**, as severe rebound hypertension may occur.

BISBETA TABLETS should be used with caution in combination with verapamil in patients with impaired ventricular function. This combination should not be given to patients with conduction abnormalities. Neither medicine should be administered intravenously within 48 hours of discontinuing the other. The intravenous administration of calcium antagonists and antidysrthythmic agents is not recommended during therapy with **BISBETA TABLETS**. The intravenous administration of verapamil in patients on treatment with **BISBETA TABLETS** may lead to profound hypotension and atrioventricular block.
BISBETA TABLETS modifies the tachycardia associated with hypoglycaemia.

Patients with phaeochromocytoma usually require treatment with an alpha-adrenergic blocker.
BISBETA TABLETS may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Adrenaline treatment does not always give the expected therapeutic effect.
BISBETA TABLETS may mask the symptoms of hyperthyroidism.

EFFECTS ON ABILITY TO DRIVE AND OPERATE MACHINERY:

BISBETA TABLETS may cause drowsiness and dizziness. Do not drive or use any tools or machines until you know how the tablets affect you.

INTERACTIONS:

It can be dangerous to administer **BISBETA TABLETS** with the following medicines:

- Concomitant use of **BISBETA TABLETS** with hypoglycaemic agents, phenothiazines and various antidysrhythmic agents can have life-threatening consequences, e.g.
    - profound hypoglycaemia with oral hypoglycaemic agents and insulin;
    - myocardial depression with antidysrhythmic agents.
- Beta-adrenoceptor stimulating agents may antagonise the effects of **BISBETA TABLETS**.
- Alpha-adrenoceptor stimulants can dangerously affect the vasoconstrictor effects as well as adrenergic neurone blocking agents may lead to life-threatening vasoconstriction in combination with **BISBETA TABLETS**.
- **BISBETA TABLETS** and digoxin may be used concomitantly for patients with congestive heart failure provided that the pulse rate and patient response is monitored. It can be dangerous to administer **BISBETA TABLETS** with digoxin which can lead to a reduction of heart rate and an increase of atrio-ventricular conduction time.
- The half-life of **BISBETA TABLETS** can be slightly shortened by the simultaneous administration of rifampicin. An increase in the dose is generally unnecessary.
- Calcium antagonists have a negative influence on contractility, atrio-ventricular conduction and blood pressure. (see **WARNINGS AND SPECIAL PRECAUTIONS**)
- Clonidine and other centrally acting antihypertensives increases the risk of
- "rebound hypertension" and as well as exaggerated decrease in heart rate and cardiac conduction.
- Monoamineoxidase inhibitors (except MAO-B inhibitors) enhance the hypotensive effect
- of β-blockers but also risk of hypertensive crisis.
- The pharmacokinetics of bisoprolol are not significantly influenced by cimetidine.
- The following combinations should be used with caution together with bisoprolol:
    - Class-I antidysrhythmic medicines (e.g. disopyramide, quinidine),

due to a potentiated effect on the atrial conduction time and an increased negative inotropic effect.

- Class-III antidysrhythmic medicines (e.g. amiodarone), where the effect an atrial conduction time may be potentiated.

- Parasympathomimetic medicines (including tacrine), where atrio-ventricular conduction time and risk of bradycardia may be increased.
- Other β-blockers, including eye drops, have additive effects.
- Insulin and oral antidiabetic medicines, where it can lead to an intensification of blood sugar lowering effect. Blockade of β-adrenoceptors may mask symptoms of hypoglycaemia.
- Anaesthetic agents which can lead to attenuation of the reflex tachycardia and increase of the risk of hypotension. Continuation of β-blockade reduces the risk of dysrhythmia during induction and intubation. The anaesthetist should be informed when the patient is receiving **BISBETA TABLETS**.
- Prostaglandin synthetase inhibiting medicines, where the hypotensive effect is decreased.
- Ergotamine derivatives which can lead to the exacerbation of peripheral circulatory disturbances.
- Combinations of sympathomimetic agents with **BISBETA TABLETS** may reduce the effect of both agents. Higher doses of epinephrine (adrenaline) may be necessary for treatment of allergic reactions.
- **BISBETA TABLETS** in combination with tricyclic antidepressants, barbiturates, phenothiazines, as well as other antihypertensive agents, can lead to an increased blood pressure lowering effect.
- The combination of **BISBETA TABLETS** with mefloquine should be considered, as there is an increased risk of bradycardia.

PREGNANCY AND LACTATION:

Administration of **BISBETA TABLETS** to pregnant mothers shortly before birth or during labour

may result in hypotonia, collapse or hypoglycaemia in the newborn. (See **CONTRA-INDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE:

The treatment of stable chronic heart failure with **BISBETA TABLETS** has to be initiated with a titration phase as given in the description below:

The treatment with **BISBETA TABLETS** is to be started with a gradual uptitration according to the following steps:

- 1,25 mg once daily for 1 week, if well tolerated increase to
- 2.5 mg once daily for a further week, if well tolerated increase to
- 3.75 mg once daily for a further week, if well tolerated increase to
- 5 mg once daily for the 4 following weeks, if well tolerated increase to
- 10 mg once daily for maintenance therapy.

After initiation of treatment with 1,25 mg, the patients should be observed over a period of approximately 4 hours (especially as regards blood pressure, heart rate, conduction disturbances,signs of worsening of heart failure).

The maximum recommended dose is 10 mg once daily.

Occurrence of adverse events may prevent all patients being treated with the maximum recommended dose. If necessary, the dose reached can also be decreased step by step. The treatment may be interrupted if necessary and reintroduced as appropriate. During the titration phase, in case of worsening of the heart failure or intolerance, it is recommended first to reduce the dose of **BISBETA TABLETS**, or to stop immediately if necessary (in case of severe hypotension, worsening of heart failure with acute pulmonary oedema, cardiogenic shock, symptomatic bradycardia or AV block).

Treatment of stable chronic heart failure with **BISBETA TABLETS** is generally a long-term treatment. The treatment with **BISBETA TABLETS** is not recommended to be stopped abruptly since this might lead to transitory worsening of heart failure. If discontinuation is necessary, the dose should be gradually decreased divided into halves weekly.

BISBETA TABLETS should be taken in the morning and can be taken with food. They should be swallowed with liquid and should not be chewed.

No dosage adjustment is required in elderly patients. Elderly patients are more likely to have age-related peripheral vascular disease which may require caution.

There is a wide interindividual variation in sensitivity to one single high dose of bisoprolol. Therefore it is mandatory to initiate the treatment of these patients with a gradual uptitration according to the scheme given.

SIDE-EFFECTS:

Blood and the lymphatic system disorders

Less frequent: leukopenia, thrombocytopenia, agranulocytosis, non thrombocytopenia purpura, transient eosinophilia

Immune system disorders

Less frequent: hypersensitivity reactions (itching, flush, rash),systemic lupus erythematosus (SLE)

Metabolism and nutrition disorders

Less frequent: metabolic disturbances

Frequency unknown: Hypoglycaemia, hyperglycaemia, increase in uric acid levels, hypercholesterolaemia, changed in blood concentrations of triglycerides.

Psychiatric disorders

Less frequent: sleep disturbances, depression, nightmares, hallucinations, overt psychosis has been observed with other beta-blockers.

Nervous system disorders

Frequent: lassitude, fatigue, dizziness, mild headache, tiredness, exhaustion, dizziness, Headache (these symptoms generally occur at the beginning of treatment).

Less frequent: sleep disorders, coma, convulsions

Eye disorders

Frequency unknown: conjunctivitis, decreased tear production, blurred vision, soreness, disturbances of vision

Ear and labyrinth disorders

Less frequent: transient hearing loss, hearing impairment

Cardiac disorders

Less frequent: bradycardia, heart block, fluid retention, syncope, congestive cardiac failure, AV-stimulus disturbances, worsening of heart failure, orthostatic hypotension

Vascular disorders

Frequent: cold extremities, hypotension, paraesthesia, feeling of coldness and numbness in the extremities

Less frequent: paradoxical hypertension, exacerbation of peripheral vascular disease or the development of Raynaud's phenomenon, restlessness, severe peripheral vascular disease and peripheral gangrene

Respiratory, thoracic and mediastinal disorders

Less frequent: bronchospasm in patients with bronchial asthma or history of obstructive airways disease, shortness of breath, dyspnea, pneumonia, pulmonary fibrosis, pleurisy

Gastrointestinal disorders

Frequent: nausea, vomiting, diarrhoea, constipation, abdominal cramping, other gastro-intestinal disturbances, nausea, vomiting, diarrhoea, constipation

Frequency not known: stomatitis

Hepato-biliary disorders

Less frequent: hepatotoxicity, hepatitis

Skin and subcutaneous tissue disorders

Frequent: perspiration

Rare Less frequent: skin rash, allergic reactions

Very rare: alopecia, rashes, pruritus, exacerbation of psoriasis

Musculoskeletal, connective tissue and bone disorders

Less frequent: muscle weakness, cramps, myopathies, back and joint pain

Reproductive system and breast disorders

Less frequent: potency disorders

General disorders and administrative conditions

Less frequent: mass gain, asthenia

Adverse reactions are more common in patients with renal decompensation.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdosage may produce bradycardia and severe hypotension. Bronchospasm and heart failure may be produced in certain individuals.

Cases of mild overdose should be observed for at least 4 hours, as apnoea and cardiovascular collapse may appear suddenly. Gastric lavage should be performed within four hours of suspected overdose. Repeated activated charcoal may be necessary in overdose.

Atropine may be used to treat severe bradycardia. If the response is inadequate, glucagon may be given intravenously. Alternatively, dobutamine may be required to reverse beta-blockade. Cardiac pacing may be required for severe bradycardia. Bronchospasm should be treated with IV aminophylline or inhaled or IV beta-agonist e.g. salbutamol.

IDENTIFICATION:

BISBETA 2.5 mg TABLETS:

White, circular, biconvex, film-coated tablets, debossed with 'I and break line' on one side and '7' on the other side.

BISBETA 5 mg TABLETS:

White, circular, biconvex, film-coated tablets, debossed with 'I and break line' on one side and '33' on the other side.

BISBETA 10 mg TABLETS:

White, circular, biconvex, film-coated tablets, debossed with 'I and break line' on one side and '34' on the other side.

PRESENTATION:

BISBETA 2.5 mg TABLETS, BISBETA 5 mg TABLETS AND BISBETA 10 mg TABLETS:

Blister pack:

Tablets are packed in printed peelable lidding foil and cold form film.

Peelable lidding foil: Aluminium foil, one side bright, soft, plain, dull side lacquer laminated to polyester film, polyester film lacquer laminated to sulphate paper, bright side heat sealable lacquer.

This peelable lidding foil is consisting of 50 g/m^2 paper / 12micron polyster / 20 micron Aluminium foil / 7 g/m^2Heat seal lacquer.

Cold form film: Cold formable, triple laminated film.This cold form film is consisting of 25 micron polyamide / 45 micron Aluminium foil / 60 micron PVC film.

One blister contains 10 tablets.

Pack size: 30's: Each carton contains 3 blisters of 10 tablets each

HDPE Container Pack:

Tablets are packed in white opaque 40 ml HDPE container and white opaque RS closure, with induction sealing wad containing 1 No. of silica gel sachet. Each container contains 30 tablets.

Pack size: 30's - One HDPE container contains 30 tablets.

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Keep blisters in the original carton until required for use.

Keep the containers tightly closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

SOUTH AFRICA

BISBETA 2.5 mg: 45/5.2/0789

BISBETA 5 mg: 45/5.2/0790

BISBETA 10 mg: 45/5.2/0791

NAMIBIA

BISBETA 2.5 mg: 18/5.2/0065

BISBETA 5 mg: 18/5.2/0066

BISBETA 10 mg: 18/5.2/0067

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF

REGISTRATION:

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