APPROVED PACKAGE INSERT (CLEAN) – 10 October 2014

SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

MYLAN BISOPROLOL 5 mg (film-coated tablets)

MYLAN BISOPROLOL 10 mg (film-coated tablets)

COMPOSITION:

Each **MYLAN BISOPROLOL 5 mg** film-coated tablet contains:

Bisoprolol fumarate 5 mg

Contains lactose anhydrous (sugar) 30 mg

Excipients: Cellulose microcrystalline (Avicel PH 103), colloidal anhydrous silica, croscarmellose sodium, ferric oxide yellow, Stear-o-wet m [magnesium stearate/sodium lauryl sulphate (94/6)]

{film-coat: Opadry II yellow 40C82498 (composition of Opadry II yellow 40C82498: FD & C blue #2/Indigo carmine aluminium lake, FD & C yellow #5/tartrazine aluminium lake, HPMC 2910/hypromellose 3 cP, HPMC

2910/hypromellose 6 cP, HPMC 2910/hypromellose 50 cP, macrogol/PEG 400, macrogol/PEG 8000, polydextrose FCC, titanium dioxide)}

Each **MYLAN BISOPROLOL 10 mg** film-coated tablet contains:

Bisoprolol fumarate 10 mg

Contains lactose anhydrous (sugar) 30 mg

Excipients: Cellulose microcrystalline (Avicel PH 103), colloidal anhydrous silica, croscarmellose sodium, ferric oxide red, Stear-o-wet m [magnesium stearate/sodium lauryl sulphate (94/6)]
{film-coating: Opadry II orange 40C83047 (composition of Opadry II orange 40C83047: FD & C yellow #6/Sunset yellow FCF Aluminium lake, HPMC 2910/hypromellose 3 cP, HPMC 2910/hypromellose 6 cP, HPMC 2910/hypromellose 50 cP, iron oxide yellow, macrogol/PEG 400, macrogol/PEG 8000, polydextrose FCC, titanium dioxide)}

PHARMACOLOGICAL CLASSIFICATION:

A 5.2 Adrenolytics (sympathicolytics).

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Bisoprolol is a selective β1-adrenoceptor antagonist devoid of intrinsic sympathomimetic and membrane-stabilising activity.

Pharmacokinetic properties:

Bisoprolol is well absorbed following oral administration with a resultant bioavailability of about 90 %. Bisoprolol undergoes minimal hepatic first-pass metabolism. 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 and the duration of action is about 24 hours.

INDICATIONS:

MYLAN BISOPROLOL tablets are indicated for the management of mild to moderate of hypertension and angina pectoris.

CONTRA-INDICATIONS:

Hypersensitivity to **MYLAN BISOPROLOL** or any other ingredient in the tablets.

Second and third-degree heart block and bradycardia (less than 50 beats per minute).

Pregnancy or lactation (see **PREGNANCY AND LACTATION**)

Uncontrolled cardiac failure.

Metabolic acidosis.

Sick sinus syndrome and sinoatrial block.

Phaeochromocytoma

Peripheral arterial occlusive disease

Hyperthyroidism, as clinical manifestations may be masked.

Particular caution should be exercised with patients suffering from the following: Asthma, bronchitis, chronic respiratory diseases, peripheral vascular disease and Raynaud's phenomenon.

Cardiogenic shock.

Hypotension.

WARNINGS and SPECIAL PRECAUTIONS:

Safety and efficacy in children below 18 years have not been established.

The anaesthetist should be informed of therapy with **MYLAN BISOPROLOL** prior to any operation.

If **MYLAN BISOPROLOL** is to be withdrawn prior to anaesthesia, at least 48 hours should be allowed to elapse between the last dose and surgery. If **MYLAN BISOPROLOL** treatment is to be continued during surgery, care should be taken when using halogenated medicines. Atropine (1 – 2 mg i.v.) may be used to correct vagal dominance. The patient must be maintained on their usual dosage perioperatively to avoid aggravation of angina pectoris or hypertension.

Tachycardiac responses may be obscured. Particular caution should be taken in this regard.

The dosage of **MYLAN BISOPROLOL** should be adjusted in severe renal impairment (see **DOSAGE AND DIRECTIONS FOR USE**).

Care should be taken in prescribing **MYLAN BISOPROLOL** together with Class 1 antidysrhythmic medicines 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, which may give rise to a hypertensive crisis. If **MYLAN BISOPROLOL** is administered in these circumstances, the unopposed alpha receptor stimulation may potentiate this effect. If **MYLAN BISOPROLOL** and clonidine are given concurrently, the clonidine should not be discontinued until several days after the withdrawal of **MYLAN BISOPROLOL,** as severe rebound hypertension may occur.

MYLAN BISOPROLOL 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 antidysrhythmic medicines is not recommended during therapy with **MYLAN BISOPROLOL.**

The intravenous administration of verapamil in patients on **MYLAN BISOPROLOL** treatment may lead to profound hypotension and atrioventricular block.

MYLAN BISOPROLOL modifies the tachycardia associated with hypoglycaemia.

Patients with phaeochromocytoma usually require treatment with an alpha-adrenergic blocker.

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 tachycardiac response to hypovolaemia or blood loss may be obscured during or after surgery. Particular caution should be taken in this regard.

In diabetes mellitus symptoms and signs of hypoglycaemia may be masked as responses to hypoglycaemia is diminished.

MYLAN BISOPROLOL and digoxin may be used concomitantly for patients with congestive heart failure provided that the pulse rate and patient's response is monitored (see "**INTERACTIONS**")

Mefloquine may increase the risk of bradycardia (see "**INTERACTIONS**").

Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischaemic heart disease. Discontinuation of therapy should be gradual and patients should be advised to limit the extent of their physical activity during the period in which the medicine is being discontinued.

Patients with psoriasis or with history of psoriasis should only be given beta-blockers (e.g. bisoprolol, as contained in **MYLAN BISOPROLOL**) after carefully balancing the benefits against the risk (see **SIDE-EFFECTS**).

Effects on the ability to drive and use machines:

Drowsiness and dizziness can occur. This should be considered when driving or operating machinery.

Information about some of the ingredients of MYLAN BISOPROLOL tablets:

MYLAN BISOPROLOL tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take **MYLAN BISOPROLOL** tablets.

INTERACTIONS:

Concomitant use of **MYLAN BISOPROLOL** 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 anti[~~ar~~]dysrhythmic agents.

Rifampicin: Slight reduction of the half-life of bisoprolol possible due to the induction of hepatic metabolising enzymes. Normally no dosage adjustment is necessary.

Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

Concomitant use with antihypertensive agents as well as with other medicines with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates) may increase the risk of hypotension.

Mefloquine: increased risk of bradycardia.

Beta-adrenoceptor stimulating agents may antagonise the effects of **MYLAN BISOPROLOL**.

Monoamine oxidase inhibitors enhance the hypotension effect of **MYLAN BISOPROLOL** but also the risk of hypotensive crisis.

Alpha-adrenoreceptor stimulants as well as adrenergic neurone blocking agents may lead to life-threatening vasoconstriction in combination with **MYLAN BISOPROLOL**.

Other beta-blockers including eye drops have additive effects.

Digitalisation of patients receiving long-term therapy with **MYLAN BISOPROLOL** may be necessary. This combination can be considered despite the potential of the negative chronotropic effect.

MYLAN BISOPROLOL and digoxin may be used concomitantly for patients with congestive heart failure provided that the pulse rate and patient's response is monitored.

MYLAN BISOPROLOL 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 antidysrhythmic medicines is not recommended during therapy with **MYLAN BISOPROLOL.**

PREGNANCY AND LACTATION:

Administration of **MYLAN BISOPROLOL** to pregnant mothers shortly before giving birth or during labour may result in hypotonia, collapse or hypoglycaemia in the newborn (see **CONTRA-INDICATIONS).**

The safety of **MYLAN BISOPROLOL** in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

Adults: 5 to 10 mg of **MYLAN BISOPROLOL** once a day in the morning with or without food.

The dose must be individualised according to response and tolerance.

The maximum recommended daily dose is 20 mg daily.

Severe renal impairment (creatinine clearance < 30 ml/min) or severe hepatic impairment:

Do not exceed the daily dose of 10 mg.

SIDE-EFFECTS:

Side-effects have been reported:

Blood and the lymphatic system disorders:

Less frequent: Agranulocytosis, non-thrombocytopenic purpura, transient eosinophilia. Blood disorders such as leukopenia and thrombocytopenia.

Immune system disorders:

Less frequent: Hypersensitivity reactions and skin rash.

Metabolism and nutrition disorders:

Less frequent: Metabolic disturbances, hypotlycaemia, increase in uric acid levels, hypercholesterolaema, changes in blood concentration of triglycerides.

Psychiatric disorders:

Less frequent: Sleep disorders, depression, hallucinations, psychosis. A variety of neuropsychiatric disorders, ranging from vague fatigue, nightmares to overt psychoses have been observed, confusion.

Nervous system disorders:

Less frequent: Lassitude, dizziness, mild headache, sleep disorders, restlessness, paraesthesia, anxiety, coma, convulsions.

Eye disorders:

Less frequent: Disturbances of vision, decreased lacrimation.

Ear and labyrinth disorders:

Less frequent: Transient hearing loss

Cardiac disorders:

Less frequent: Bradycardia and congestive cardiac failure, heart block, fluid retention. Congestive cardiac failure and marked bradycardia may occur; dysrhythmia.

Vascular disorder:

Frequent: Hypotension, cold extremities, paraesthesia.

Less frequent: Paradoxical hypertension. Exacerbation of peripheral vascular disease or the development of Raynaud's phenomenon. Peripheral gangrene may be precipitated.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Bronchoconstriction may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases, nasal congestion, dyspnea, pulmonary fibrosis, pleurisy and pneumonitis.

Gastrointestinal disorders:

Less frequent: Nausea, vomiting, diarrhea, constipation, abdominal cramping, stomatitis, taste disturbances.

Hepatobiliary disorders:

Less frequent: Raised liver enzymes, hepatotoxicity.

Skin and subcutaneous tissue disorders:

Less frequent: Alopecia, rashes, pruritus, exacerbation of psoriasis.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Muscle cramps, myopathy, skeletal muscle weakness.

Reproductive system and breast disorders:

Less frequent: Sexual impotence.

General disorders and administrative site conditions:

Less frequent: General feeling of discomfort, illness or weakness. Mass gain.

Elderly:

The normal dose should be reduced in these patients.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

(See SIDE-EFFECTS AND SPECIAL PRECAUTIONS)

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 severe overdose.

Atropine may be used to treat severe bradycardia. If the response is inadequate, glucagons 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:

MYLAN BISOPROLOL 5 mg: Pale yellow, oval, biconvex film coated tablets with side notches and debossed with “BL & 4” on either side of the scoreline on one side and “M” on the other side.

MYLAN BISOPROLOL 10 mg: Pale orange to light orange, oval, biconvex film coated tablets with side notches and debossed with “BL & ^” on either side of the scoreline on one side and “M” on the other side.

PRESENTATION:

Blister pack comprising of clear transparent PVC film with backing of aluminium foil coated with heat seal lacquer. Blister strips packaged in an outer carton.
High density polyethylene (HDPE) bottle pack consisting of a white HDPE bottle with white opaque cap and with a desiccant and packaged into an outer carton.
Pack sizes of 30’s.

STORAGE INSTRUCTIONS:

Store at or below 25 ˚C.
Store in original container. Keep the container tightly closed. Blisters to be kept in the carton until required for use.
KEEP OUT OF REACH AND SIGHT OF CHILDREN

REGISTRATION NUMBERS:

MYLAN BISOPROLOL 5 mg: 45/5.2/0525

MYLAN BISOPROLOL 10 mg: 45/5.2/0526

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Mylan (Pty) Ltd

Building 6, Greenstone Hill Office Park

Emerald Boulevard

MODDERFONTEIN, 1645

Republic of South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT: 26 February 2015