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SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

BILOCOR 5 tablets

BILOCOR 10 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BILOCOR 5: Each tablet contains 5 mg bisoprolol fumarate.

BILOCOR 10: Each tablet contains 10 mg bisoprolol fumarate.

BILOCOR 5: Contains sugar (lactose monohydrate 136,16 mg).

BILOCOR 10: Contains sugar (lactose monohydrate 130,86 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

BILOCOR 5: Pale yellow, mottled round normal convex tablet debossed with BI over break-line and 5 on one side and plain on the reverse.

BILOCOR 10: Mottled beige round normal convex tablet debossed with BI over break-line and 10 on one side and plain on the reverse.

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BILOCOR can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BILOCOR is indicated for the management of mild to moderate hypertension and angina pectoris.

BILOCOR may be used alone or in combination with other hypertensive medicines.

4.2 Posology and method of administration

Posology

Adults: 5 to 10 mg 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.

In those patients treated for angina pectoris, no benefit was shown by increasing the dose to 20 mg once daily.

Special populations

Hepatic and/or renal insufficiency:

In patients with liver or kidney function disorders of mild to moderate severity, no dosage adjustment is normally required.

There is only limited experience with the use of BILOCOR in dialysis patients. There are no indications of the necessity to alter the dose regimen.

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Severe renal impairment (creatinine clearance < 20 mL/min) or severe hepatic impairment:

Do not exceed the daily dose of 10 mg.

Elderly:

The normal dose should be reduced in these patients.

Paediatric population

The safety and efficacy of BILOCOR in children have not yet been established. No data are available.

Method of administration

The tablets are to be swallowed whole with some liquid in the morning before, during or after breakfast.

The duration of treatment is not limited. It depends upon the nature and severity of the disease. BILOCOR therapy should not be stopped abruptly, particularly not in patients with ischaemic heart disease, as this may lead to acute deterioration of the patient's state of health (see section 4.4). If discontinuation of therapy becomes necessary, the dose should be gradually reduced (e.g. halving of the dose at weekly intervals).

BILOCOR can be divided into equal halves if required.

4.3 Contraindications

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- hypersensitivity to bisoprolol or to any of the ingredients of BISOPROLOL (see section 6.1)
- uncontrolled asthma
- second and third-degree heart block (without a pacemaker) and bradycardia (less than 50 beats per minute – sick sinus syndrome)
- pregnancy and lactation (see section 4.6)
- uncontrolled cardiac failure
- metabolic acidosis
- sinus bradycardia (less than 50 beats per minute)
- phaeochromocytoma before full alpha blockade is achieved (see section 4.4)
- hyperthyroidism, as clinical manifestations may be masked
- cardiogenic shock
- sinoatrial block
- symptomatic hypotension
- peripheral arterial occlusive disease and Raynaud's phenomenon
- safety and efficacy in children have not been established.

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4.4 Special warnings and precautions for use

Discontinuation

Abrupt discontinuation of therapy with BILOCOR may cause exacerbation of angina

pectoris in patients suffering from ischaemic heart disease. Discontinuation of BILOCOR should be gradual, and patients should be advised to limit the extent of their physical activity during the period that the medicine is being discontinued.
Caution is warranted when treating patients with hypertension or angina pectoris and concomitant heart failure with BILOCOR.

Digitalisation of patients receiving long-term beta-blocker therapy including BILOCOR may be necessary if congestive cardiac failure is likely to develop. This combination can be considered despite the potentiation of the negative chronotropic effect of the two medicines. Careful control of dosages, and of the individual patient's response (and notably pulse rate), is essential in this situation.

It is dangerous to administer BILOCOR concomitantly with the following medicines: hypoglycaemic medicines, phenothiazines and various antiarrhythmic agents. Such drug-drug interactions can have life-threatening consequences (see section 4.5).

General anaesthesia

If the decision is made to withdraw BILOCOR 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 anaesthetics such as ether, cyclopropane and trichloroethylene. Atropine (1-2 mg I.V.) may be used to correct vagal dominance. The patient must be maintained on their usual dosage peri-operatively to avoid aggravation of

angina pectoris or hypertension.

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.

The anaesthetist must be made aware of beta-blockade because of the potential for interactions with other medicines as indicated above.

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

BILOCOR may be used only with special caution in the following instances:

- diabetes mellitus, as symptoms and signs of hypoglycaemia may be masked, and as responses to hypoglycaemia (e.g. tachycardia, palpitations or sweating) is diminished
- strict fasting
- ongoing desensitisation therapy. As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine (adrenaline) treatment does not always yield the expected therapeutic effect
- first degree AV block.
- in patients with Prinzmetal's angina, as cases of coronary vasospasm have been observed. Despite its high beta1-selectivity, angina attacks cannot be completely excluded when BILOCOR is administered to patients with Prinzmetal's angina

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- peripheral arterial occlusive disease (intensification of complaints may occur especially when starting therapy).

  The following may occur: exacerbation of peripheral vascular disease, or the development of Raynaud's phenomenon (due to unopposed arteriolar alpha-sympathetic activation), sexual impotence, hypoglycaemia, skeletal muscle weakness and gastro-intestinal disturbances. Severe peripheral vascular disease and even peripheral gangrene may be precipitated. Adverse reactions are more common in patients with renal decompensation, and in patients who receive BILOCOR intravenously
- care should be taken in prescribing BILOCOR together with Class 1 anti-dysrhythmic medicines such as disopyramide, myocardial depressants and inhibitors of AV conduction such as calcium antagonists (see section 4.5).

The normal dose should be reduced in elderly patients.

The dosage of BILOCOR should be adjusted in severe renal impairment (see section 4.2).

Chronic pulmonary diseases

Bronchoconstriction may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases. Congestive cardiac failure and marked bradycardia may also manifest. A variety of neuropsychiatric disorders, ranging from vague fatigue and nightmares to overt psychosis, have been observed.

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Asthma and Chronic Obstructive Pulmonary Disease

Although cardioselective (β1) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, BILOCOR may be used with caution. In patients with obstructive airways diseases, the treatment with BILOCOR should be started at the lowest possible dose and patients should be carefully monitored for new symptoms (e.g. dyspnea, exercise intolerance, cough). In bronchial asthma or other chronic obstructive lung diseases, which may cause symptoms, bronchodilating therapy should be given concomitantly. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of β2-stimulants may have to be increased.

Psoriasis

Patients with psoriasis or with a history of psoriasis must only be given BILOCOR after careful consideration.

Clonidine

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 (see section 4.5). If BILOCOR is administered in these circumstances, the unopposed alpha-receptor stimulation may potentiate this effect. If BILOCOR and clonidine are given concurrently, the clonidine should not be discontinued

until several days after the withdrawal of BILOCOR, as severe rebound hypertension may occur.

Impaired ventricular function

BILOCOR should be used with caution in combination with verapamil in patients with impaired ventricular function (see section 4.5). 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 antiarrhythmic medicines is not recommended during therapy with BILOCOR (see section 4.5).

Hyperthyroidism

The symptoms of hyperthyroidism may be masked under treatment with BILOCOR.

Pheochromocytoma

Patients with phaeochromocytoma usually require treatment with an alpha-adrenergic blocker. BILOCOR must therefore not be administered until after full alpha-receptor blockade has been established. Beta blockade is seldom required in the peri-operative preparation of these patients.

Information on excipients of BILOCOR

BILOCOR contains lactose. Patients with rare hereditary problems of galactose intolerance,

total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Paediatric population

Safety and efficacy of BILOCOR have not been established in children.

4.5 Interaction with other medicines and other forms of interaction

Combinations not recommended

Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type:

Negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients on β-blocker treatment may lead to profound hypotension and atrioventricular block.

Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonidine, rilmenidine):

Concomitant use of centrally acting antihypertensive medicines may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly if prior to β-blocker discontinuation, may increase risk of “rebound hypertension”. If the two medicines are co-administered, the β-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by β-blocker therapy, the introduction of β-blockers should be delayed for several days after clonidine administration has stopped.

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Combinations to be used with caution

Calcium antagonists of the dihydropyridine type such as nifedipine, felodipine and amlodipine:

Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Class-III antiarrhythmic medicines (e.g. amiodarone):

Effect on atrio-ventricular conduction time may be potentiated.

Class I antiarrhythmic medicines (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide, propafenone):

Effect on atrioventricular conduction time may be potentiated and negative inotropic effect increased.

Topical β-blockers (e.g. eye drops for glaucoma treatment):

May add to the systemic effects of BILOCOR.

Parasympathomimetic medicines:

Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.

Insulin and oral antidiabetic medicines:

Increase of blood sugar lowering effect. Blockade of β-adrenoreceptors may mask symptoms of hypoglycaemia (see section 4.4).

Anaesthetic medicines:

Attenuation of the reflex tachycardia and increase of the risk of hypotension (see section

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4.4.).

Digitalis glycosides:

Reduction of heart rate, increase of atrio-ventricular conduction time. BILOCOR and digoxin may be used concomitantly for patients with congestive heart failure provided that the pulse rate and patient response is monitored.

Non-steroidal anti-inflammatory drugs (NSAIDs):

NSAIDs may reduce the hypotensive effect of BILOCOR.

Beta-sympathomimetics (e.g. dobutamine):

Combination with BILOCOR may reduce the effect of both agents. Higher doses of epinephrine (adrenaline) may be necessary for
treatment of allergic reactions.

Sympathomimetics that activate both β- and α-adrenoceptors (e.g. noradrenaline, adrenaline):

Combination with BILOCOR may unmask the α-adrenoceptor-mediated vasoconstrictor effects of these medicines leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective β-blockers.

Beta-adrenoceptor stimulating medicines:

(e.g. isoprenaline) may antagonise the effects of BILOCOR.

Alpha-adrenoceptor stimulants as well as adrenergic neurone blocking medicines such as guanethidine and reserpine:

May lead to life-threatening vasoconstriction in combination with BILOCOR.

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Concomitant use with antihypertensive medicines as well as with other medicines with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines):

May increase the risk of hypotension. The concomitant use of BILOCOR with phenothiazines and various anti-dysrhythmic medicines can have life-threatening consequences, e.g. myocardial depression with anti-dysrhythmic medicines.

Combinations to be considered

Mefloquine: Increased risk of bradycardia.

***Monoamine oxidase inhibitors (except MAO-B inhibitors)*:** Enhanced hypotensive effect of the β-blockers but also risk for hypertensive crisis.

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

Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances. In high-dose salicylate administration the toxic effect of salicylates on the central nervous system may be enhanced.

4.6 Fertility, pregnancy and lactation

Pregnancy

BILOCOR is contraindicated in pregnancy (see section 4.3).

Administration of BILOCOR to pregnant mothers shortly before birth or during labour may result in hypotonia, collapse or hypoglycaemia in the newborn.

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BILOCOR reduces placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour.

Breastfeeding

BILOCOR is contraindicated during breastfeeding (see section 4.3). It is not known whether BILOCOR is excreted in human breastmilk.

Fertility

No effect on fertility was observed in male or female rats treated with bisoprolol at oral doses up to 150 mg/kg/day.

4.7 Effects on ability to drive and use machines

BILOCOR has no or negligible influence on the ability to drive or use machinery. However, due to individual variations in reactions to BILOCOR (e.g. dizziness or fatigue), the ability to drive a vehicle or to operate machinery may be impaired. This should be considered particularly at start of treatment and upon change of medicine, as well as in conjunction with alcohol.

4.8 Undesirable effects

Tabulated list of adverse effects

System Organ Class	Frequency	Side effects

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Blood and lymphatic system disorders	Less frequent	Leukopenia and thrombocytopenia
Immune system disorders	Less frequent	Hypersensitivity (allergic) reactions
Metabolism and nutrition disorders	Frequency unknown	Metabolic disturbances, hypoglycaemia, increase in uric acid levels, hypercholesterolaemia
Psychiatric disorders	Less frequent Frequency unknown	Sleep disorders or trouble sleeping, mental depression, nightmares and vivid dreams, hallucinations, confusion Psychosis
Nervous system disorders	Frequent Less frequent Frequency unknown	Drowsiness, unusual tiredness or weakness, dizziness, mild headache Anxiety, nervousness, syncope Restlessness, lassitude, paraesthesia
Eye disorders	Less frequent Frequency unknown	Dry, sore eyes, reduced tear flow (to be considered if the patient uses lenses), conjunctivitis Disturbances of vision
Ear and labyrinth disorders	Frequency unknown	Transient hearing loss

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Cardiac disorders	Frequent Less frequent Frequency unknown	Bradycardia Worsening of pre-existing cardiac failure, dysrhythmias, reduced peripheral circulation Heart block, fluid retention
Vascular disorders	Frequent Less frequent Frequency unknown	Cold extremities, hypotension Orthostatic hypotension 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 or bronchospasm may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases, nasal congestion, allergic rhinitis
Gastrointestinal disorders	Frequent Frequency unknown	Nausea, vomiting, diarrhoea, constipation Mass gain, stomatitis
Hepatobiliary disorders	Less frequent Frequency unknown	Hepatotoxicity, hepatitis Raised liver enzymes

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Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Skin rash, psoriasiform eruption, pruritus, flush, angioedema, alopecia. Beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash Perspiration
Musculoskeletal, connective tissue and bone disorders	Less frequent Frequency unknown	Back pain or joint pain, chest pain, muscle cramps, skeletal muscle weakness Myopathy
Reproductive system and breast disorders	Less frequent	Decreased sexual ability or impotence, sexual dysfunction
General disorders and administrative site conditions	Less frequent	Asthenia, fatigue
Investigations	Less frequent	Increased triglycerides, increased liver enzymes (ALAT, ASAT).

Description of selected adverse reactions

Adverse reactions are more common in patients with renal decomposition.

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by using either of the followinglinks:

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https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/ or

https://www.sahpra.org.za/Publications/Index/8.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms

In general, the most common signs expected with overdosage of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is limited experience with overdose of bisoprolol, only a few cases of overdose with bisoprolol have been reported. Bradycardia and severe hypotension were noted. All patients recovered. There is a wide inter-individual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive.

Management of overdose

Cases of overdose should be observed for at least 4 hours, as apnoea and cardiovascular collapse may appear suddenly.

Repeated activated charcoal may be necessary in overdose.

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If overdose occurs, BILOCOR treatment should be stopped and supportive and symptomatic treatment should be provided. Limited data suggest that bisoprolol is hardly dialysable. Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures should be considered when clinically warranted.

Bradycardia: 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. Intravenous cardiac pacing may be required for severe bradycardia.

Hypotension: Intravenous fluids and vasopressors should be administered. Intravenous glucagon may be useful.

AV block (second or third degree): Patients should be carefully monitored and treated with isoprenaline infusion or transvenous cardiac pacemaker insertion.

Bronchospasm: Bronchospasm should be treated with I.V. aminophylline or inhaled or I.V. beta-agonist e.g. salbutamol.

Hypoglycaemia: Administer I.V. glucose.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective

ATC code: C07AB07

Pharmacological classification: A 5.2 Adrenolytics (sympathicolytics)

Mechanism of action

Bisoprolol is a selective ß1-adrenoceptor antagonist devoid of intrinsic sympathomimetic and membrane-stabilising activity, with low ß2-receptor affinity.
It blocks beta-adrenergic receptors in the heart and the juxtaglomerular apparatus (kidneys), thus decreasing the excitability of the heart, the cardiac output, the oxygen myocardial consumption and the release of renin from the kidneys. Another factor that may be involved in contributing to the antihypertensive action is the decrease of the tonic sympathetic outflow from the vasomotor centres in the brain.
It has no intrinsic sympathomimetic activity nor membrane-stabilising properties. It reduces blood pressure, and by blockade of the cardiac ß1-receptors, reduces heart rate and depresses plasma renin levels.

5.2 Pharmacokinetic properties

Absorption:

Bisoprolol is well absorbed following oral administration with a resultant bioavailability of about 90 %.

Absorption is not affected by food. T_{max} varies from 1 - 4 hours.

Distribution:

The distribution volume is 3,5 L/kg. The plasma protein binding of bisoprolol is about 30 %. Total clearance is approximately 15 L/h.

Biotransformation:

Bisoprolol undergoes minimal hepatic first-pass metabolism. 50 % of a dose is metabolised in the liver to inactive metabolites. None of the metabolites have ß1-receptor blocking action.

Elimination:

The inactive metabolites are excreted by the kidneys. The remaining 50 % is excreted unchanged via the kidneys. Total clearance is approximately 15 L/h. The plasma elimination half-life is approximately 10 to 12 hours and the duration of action is about 24 hours. Less than 2 % of the dose is excreted in the faeces.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone

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Iron oxide red (BILOCOR 10 only)

Iron oxide yellow

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Keep blister packs in carton until required for use.

6.5 Nature and contents of container

Opaque or clear Al/PVC/PVdC blister packs containing 30 tablets.

6.6 Special precautions for disposal

No special requirements.

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7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER(S)

BILOCOR 5: A38/5.2/0053

BILOCOR 10: A38/5.2/0051

9. DATE OF FIRST AUTHORISATION

08 April 2005

10. DATE OF REVISION OF THE TEXT

18 October 2024

NAMIBIA

BILOCOR 5: NS2 06/5.2/0061

BILOCOR 10: NS2 06/5.2/0062

BOTSWANA

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BILOCOR 5: S2 1101939

BILOCOR 10: S2 1101940

MOZAMBIQUE

BILOCOR 5: 4353

BILOCOR 10: 4354

ZIMBABWE

BILOCOR 5: P.P. 2018/12.3.2/5552

BILOCOR 10: P.P. 2018/12.3.2/5553