BILOCOR CO

SCHEDULING STATUS S3

1. NAME OF THE MEDICINE
BILOCOR CO 2,5/6,25 film coated tablets
BILOCOR CO 5/6,25 film coated tablets
BILOCOR CO 10/6,25 film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
BILOCOR CO 2,5/6,25: Each film coated tablet contains bisoprolol fumarate 2,5 mg and hydrochlorothiazide 6,25 mg.
BILOCOR CO 5/6,25: Each film coated tablet contains bisoprolol fumarate 5 mg and hydrochlorothiazide 6,25 mg.
BILOCOR CO 10/6,25: Each film coated tablet contains bisoprolol fumarate 10 mg and hydrochlorothiazide 6,25 mg.
BILOCOR CO film coated tablets are sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
Film coated tablets.
BILOCOR CO 2,5/6,25: Yellow coloured, film coated, round tablets debossed with "2,5" on one side and plain on the other side.
BILOCOR CO 5/6,25: Pink coloured, film coated, round tablets debossed with "5" on one side and plain on the other side.
BILOCOR CO 10/6,25: White to off white coloured, film coated, round tablets debossed with "10" on one side and plain on the other side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
BILOCOR CO is indicated for the treatment of hypertension in patients who have been stabilised on the individual components given in the same proportions.

4.2 Posology and method of administration
Posology
Adults
Antihypertensive therapy may be initiated with the lowest dose of BILOCOR CO, one 2,5/6,25 mg tablet once daily. Subsequent dose adjustment may be carried out with BILOCOR CO tablets up to the maximum recommended dose of one 10/6,25 mg tablet once daily as appropriate.
Withdrawal of BILOCOR CO therapy should be achieved gradually over a period of about two weeks. Patients should be carefully monitored. A daily dose of 10 mg should not be exceeded in patients with mild to moderate renal or hepatic impairment.

Special populations
Elderly
Dosage adjustment on the basis of age is not usually necessary, unless there is also significant renal or hepatic dysfunction.

Paediatric population
Efficacy and safety in children less than 12 years have not been established (see section 4.4).

Method of administration
For oral administration.

Missed dose:
Medical practitioners should advise patients who forget to take BILOCOR CO to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications
BILOCOR CO is contraindicated in:
- hypersensitivity to bisoprolol or to any of the ingredients of BILOCOR CO
- hypersensitivity to hydrochlorothiazide or other sulphonamide derived medicines
- patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinoma of the skin and lip
- second and third-degree heart block and bradycardia (less than 50 beats per minute)
- pregnancy and lactation (see section 4.6)
- uncontrolled cardiac failure
- cardiogenic shock
- severe hypotension (systolic blood pressure of less than 100 mHg)
- metabolic acidosis
- sinus bradycardia (less than 50 beats per minute)
- hyperthyroidism, as clinical manifestations may be masked
- bronchospasm or asthma, or patients with a history of bronchitis or chronic respiratory diseases
- late stage peripheral vascular diseases and Raynaud's phenomenon
- Addison's disease
- severe renal impairment (creatinine clearance < 30 ml/minute)
- severe hepatic impairment, in whom encephalopathy may be precipitated (see section 4.4)
- phaeochromocytoma
- sick sinus syndrome.

4.4 Special warnings and precautions for use
Peripheral vascular disease and Raynaud's phenomenon
The development of Raynaud's phenomenon may occur with the use of BILOCOR CO due to unopposed arteriolar alpha-sympathomimetic activation. Peripheral gangrene may be precipitated (see section 4.3).

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies. Photosensitising actions of HCTZ could act as a possible mechanism for NMSC.
Patients taking BILOCOR CO should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. BILOCOR CO should not be used by patients who have had previous and/or current basal cell carcinoma and/or squamous cell carcinomas of the skin or lip (see section 4.3).

Quinidine
A potentially life threatening reaction may occur between BILOCOR CO and quinidine. The thiazide induced K+ depletion worsens the quinidine-induced torsade de pointes and the bisoprolol aggravates these effects further.

Anaesthesia
If the decision is made to withdraw BILOCOR CO before anaesthesia, at least 48 hours should be allowed to elapse between the last dose and surgery. If BILOCOR CO is to be continued, care should be taken when using anaesthetics such as ether, cyclopropane and trichloroethylene.
Atropine (1 - 2 mg intravenous (IV)) may be used to correct vagal dominance.
The patient must be maintained on the usual dosage perioperatively to avoid aggravation of angina pectoris or hypertension.

Metabolic and endocrine effects
Diabetic patients
Particular caution should be taken in diabetes mellitus, as symptoms and signs of hypoglycaemia, such as tachycardia, may be masked by BILOCOR CO, and response to hypoglycaemia is diminished. BILOCOR CO may also delay recovery of insulin-induced hypoglycaemia.
Hydrochlorothiazide diuretics as in BILOCOR CO may impair glucose tolerance. Dosage adjustment of antidiabetic medicines, including insulin, may be required.

Calcium levels
Decreased urinary calcium excretion caused by hydrochlorothiazides may result in intermittent and a slightly raised serum calcium concentration. Should marked hypercalcaemia occur, it may be evidence of underlying hyperparathyroidism. BILOCOR CO therapy should be discontinued before carrying out tests for parathyroid function (see section 4.3). Increased cholesterol and triglyceride levels may be a result of hydrochlorothiazide diuretic (contained in BILOCOR CO) therapy.

Uric acid
Hydrochlorothiazide diuretics may precipitate hyperuricaemia and/or gout in certain patients.

Sensitivity reactions
In patients receiving hydrochlorothiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of hydrochlorothiazides, as contained in BILOCOR CO.

Hypovolaemia/blood loss
Tachycardiac responses, due to hypovolaemia or blood loss, may be obscured during or after surgery. Particular caution should be taken in this regard.

Renal insufficiency
Hydrochlorothiazides, such as in BILOCOR CO, should be used with caution in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min or below (i.e. moderate or severe renal insufficiency). The dosage of BILOCOR CO should be adjusted in patients with renal impairment (see section 4.2).

Hepatic disease
Caution should be exercised when hydrochlorothiazides, as in BILOCOR CO, are used in patients with hepatic impairment or progressive liver disease, as minor alterations of fluid and electrolyte balance may precipitate hepatic coma in these patients.

Antidysrhythmic medicines
Care should be taken in prescribing BILOCOR CO together with class 1 antidysrhythmic medicines such as disopyramide, myocardial depressants and inhibitors of atrioventricular (AV) conduction such as calcium antagonists.
BILOCOR CO 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 within 48 hours of discontinuing the other. The intravenous administration of calcium antagonists and antidysrhythmic medicines should be avoided during therapy with BILOCOR CO.

Anaphylaxis
BILOCOR CO may increase sensitivity towards allergens and the incidence of anaphylactic reactions. Treatment of anaphylaxis with adrenaline (epinephrine) does not always have the expected effect.

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. If BILOCOR CO is administered in these circumstances, the unopposed alpha receptor stimulation may potentiate this effect. If BILOCOR CO and clonidine are given concurrently, the clonidine should not be discontinued until several days after the withdrawal of BILOCOR CO as severe rebound hypertension may occur.

Abrupt discontinuation of therapy
Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischaemic heart disease. Discontinuation of therapy should be gradual (see section 4.2). Patients should be advised to limit the extent of their physical activity during the period that BILOCOR CO is being discontinued.

Psoriasis
Patients with psoriasis should be given BILOCOR CO with caution.

Long-term beta blocker therapy
Digitalisation of patients receiving long-term beta blocker therapy 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 (see section 4.5).

Contact lenses
BILOCOR CO may reduce tear flow causing irritation of the eye in contact lens wearers.

Ocular Effects:
Hydrochlorothiazide, such as in BILOCOR CO, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. The risk is greater in patients with a history of sulphonamide or penicillin allergy. Symptoms include active onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of therapy initiation. Primary treatment is discontinuation of BILOCOR CO as rapidly as possible. Untreated acute angle-closure glaucoma can lead to permanent vision loss. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled.

Electrolyte imbalance
Hyponatraemia and hypochloraemia may occur. Hypochloraemic alkalosis and hypokalaemia may also occur, but its likelihood is reduced by the presence of bisoprolol in the combination with hydrochlorothiazide. All patients should be carefully observed for signs of fluid and electrolyte imbalance, especially in the presence of vomiting or during parenteral fluid therapy. Elderly patients are at higher risk of electrolyte imbalance.

Prinzmetal's angina
Cases of coronary vasospasm have been observed. Despite its high beta,-selectivity, angina attacks cannot be completely excluded when bisoprolol is administered to patients with Prinzmetal's angina.

Paediatric population
Safety and efficacy in children have not been established.

4.5 Interaction with other medicines and other forms of interaction
Combinations not recommended
- calcium channel blockers, such as verapamil and diltiazem should not be given concomitantly with BILOCOR CO (see section 4.4)
- BILOCOR CO, containing bisoprolol, may potentiate the effect of other concomitantly administered antihypertensives. Centrally acting antihypertensives, such as methyldopa, may worsen heart failure by a decrease in central sympathetic tone
- concomitant use of BILOCOR CO with hypoglycaemic medicines, phenothiazines and various antidysrhythmic medicines can have life-threatening consequences for example:
  - profound hypoglycaemia with oral hypoglycaemic medicines and insulin
  - impaired myocardial function with antidysrhythmic medicines such as lidocaine, quinidine, disopyramide, flecainide and propafenone.

Combinations to be used with caution
- strong inducers of the hepatic cytochrome P450 isoenzymes, CYP3A4 and CYP2D6, such as rifampicin and the barbiturates, may shorten the half-life of bisoprolol. An increase in the dose of BILOCOR CO however, is generally unnecessary with rifampicin
- strong inhibitors of the hepatic cytochrome P450 isoenzymes CYP3A4 and CYP2D6, such as cimetidine, erythromycin, fluoxetine and hydralazine may increase the half-life of bisoprolol. The pharmacokinetics of bisoprolol are not significantly influenced by cimetidine
- topical beta blocker eye drops may add to the systemic side effects of BILOCOR CO
- beta-adrenoceptor stimulating medicines (such as dopamine, dobutamine and isoprenaline) may antagonise the effects of BILOCOR CO
- alpha-adrenoceptor stimulants, such as pseudoephedrine and phenylephrine, as well as adrenergic neurone blocking medicines such as reserpine may lead to life-threatening vasoconstriction in combination with BILOCOR CO
- BILOCOR CO and digoxin may be used concomitantly for patients with congestive heart failure provided that the pulse rate and patient response is monitored (see section 4.4)
- BILOCOR CO, containing thiazides, may increase the responsiveness to neuromuscular blockers such as atracurium and other competitive muscle relaxants
- potentiation of orthostatic hypotension caused by thiazides may occur with concurrent use of BILOCOR CO with alcohol, barbiturates or narcotics
- concomitant use of a thiazide diuretic with corticosteroids or adrenocorticotropic hormone (ACTH), may intensify electrolyte depletion and hypokalaemia
- thiazide diuretics may decrease response to pressor amines e.g. adrenaline (epinephrine). This decrease in response is not sufficient to preclude the use of pressor amines
- nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin may reduce the antihypertensive effects of beta-adrenergic blocking medicines, such as BILOCOR CO, possibly by inhibiting renal prostaglandin synthesis and/or causing sodium and fluid retention
- severe hyponatraemia has occurred in patients taking trimethoprim or carbamazepine with BILOCOR CO.

4.6 Fertility, pregnancy and lactation
Do not use BILOCOR CO during pregnancy and lactation (see section 4.3).

Pregnancy
Administration of BILOCOR CO to pregnant mothers shortly before birth or during labour may result in hypotonia, bradycardia, collapse or hypoglycaemia in the newborn (see section 4.3). Hydrochlorothiazides cross the placental barrier and appear in cord blood. Hazards include foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which occur in the adult.

Breastfeeding
Hydrochlorothiazides appear in human milk. If BILOCOR CO is deemed essential, the patient should stop breastfeeding.

Fertility
There is no data on fertility with BILOCOR CO.

4.7 Effects on ability to drive and use machines
BILOCOR CO has a moderate influence on the ability to drive and use machines.
Patients should be advised not to drive or use machinery if dizziness or drowsiness is experienced.

4.8 Undesirable effects
a. Summary of the safety profile
Adverse reactions are more common in patients with renal decompensation.

b. Tabulated list of adverse reactions
Side effects for bisoprolol

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	*Frequent* *Less frequent*	Thrombocytopaenia Leukopaenia
Immune system disorders	*Less frequent*	Hypersensitivity (allergic) reactions
Endocrine disorders	*Frequency unknown*	Hypoglycaemia
Metabolism and nutrition disorders	*Frequency unknown*	Metabolic disturbances increase in uric acid levels, hypercholesterolaemia
Psychiatric disorders	*Less frequent* *Frequency unknown*	Anxiety, nervousness, mental depression, nightmares and vivid dreams Psychosis, hallucinations
Nervous system disorders	*Frequent* *Less frequent* *Frequency unknown*	Drowsiness, unusual tiredness or weakness, sleep disorders or trouble sleeping Dizziness, mild headache, restlessness, syncope Lassitude, paraesthesia
Eye disorders	*Less frequent* *Frequency unknown*	Dry, sore eyes, reduced tear flow, conjunctivitis Disturbances of vision
Ear and labyrinth disorders	*Frequency unknown*	Transient hearing loss
Cardiac disorders	*Less frequent*	Bradycardia and congestive heart failure, heart block, dysrhythmias
Vascular disorders	*Less frequent* *Frequency unknown*	Fluid retention, reduced peripheral circulation, orthostatic hypotension Exacerbation of peripheral vascular disease or the development of Raynaud's phenomenon. Peripheral gangrene may be precipitated, paradoxical hypertension
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Allergic rhinitis, nasal congestion, bronchoconstriction or bronchospasm may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases
Gastrointestinal disorders	*Less frequent* *Frequency unknown*	Nausea, vomiting, diarrhoea, constipation Mass gain, stomatitis
Hepatobiliary disorders	*Less frequent* *Frequency unknown*	Hepatotoxicity Raised liver enzymes
Skin and subcutaneous tissue disorders	*Less frequent* *Frequency unknown*	Skin rash, psoriasiform eruption Perspiration, alopecia
Musculoskeletal, connective tissue and bone disorders	*Less frequent* *Frequency unknown*	Back pain or joint pain, chest pain Muscle cramps, myopathy, skeletal muscle weakness
Reproductive system and breast disorders	*Frequent*	Decreased sexual ability
General disorders and administrative site conditions	*Less frequent*	Asthenia

Side effects for hydrochlorothiazide

System Organ Class	Frequency	Side effects
Neoplasms benign and malignant (including cysts and polyps)	*Frequency unknown*	Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)
Blood and lymphatic system disorders	*Less frequent* *Frequency unknown*	Hyperuricaemia, thrombocytopaenia, blood dyscrasias Leukopaenia, aplastic anaemia, haemolytic anaemia, agranulocytosis, hyperglycaemia, glycosuria, neutropaenia, bone marrow depression
Immune system disorders	*Less frequent*	Anaphylactic reactions
Endocrine disorders	*Less frequent* *Frequency unknown*	Pancreatitis Sialadenitis
Metabolism and nutrition disorders	*Frequent* *Less frequent*	Electrolyte imbalance including hyponatraemia, hypochloraemic alkalosis, hypokalaemia Anorexia, metabolic disturbances, hyperglycaemia, hyperuricaemia precipitating attacks of gout, hypomagnesaemia
Psychiatric disorders	*Frequent* *Less frequent*	Restlessness Depression, sleep disturbances
Nervous system disorders	*Frequent* *Less frequent* *Frequency unknown*	Vertigo, fever, restlessness, seizures Headache, dizziness, paraesthesia Light-headedness
Eye disorders	*Frequency unknown*	Xanthopsia, transient blurred vision, choroidal effusion
Cardiac disorders	*Frequency unknown*	Cardiac dysrhythmias
Vascular disorders	*Less frequent* *Frequency unknown*	Postural hypotension Necrotising vasculitis (cutaneous vasculitis)
Respiratory, thoracic and mediastinal disorders	*Frequency unknown*	Respiratory distress including pneumonitis and pulmonary oedema
Gastrointestinal disorders	*Frequent* *Less frequent*	Gastrointestinal disturbances, dry mouth Gastric irritation, nausea, vomiting, constipation, diarrhoea, intestinal ulceration (in tablets containing thiazides with an enteric-coated core of potassium chloride), cramping
Hepatobiliary disorders	*Less frequent*	Jaundice (intrahepatic cholestatic jaundice)
Skin and subcutaneous tissue disorders	*Less frequent* *Frequency unknown*	Photosensitivity Purpura, urticaria, activation of worsening psoriasis or inducing a psoriasis-like rash, erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, urticaria
Musculoskeletal, connective tissue and bone disorders	*Frequent* *Less frequent*	Muscle pain and cramps Muscle spasm
Renal and urinary disorders	*Frequent* *Less frequent* *Frequency unknown*	Oliguria Glycosuria, urinary excretion of calcium is reduced Renal failure, renal dysfunction and interstitial nephritis
Reproductive system and breast disorders	*Less frequent*	Impotence
General disorders and administrative site conditions	*Frequent* *Frequency unknown*	Thirst, weakness Fever
Investigations	*Less frequent* *Frequency unknown*	Adverse changes in plasma lipids have been noted but their clinical significance is unclear Increases in cholesterol and triglycerides

Eye disorders: Cases of choroidal effusion with visual field defect have been reported after the use of thiazide and thiazide-like diuretics.

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.
An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of BILOCOR CO.

4.9 Overdose
Signs and symptoms:
Bisoprolol
Overdosage may produce bradycardia, severe hypotension and/or third degree AV block. Bronchospasm and heart failure may be produced. Cases of overdose should be observed for at least 4 hours, as apnoea and cardiovascular collapse may appear suddenly.

Hydrochlorothiazide
The most common signs and symptoms observed are those caused by electrolyte depletion [hypokalaemia, hypochloraemia, hyponatraemia] and dehydration resulting from excessive diuresis. If digitalis has been used concomitantly, hypokalaemia may accentuate cardiac dysrhythmias.

Management of overdose:
Bisoprolol
Repeated activated charcoal may be necessary in overdose, intravenous 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 intravenous aminophylline or inhaled or intravenous $beta_2$ adrenergic agonist e.g. salbutamol.

Hydrochlorothiazide
In massive overdosage, treatment is symptomatic and supportive. Recommended treatment for overdose includes supportive, symptomatic treatment, monitoring of serum electrolyte concentrations and renal function and immediate institution of appropriate treatment for hypokalaemia. Correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures. If required, give oxygen or artificial respiration for respiratory impairment. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Beta blocking agents, selective, and thiazides
ATC code: C07BB07
Pharmacological classification: A. 7.1.3 Other hypotensives

Mechanism of action
BILOCOR CO is a combination of bisoprolol and hydrochlorothiazide.
Bisoprolol is a selective β1-adrenoceptor antagonist devoid of intrinsic sympathomimetic and membrane-stabilising activity.
Hydrochlorothiazide is a thiazide diuretic. It affects the distal renal tubular mechanism of electrolyte reabsorption and increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. The mechanism of the antihypertensive effects of the thiazides is unknown.

Non-melanoma skin cancer: Based on available data from epidemiological studies, a cumulative dose-dependent association between hydrochlorothiazide (HCTZ) and non-melanoma skin cancer (NMSC) has been observed. One study included a population comprised of 71 533 cases of basal cell carcinoma (BCC) and of 8 629 cases of squamous cell carcinoma (SCC) matched to 1 430 833 and 172 462 population controls, respectively. High HCTZ use (≥ 50 000 mg cumulative) was associated with an adjusted odds-ratio (OR) of 1,29 (95 % CI: 1,23 - 1,35) for BCC and 3,98 (95 % CI: 3,68 - 4,31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. A 50 000 mg cumulative dose corresponds to 12,5 mg HCTZ taken daily for about 11 years.

Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip cancer were matched with 63 067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2,1 (95 % CI: 1,7 - 2,6) increasing to OR 3,9 (3,0 - 4,9) for high use (~ 25 000 mg) and OR 7,7 (5,7 - 10,5) for the highest cumulative dose (~ 100 000 mg) (see section 4.4).

Incidence rates of NMSC depend on skin phenotypes and other factors leading to different baseline risks and varying incidence rates in different countries. Estimated incidence rates vary across different regions in Europe and are estimated at rates of around 1 - 34 cases per 100 000 inhabitants per year for SCC and 30 - 150 per 100 000 inhabitants per year for BCC. Based on the results of the two Danish epidemiological studies, this risk may increase approximately 4 - 7,7-fold for SCC and 1,3-fold for BCC depending on the cumulative dose of HCTZ.

5.2 Pharmacokinetic properties
Absorption:
Bisoprolol
Bisoprolol is well absorbed following oral administration with a resultant bioavailability of about 90 %.

Hydrochlorothiazide
Hydrochlorothiazide is not metabolised.

Distribution:
Hydrochlorothiazide
Hydrochlorothiazide crosses the placental barrier but not the blood-brain barrier.

Biotransformation:
Bisoprolol
Bisoprolol undergoes minimal hepatic first-pass metabolism.

Hydrochlorothiazide
The plasma half-life has been observed to vary between 5,6 and 14,8 hours after 24 hour observation. It is reported to have a bioavailability of about 65 - 70 %. At least 61 % of the oral dose is eliminated unchanged within 24 hours.

Elimination:
Bisoprolol
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 - 12 hours and the duration of action is about 24 hours.

Hydrochlorothiazide
Hydrochlorothiazide is eliminated rapidly by the kidney.

5.3 Preclinical safety data
Not applicable.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Tablet core:
Colloidal silicon dioxide
Corn starch
Crospovidone
Dibasic calcium phosphate
Magnesium stearate
Microcrystalline cellulose
Pregelatinised starch.

Film Coating
Iron oxide red (5/6,25 tablet only)
Iron oxide yellow (2,5/6,25 tablet only)
Opadry white (hypromellose 6 cps, macrogol/PEG 400, titanium dioxide and polysorbate 80).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store at or below 25 °C.
Keep the blisters in the carton until required for use.

6.5 Nature and contents of container
BILOCOR CO tablets are available in clear PVC/PVDC/Aluminium foil blister strips, in a pack size of 30 tablets, placed with a leaflet in an outer carton.

6.6 Special precautions for disposal
No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Pharma Dynamics (Pty) Ltd
1st Floor Grapevine House, Steenberg Office Park
Silverwood Close
Westlake, 7945
Cape Town, South Africa
Tel: +27 21 707 7000
or 0860-PHARMA (742 762)

8. REGISTRATION NUMBERS
BILOCOR CO 2,5/6,25: A44/7.1.3/1010
BILOCOR CO 5/6,25: A44/7.1.3/1011
BILOCOR CO 10/6,25: A44/7.1.3/1012

9. DATE OF FIRST AUTHORISATION
15 August 2013

10. DATE OF REVISION OF THE TEXT
10 January 2025

NAMIBIA:
BILOCOR CO 2,5/6,25: NAM NS2 13/7.1.3/0260
BILOCOR CO 5/6,25: NAM NS2 13/7.1.3/0261
BILOCOR CO 10/6,25: NAM NS2 13/7.1.3/0262

G6089

pharma dynamics

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS S3

BILOCOR CO 2,5/6,25 film coated tablets
BILOCOR CO 5/6,25 film coated tablets
BILOCOR CO 10/6,25 film coated tablets
Bisoprolol fumarate and hydrochlorothiazide
BILOCOR CO is sugar free

Read all of this leaflet carefully before you start taking BILOCOR CO
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other healthcare provider.
- BILOCOR CO has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet
1. What BILOCOR CO is and what it is used for
2. What you need to know before you take BILOCOR CO
3. How to take BILOCOR CO
4. Possible side effects
5. How to store BILOCOR CO
6. Contents of the pack and other information

1. What BILOCOR CO is and what it is used for
BILOCOR CO is a combination tablet containing two active ingredients:
- bisoprolol fumarate, a type of medicine called a beta blocker. Bisoprolol works by changing the way your body responds to some nerve impulses, especially in the heart. It slows down your heart rate and makes it easier for your heart to pump blood around your body
- hydrochlorothiazide a class of medications called diuretics ('water pills'). It works by causing the kidneys to get rid of unneeded water and salt from the body into the urine.

BILOCOR CO is used to treat high blood pressure.

2. What you need to know before you take BILOCOR CO
Do not take BILOCOR CO if:
- you are hypersensitive (allergic) to bisoprolol, hydrochlorothiazide, or other sulphonamide derived medicines, or to any of the ingredients of BILOCOR CO (see section 6)
- you have a history of previous and/or current cancer of the skin and lip
- you have problems with a very slow heartbeat or a heart block
- you are pregnant or breastfeeding (see Pregnancy and breastfeeding)
- you suffer from uncontrolled heart failure or if you are receiving therapy for a weak heart
- you have cardiogenic shock which is a heart condition causing low blood pressure and circulatory failure
- you have very low blood pressure
- you suffer from metabolic acidosis, a condition in which the blood is too acidic
- you suffer from a condition marked by excessive production of thyroid hormones
- you suffer from asthma or from another disease causing severe breathing difficulties
- you suffer from severe blood circulation problems in your limbs (such as Raynaud's syndrome) which may cause your fingers and toes to tingle or turn pale or blue
- you have Addison's disease (your adrenal glands do not produce enough of their hormones)
- you suffer from severe kidney or liver problems
- you suffer from untreated phaeochromocytoma, which is a tumour of the adrenal gland
- you suffer from sick sinus syndrome which causes slow heartbeats, pauses (long periods between heartbeats) or irregular heartbeats (dysrhythmias).

Warnings and precautions
Take special care with BILOCOR CO:
- if you have been diagnosed with peripheral vascular disease (a circulatory condition in which narrowed blood vessels reduce blood flow to the limbs)
- treatment with hydrochlorothiazide, particularly long-term use with high doses, may increase the risk of some types of skin and lip cancer (non-melanoma skin cancer). Protect your skin from sun exposure and UV rays while taking BILOCOR CO
- taking BILOCOR CO with quinidine may cause life threatening effects on the heart
- if you are due to have an operation, tell the anaesthetist or the medical staff you are taking BILOCOR CO tablets, at least 48 hours before the operation
- if you suffer from diabetes and are taking antidiabetic medicines such as insulin you should monitor your blood for low blood glucose levels. Signs of low blood sugar, such as fast heartbeat, may be masked by BILOCOR CO
- if you have high calcium levels in your body
- if you have had gout
- if you have a history of allergies, BILOCOR CO may make it more likely that you experience an allergic reaction, or that a reaction may be more severe
- if you suffer from kidney or liver problems
- if you are taking certain medicines to treat irregular heartbeat, angina pectoris or to treat high blood pressure (e.g. disopyramide, clonidine, myocardial depressants or calcium antagonists such as verapamil)
- if you suffer from psoriasis (marked by severe skin rashes)
- if you experience sudden onset of chest pain, or if you already suffer from a mild form of angina BILOCOR CO may decrease tear flow, causing eye irritation to contact lens wearers
- if you experience a decrease in vision or eye pain. These could be symptoms of fluid accumulation in the vascular layer of the eye (choroidal effusion) or an increase of pressure in your eye. This can lead to permanent vision loss, if not treated. If you have had a penicillin or sulphonamide allergy, you can be at higher risk of developing this
- if you are experiencing a dry mouth, thirst, weakness, tiredness, drowsiness, restlessness, confusion, fits, muscle pains, cramps or weakness, low blood pressure, passing a reduced amount of urine, a fast, irregular heartbeat or nausea and vomiting as these may be signs of disturbances of the amount of different salts in your body (electrolyte imbalances). You should be carefully observed for signs of fluid and electrolyte imbalance, especially if you are vomiting or receiving parenteral fluid (intravenous) therapy. If you are an elderly patient, you may be more prone to electrolyte imbalances
- if you have Prinzmetal's angina (caused by a spasm in the heart's arteries that temporarily reduces blood flow).

Children
DO NOT give BILOCOR CO to children younger than 12 years as safety and efficacy have not been established.

Other medicines and BILOCOR CO
Always tell your healthcare provider if you are taking any other medicine. (This includes complementary or traditional medicines.)

The following medicines must not be taken with BILOCOR CO:
- you may have impaired myocardial function (problems of the heart muscle or a heart block) when taking calcium channel blockers such as verapamil (used to treat chest pain and irregular heartbeats) or diltiazem (used to treat high blood pressure or control angina (chest pain))
- you may experience a worsening of heart failure if you take BILOCOR CO with other antihypertensives such as methyldopa
- you may experience extremely low blood sugar levels when taking BILOCOR CO with oral blood sugar lowering medicine or insulin
- you may have impaired myocardial function (problems of the heart muscle or a heart block) when taking antidysrhythmic medicines used to treat an irregular or rapid heartbeat (such as lidocaine, quinidine, disopyramide, flecainide and propafenone) phenothiazines (used for mental illness) medicines in the beta-adrenoceptor agonist class (such as dopamine, dobutamine and isoprenaline) may alter the effects of BILOCOR CO
- nasal decongestants used for colds such as phenylephrine, pseudoephedrine or phenylpropanolamine may increase your blood pressure
- using reserpine with BILOCOR CO may cause life-threatening vasoconstriction (constricting of the blood vessels) causing an increase in blood pressure
- digoxin (used to improve the strength and efficiency of the heart or control the rate and rhythm of the heart) may be used with BILOCOR CO. Your doctor should monitor your pulse rate and response regularly
- the effects of strong muscle relaxants used together with general anaesthesia may be enhanced by BILOCOR CO
- a form of low blood pressure called orthostatic hypotension (that happens when standing up from sitting or lying down) may be increased when BILOCOR CO is taken with alcohol, sedatives, sleeping tablets and narcotics
- when BILOCOR CO are used for a prolonged time with medication such as corticosteroids, the hypokalaemic effect (a condition in which an inadequate amount of potassium is found in the circular bloodstream and may lead to weakness, confusion and mental depression) may be enhanced
- anti-inflammatory medication, (nonsteroidal anti-inflammatory drug (NSAID) painkillers such as indomethacin) may reduce the blood pressure lowering effects of BILOCOR CO and may cause sodium and fluid retention (the ability of the digestive system to retain salt and fluid)
- low salt content in the body may occur in patients taking trimethoprim or carbamazepine with BILOCOR CO.

BILOCOR CO with food and drink
The tablets can be taken with or without food.

Pregnancy, breastfeeding and fertility
If you are pregnant or breastfeeding your baby, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice before using BILOCOR CO.

DO NOT take BILOCOR CO if you are pregnant, plan to become pregnant, or suspect that you are pregnant. Contact your doctor, pharmacist or other healthcare professional immediately.
DO NOT take BILOCOR CO during breastfeeding.

Administration of BILOCOR CO to pregnant mothers shortly before giving birth or during labour may result in the baby being born with low blood sugar, low muscle tone and/or a slow heartbeat.

Driving and using machines
BILOCOR CO may make you drowsy. Therefore, please make sure you know how BILOCOR CO affects you before driving or using machinery.
It is not always possible to predict to what extent BILOCOR CO may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which BILOCOR CO affects them.

3. How to take BILOCOR CO
Do not share medicines prescribed for you with any other person. Always use BILOCOR CO exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure.

Adults:
Your doctor will advise you what the best dosage for you is. Therapy begins with the lowest dose of 2,5/6,25 mg per day. The maximum recommended dose is 10/6,25 mg per day. The tablets should be taken at about the same time each day.

Treatment with BILOCOR CO should not be stopped abruptly.

Children:
BILOCOR CO should not be given to children less than 12 years old (see Take special care with BILOCOR CO).

Your doctor will tell you how long your treatment with BILOCOR CO will last. Do not stop treatment early because your high blood pressure may return.
If you have the impression that the effect of BILOCOR CO is too strong or too weak, tell your doctor or pharmacist.

If you take more BILOCOR CO than you should
In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

Symptoms of overdose may include:
- irregular heartbeat, dizziness, low blood sugar, severe low blood pressure, wheezing, coughing, asthma, heart failure, electrolyte depletion, dehydration.

If you forget to take BILOCOR CO
Take the missed dose as soon as possible. However, if it is almost time for your next dose, continue to take the next tablet at the usual time. Do not take a double dose to make up for forgotten individual doses.

4. Possible side effects
BILOCOR CO can have side effects.
Not all side effects reported for BILOCOR CO are included in this leaflet. Should your general health wors