PROFESSIONAL INFORMATION (APPROVED)

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 2,5 mg bisoprolol fumarate and 6,25 mg hydrochlorothiazide.

BILOCOR CO 5/6,25: Each film coated tablet contains 5 mg bisoprolol fumarate and 6,25 mg hydrochlorothiazide.

BILOCOR CO 10/6,25: Each film coated tablet contains 10 mg bisoprolol fumarate and 6,25 mg hydrochlorothiazide.

BILOCOR CO film coated tablets are sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablets.

PROFESSIONAL INFORMATION (APPROVED)

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

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

PROFESSIONAL INFORMATION (APPROVED)

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:

Doctors 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

- 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

PROFESSIONAL INFORMATION (APPROVED)

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 torsades des 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 I.V.) may be used to correct vagal dominance.

PROFESSIONAL INFORMATION (APPROVED)

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.

PROFESSIONAL INFORMATION (APPROVED)

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

Hydrochlorothiazide's, 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

PROFESSIONAL INFORMATION (APPROVED)

Care should be taken in prescribing BILOCOR CO together with Class 1 antidysrhythmic medicines such as disopyramide, myocardial depressants and inhibitors of 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

PROFESSIONAL INFORMATION (APPROVED)

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 $beta_1$-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

PROFESSIONAL INFORMATION (APPROVED)

- 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 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
- 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.

PROFESSIONAL INFORMATION (APPROVED)

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.

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

Summary of the safety profile

Adverse reactions are more common in patients with renal decompensation.

Tabulated summary of adverse reactions

PROFESSIONAL INFORMATION (APPROVED)

Side effects for bisoprolol

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Frequent Less frequent	Thrombocytopenia Leukopenia
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

PROFESSIONAL INFORMATION (APPROVED)

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 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, thrombocytopenia, blood dyscrasias Leucopenia, aplastic anaemia, haemolytic anaemia, agranulocytosis, hyperglycaemia, glycosuria, neutropenia, 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

PROFESSIONAL INFORMATION (APPROVED)

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)

PROFESSIONAL INFORMATION (APPROVED)

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

PROFESSIONAL INFORMATION (APPROVED)

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 asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/Publications/Index/8 or http://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problemreporting-form/.

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:

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

PROFESSIONAL INFORMATION (APPROVED)

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 to 34 cases per 100 000 inhabitants per year for SCC and 30 to 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 to 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:

PROFESSIONAL INFORMATION (APPROVED)

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 to 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

PROFESSIONAL INFORMATION (APPROVED)

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 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 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

PROFESSIONAL INFORMATION (APPROVED)

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

MOZAMBIQUE:

BILOCOR CO 2,5/6,25: C5078

BILOCOR CO 5/6,25: C5079

BILOCOR CO 10/6,25: C5080