PACKAGE INSERT FOR BISOZYD CO
2,5 mg /6,25 mg; 5 mg/6,25 mg; 10 mg/6,25 mg

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

BISOZYD CO 2,5/6,25 mg

BISOZYD CO 5/6,25 mg

BISOZYD CO 10/6,25 mg

COMPOSITION

Active ingredients:

BISOZYD CO 2,5/6,25 mg: Each film coated tablet contains 2,5 mg bisoprolol fumarate and 6,25 mg hydrochlorothiazide.

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

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

Inactive ingredients:

Pregelatinised starch, calcium hydrogen phosphate anhydrous, microcrystalline cellulose, propyl gallate, colloidal anhydrous silica, crospovidone, magnesium stearate.
Sugar free.

BISOZYD CO 2,5/6,25 mg also contains Opadry Yellow (colourant) which consists of hypromellose, titanium dioxide, propylene glycol, yellow iron oxide, red iron oxide and polysorbate.

BISOZYD CO 5/6,25 mg also contains Opadry Pink (colourant) which consists of hypromellose, titanium dioxide, macrogol, red iron oxide and polysorbate.

BISOZYD CO 10/6,25 mg also contains Opadry White (colourant) which consists of hypromellose, titanium dioxide, propylene glycol and polysorbate.

PHARMACOLOGICAL CLASSIFICATION

A. 7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION

Pharmacodynamics:

BISOZYD CO is a combination of bisoprolol and hydrochlorothiazide. Bisoprolol is a selective β_1-adrenoceptor antagonist devoid of intrinsic sympathomimetic and membrane-stabilising activity. Hydrochlorothiazide is a thiazide diuretic. It affects the distal renal tubular mechanism of electrolyte re-absorption and increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium phosphate and bicarbonate. When administered chronically it decreases calcium excretion. The mechanism of the antihypertensive effects of the thiazides is unknown.

Pharmacokinetics:

Bisoprolol:

Bisoprolol is well absorbed following oral administration with a resultant bioavailability of about 90 %. Bisoprolol undergoes minimal hepatic first-pass metabolism. About 50 % of a dose is metabolized in the liver and the remainder is excreted unchanged via the kidneys. Bisoprolol is a substrate of CYP3A4 (major) and CYP2D6 (minor). The plasma elimination half-life is approximately 10 to 12 hours and the duration of action is about 24 hours.

Hydrochlorothiazide:

Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. 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. Hydrochlorothiazide crosses the placental barrier but not the blood-brain barrier.

CONTRAINDICATIONS

- Hypersensitivity to bisoprolol, hydrochlorothiazide and other sulphonamide derived agents or to any of the ingredients of **BISOZYD CO** (see **COMPOSITION**).
- Bronchoconstriction, asthma or patients with a history of obstructive airway disease.
- Second and third-degree heart block.
- Bradycardia (less than 50 beats per minute).
- Pregnancy and lactation (see **PREGNANCY AND LACTATION**).
- Cardiogenic shock.
- Uncontrolled cardiac failure.
- Hypotension (systolic blood pressure of less than 100 mm Hg).
- Porphyria.
- Patients with Addison's disease, severe renal impairment or anuria.
- Patients with severe hepatic impairment, in whom encephalopathy may be precipitated.
- Metabolic acidosis.
- Phaeochromocytoma (see **WARNINGS AND SPECIAL PRECAUTIONS**).
- Hyperthyroidism, as clinical manifestations may be masked.
- Safety and efficacy in children have not been established (see **DOSAGE AND DIRECTIONS FOR USE**).
- Late stage peripheral vascular diseases and Raynaud's phenomenon.

WARNINGS AND SPECIAL PRECAUTIONS

Digitalisation:

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.
It should be noted that **BISOZYD CO** contains hydrochlorothiazide, which may increase the toxicity of digoxin.
Diuretic induced hypokalaemia may enhance the toxicity of digoxin and increase the risk of dysrhythmias with medicine that prolong the QT interval, such as astemizole, halofantrine, pimozide, and sotalol.

Phaeochromocytoma:

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

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, and patients should be advised to limit the extent of their physical activity during the period that **BISOZYD CO** is being discontinued.

General anaesthesia:

If the decision is made to withdraw **BISOZYD CO** 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 the usual dosage perioperatively to avoid aggravation of angina pectoris or hypertension.
A patient's normal tachycardic response to hypovolaemia or blood loss during or after surgery may be obscured. Particular caution should be taken in this regard.

Other medicine:

Care should be taken in prescribing **BISOZYD CO** together with Class 1 antidysrhythmic medicines such as disopyramide, myocardial depressants and inhibitors of AV conduction such as calcium antagonists.

The intravenous administration of calcium antagonists and antidysrhythmic medicines should be avoided during therapy with **BISOZYD CO** (see **INTERACTIONS**).

BISOZYD CO should be used with caution in combination with verapamil in patients with impaired ventricular function (see **INTERACTIONS**). This combination should not be given to patients with conduction abnormalities. Neither medicine should be administered intravenously within 48 hours of discontinuing the other.

Diabetics:

Particular caution should be taken in diabetes mellitus, as symptoms and signs of acute hypoglycaemia such as tachycardia may be masked, and response to hypoglycaemia is diminished. It may also delay recovery of insulin-induced hypoglycaemia.

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

Renal insufficiency:

BISOZYD CO containing hydrochlorothiazide may not be a suitable diuretic for use in patients with renal impairment and is ineffective and contra-indicated at creatinine clearance values of 30 ml/min or below (severe renal insufficiency).

BISOZYD CO should be used with caution in patients with renal impairment as it can further reduce the renal function (see **CONTRAINDICATIONS**).

The dosage of **BISOZYD CO** should be adjusted in renal impairment and in the elderly (see **DOSAGE AND DIRECTIONS FOR USE**).

Hepatic disease:

Caution should be exercised when thiazides 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.

Metabolic and endocrine effects:

BISOZYD CO may impair glucose tolerance. Dosage adjustment of antidiabetic medicines, including insulin, may be required.

Increased cholesterol and triglyceride levels may be a result of thiazide diuretic therapy.

Fluid and electrolyte imbalance:

Hydrochlorothiazide containing medicines such as **BISOZYD CO** should be used with caution in patients with existing electrolyte disturbances or those who are at risk. All patients should be carefully observed for signs of fluid and electrolyte imbalance, especially in the presence of vomiting or during parenteral fluid therapy. Hyponatraemia, hypochloraemic alkalosis, hypokalaemia and hypomagnesaemia may occur (see **Pharmacodynamics** and **SIDE EFFECTS**).

Plasma calcium:

Decreased urinary calcium excretion caused by hydrochlorothiazide contained in **BISOZYD CO** may result in intermittent and a slightly raised serum calcium concentration. Should marked hypercalcaemia occur, it may be evidence of underlying hyperparathyroidism. **BISOZYD CO** therapy should be discontinued before carrying out tests for parathyroid function (see **INTERACTIONS**).

Uric acid:

Hydrochlorothiazide contained in **BISOZYD CO** may precipitate hyperuricaemia and/or gout in certain patients.

Sensitivity reactions:

In patients receiving thiazides, 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 hydrochlorothiazide contained in **BISOZYD CO**.

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

Effects on ability to drive and use machines

Patients should be advised not to drive or use machinery if dizziness or drowsiness is experienced.

INTERACTIONS:

- Concomitant use of **BISOZYD CO** with hypoglycaemic agents, phenothiazines and various antidysrhythmic agents can have life-threatening consequences for example:
  - Profound hypoglycaemia with oral hypoglycaemic agents and insulin.
  - Impairment of myocardial function with antidysrhythmic agents.
- Beta-adrenoceptor stimulating agents (such as dopamine, dobutamine and isoprenaline) may antagonise the effects of **BISOZYD CO.**
- Alpha$_1$-adrenoceptor stimulants such as pseudoephedrine and phenylephrine as well as adrenergic neurone blocking agents such as reserpine may lead to life-threatening vasoconstriction in combination with **BISOZYD CO**.
- Bisoprolol and digoxin may be used concomitantly for patients with congestive heart failure provided that the pulse rate and patient response is monitored. It should however be taken into account that **BISOZYD CO** also contains hydrocholorthiazide, which enhances the toxicity of digoxin due to its hypokalaemic effect (see **WARNINGS AND SPECIAL PRECAUTIONS**).

- Hydrochlorothiazide may increase the responsiveness to competitive neuromuscular blockers.
- Potentiation of orthostatic hypotension caused by hydrochlorothiazide contained in **BISOPROLOL HYDROCHOLORTHIAZIDE ZYDUS TABLETS** may occur with concurrent alcohol, barbiturates or narcotics use.
- Dosage adjustment of antidiabetic medicines (oral agents and insulin) may be required with the concomitant use of hydrochlorothiazide contained in **BISOPROLOL HYDROCHOLORTHIAZIDE ZYDUS**.
- Lowering of potassium levels:
  - Concomitant use of **BISOZYD CO** with corticosteroids, ACTH, digoxin, beta$_2$-adrenergic agonists, carbenoxolone, amphotericin and reboxetine may intensify electrolyte depletion and hypokalaemia, due to the hydrochlorothiazide component.
- Thiazide diuretics may decrease response to pressor amines (e.g. adrenalin). This decrease in response is not sufficient to prelude the use of pressor amines.
- NSAIDs may reduce the antihypertensive effects of beta-adrenergic blocking agents, possibly by inhibiting renal prostaglandin synthesis and/or causing sodium and fluid retention.
- Mefloquine should be used with care with **BISOZYD CO** due to increased bradycardia.
- Calcium channel blockers such as verapamil and diltiazem should be used with care with **BISOZYD CO**.
- Strong inducers of the hepatic cytochrome P450 isoenzymes, CYP3A4 and CYP2D6, such as rifampicin and the barbiturates may shorten the half-life of **BISOZYD CO**. However, an increase in the dose of bisoprolol is generally unnecessary with rifampicin. Strong inhibitors of the hepatic cytochrome P450 isoenzymes, CYP3A4 and CYP2D6, may increase the half-life of **BISOZYD CO**. The pharmacokinetics of bisoprolol is not significantly influenced by cimetidine.
- **BISOZYD CO** 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.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established.

Administration of **BISOZYD CO** to pregnant mothers shortly before birth or during labour may result in hypotonia, collapse or hypoglycaemia in the newborn (see **CONTRAINDICATIONS**).
Thiazides such as hydrochlorothiazide contained in **BISOZYD CO** 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.
Thiazides appear in human milk. If **BISOZYD CO** is deemed essential, the patient should stop breastfeeding.

DOSAGE AND DIRECTIONS FOR USE

Adults:

Antihypertensive therapy may be initiated with the lowest dose of **BISOZYD CO**, one 2,5/6,25 mg tablet once daily. Subsequent dose adjustment may be carried out with **BISOZYD CO** up to the maximum recommended dose of one 10/6,25 mg tablet once daily as appropriate.
Withdrawal of **BISOZYD CO** therapy should be achieved gradually over a period of about two weeks. Patients should be carefully monitored.
The normal dose should be reduced in elderly patients, or in patients suffering from renal dysfunction.

Elderly:

Dosage adjustment based on age is not usually necessary, unless there is also renal or hepatic dysfunction (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Children:

Efficacy and safety in children have not been established.

If withdrawal of **BISOZYD CO** is planned, it should be achieved gradually over a period of about 2 weeks. Patients should be carefully observed.

SIDE EFFECTS

Adverse reactions are more common in patients with renal decompensation.

Blood and the lymphatic system disorders:

Bisoprolol

Frequent: Nonthrombocytopenic purpura, thrombocytopenia

The following has been reported but the frequency is unknown:

Agranulocytosis, transient eosinophilia.

Hydrochlorothiazide

Less frequent: Thrombocytopenia

The following has been reported but the frequency is unknown:

Leukopenia, aplastic anaemia, haemolytic anaemia, granulocytopenia.

Immune system disorders:

Bisoprolol

Less Frequent: Hypersensitivity (allergic reactions)

The following has been reported but the frequency is unknown:

Systemic lupus erythematosus, asymptomatic increase in antinuclear antibodies.

Hydrochlorothiazide

Less frequent: Anaphylactic reactions.

Endocrine disorders:

Hydrochlorothiazide

The following has been reported but the frequency is unknown:

Sialoadenitis

Metabolism and nutrition disorders:

Bisoprolol

The following has been reported but the frequency is unkown:

Hypoglycaemia, hyperglycaemia,hypercholesterolaemia.

Hydrochlorothiazide

Frequent: Electrolyte imbalance including hyponatraemia, hypochloraemic alkalosis, hypokalaemia and hypomagnesaemia, hyperglycaemia, hypercholesterolaemia.

Less frequent: Anorexia

Psychiatric disorders:

Bisoprolol

Frequent: Sleep disorders, including nightmares.

Less frequent: Restlessness, anxiety, nervousness, mental depression.

The following has been reported but the frequency is unkown:

Psychosis and hallucinations.

Hydrochlorothiazide

The following has been reported but the frequency is unknown:

Confusion, sleep disturbances.

Nervous system disorders:

Bisoprolol

Frequent: Drowsiness, unusual tiredness or weakness.

Less Frequent: Dizziness, mild headache.

The following has been reported but the frequency is unknown:

Lassitude, paraesthesia, amnesia, coma and convulsions.

Hydrochlorothiazide

The following has been reported but the frequency is unknown:

Vertigo, fever, drowsiness.

Eye disorders:

Bisoprolol

Frequent: Decreased tear production, conjunctivitis, soreness.

The following has been reported but the frequency is unknown:

Disturbances of vision.

Hydrochlorothiazide

The following has been reported but the frequency is unknown:

Xanthopsia, transient blurred vision.

Ear and labyrinth disorders:

Bisoprolol

The following has been reported but the frequency is unknown:

Transient hearing loss.

Cardiac disorders:

Bisoprolol

Less Frequent: Bradycardia and congestive heart failure, heart block, dysrhythmias.

Vascular disorders:

Bisoprolol

Less frequent: Fluid retention, reduced peripheral circulation, orthostatic hypotension.

The following has been reported but the frequency is unknown:

Exacerbation of peripheral vascular disease or the development of Raynaud's phenomenon.

Peripheral gangrene may be precipitated and paradoxical hypertension.

Hydrochlorothiazide

The following has been reported but the frequency is unknown:

Necrotising vasculitis (cutaneous vasculitis), orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:

Bisoprolol

Frequent: Bronchoconstriction or bronchospasm and dyspnoea may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases.

Less frequent: Allergic rhinitis, nasal congestion.

The following has been reported but the frequency is unknown:

Pneumonitis, pulmonary fibrosis, pleurisy.

Hydrochlorothiazide

The following has been reported but the frequency is unknown:

Respiratory distress including acute interstitial pneumonitis and pulmonary oedema.

Gastrointestinal disorders:

Bisoprolol

Less Frequent: Nausea, vomiting, diarrhoea, constipation and abdominal cramping.

The following has been reported but the frequency is unknown:

Weight gain, stomatitis.

Hydrochlorothiazide

Less frequent: Gastric irritation, nausea, vomiting, diarrhoea.

The following has been reported but the frequency is unknown:

Constipation.

Hepato-billary disorders:

Bisoprolol

Less Frequent: Hepatotoxicity.

The following has been reported but the frequency is unknown:

Raised liver enzymes.

Hydrochlorothiazide

Less frequent: Jaundice (intrahepatic cholestatic jaundice), pancreatitis, hyperuricaemia.

The following has been reported but the frequency is unknown:

Increased risk of cholecystitis.

Skin and subcutaneous tissue disorders:

Bisoprolol

Less Frequent: Skin rash, exacerbation of psoriasis.

The following has been reported but the frequency is unknown:

Perspiration, reversible alopecia.

Hydrochlorothiazide

Less frequent: Photosensitivity, yellow vision, skin rash.

The following has been reported but the frequency is unknown:

Purpura, urticaria.

Musculoskeletal, connective tissue and bone disorders:

Bisoprolol

Less Frequent: Back pain or joint pain, chest pain.

The following has been reported but the frequency is unknown:

Muscle cramps, myopathy, skeletal muscle weakness.

Hydrochlorothiazide

The following has been reported but the frequency is unknown:

Muscle pain and cramps.

Renal and urinary disorder:

Bisoprolol

The following has been reported but the frequency is unknown:

Increase in uric acid levels.

Hydrochlorothiazide

The following has been reported but the frequency is unknown:

Acute renal failure, renal dysfunction and interstitial nephritis.

Reproductive system and breast disorders:

Bisoprolol

Frequent: Decreased sexual ability.

Hydrochlorothiazide

The following has been reported but the frequency is unknown:

Male impotence.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

(See **SIDE EFFECTS**)

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.

Repeated activated charcoal may be necessary in overdose.

Atropine may be used to treat severe bradycardia. If the response is inadequate, glucagon may be given intravenously. Alternatively, dobutamine may be required to reverse beta-blockade. Cardiac pacing may be required for severe bradycardia. Bronchospasm should be treated with IV aminophylline or inhaled or IV beta$_2$-adrenergic agonist such as salbutamol.

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

IDENTIFICATION

BISOZYD CO 2,5/6,25 mg: Yellow, round, biconvex, beveled edge film coated tablets with plain surface on both sides. The tablet should be free of all physical defects.

BISOZYD CO 5/6,25 mg: Pink, round, biconvex, beveled edge film coated tablets with plain surface on both sides. The tablet should be free of all physical defects.

BISOZYD CO 10/6,25 mg: White, round, biconvex, beveled edge film coated tablets with plain surface on both sides. The tablet should be free of all physical defects.

PRESENTATION

BISOZYD CO 2,5/6,25 mg are packed in transparent PVC/PVDC / aluminium foil blisters strips. 10 tablets are placed into a blister strip. One or three blister strips with a package insert are placed in a cardboard carton.

BISOZYD CO 5/6,25 mg are packed in transparent PVC/PVDC / aluminium foil blisters strips. 10 tablets are placed into a blister strip. One or three blister strips with a package insert are placed in a cardboard carton.

BISOZYD CO 10/6,25 mg are packed in transparent PVC/PVDC / aluminium foil blisters strips. 10 tablets are placed into a blister strip. One or three blister strips with a package insert are placed in a cardboard carton.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Do not remove from outer carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS:

BISOZYD CO 2,5/6,25 mg: 43/7.1.3/0059

BISOZYD CO 5/6,25 mg: 43/7.1.3/0060

BISOZYD CO 10/6,25 mg: 43/7.1.3/0061

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

Zydus Healthcare SA (Pty) Ltd.

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0157

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