SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

BISOCARD 5 H (BISOPROLOL FUMARATE 5 MG AND HYDROCHLOROTHIAZIDE 6.25

MG TABLETS USP)

BISOCARD 10 H (BISOPROLOL FUMARATE 10 MG AND HYDROCHLOROTHIAZIDE 6.25

MG TABLETS USP)

2. Qualitative and quantitative composition

COMPOSITION:

BISOCARD 5 H : Each film coated tablet contains:

- Bisoprolol Fumarate USP 5 mg
- Hydrochlorothiazide USP 6.25 mg
- Titanium Dioxide BP (-)
- Excipients: q.s.

BISOCARD 10 H : Each film coated tablet contains:

- Bisoprolol Fumarate USP 10 mg
- Hydrochlorothiazide USP 6.25 mg
- Titanium Dioxide BP (-)
- Excipients: q.s.

* Isopropyl alcohol and Methylene Dichloride is used as solvents so does not appear in the final product.

3. Pharmaceutical form

Film coated Tablets

4. Clinical particulars

4.1. Therapeutic indication

Bisoprolol is a potent highly beta1-seiective-adrenoceptor blocking agent, Hydrochiorothiazide is a thiazide diuretic that has an anti-hypertensive action.

4.2. Posology and method of administration

Treatment of hypertension and chronic stable angina pectoris:

Dosage:

Dose titration ot each active ingredient to the individual patient is recommended. if clinically appropriate patients can be transferred from monotherapy to the fixed combination therapy.

In order to individually adjust the posology, This medicine is available in the following dosages:

<BISOCARD- 5H > 5 mg 16.25 mg, film-coated tablets

< BISOCARD- 10H > 10 mg 16.25 mg, film-coated tablets

In case of insufficient response to the treatment, the dosage should be increased to one tablet of 5 mg bisoprolol/6.25 mg hydrochlorothiazide once daily. If this last dose is insufficient, the dosage may be increased lo one tablet of 10 mg bisoprolol/6.25 mg hydrochlorothiazide once daily.

If the treatment needs to be interrupted, a progressive suspension of the Bisoprolol treatment is recommended. A sudden withdrawal of bisoprolol may result in a serious deterioration of the patient's condition, especially in patients suffering from ischaemic heart disease.

Special populations

Renal or liver impairment

No change in dosage is necessary in the case of mild to moderate hepatic insufficiency or mild to moderate renal insufficiency (creatinine clearance> 30 ml/min).

Elderly

No dosage adjustment is usually required.

Paediatric population

The safety and efficacy of this medicine in children has not yet been established.

There is no paediatric experience with this medicine therefore its use cannot be recommended for children.

Method of administration

For oral use.

This medicine should be taken in the morning and may be taken with food. The tablets must be swallowed with some liquid and must not be chewed.

This medicine is generally a long-term therapy.

4.3. Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1, or to other thiazides or sulphonarnides.

• Severe bronchial asthma or severe chronic obstructive pulmonary disease;

• Acute heart failure or during episodes of heart failure decompensation requiring intravenous inotropic therapy;

• Cardiogenicshock;

• Sick sinus syndrome;

• Sinoatrial block;

• Second or third degree atria-ventricular block;

• Symptomatic bradycardia;

• Untreated phaeochromocytoma;

• Severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome;

• Metabolic acidosis;

• Severe renal impairment (creatinine clearances 30ml/min);

• Severe hepatic impairment;

• Refractory hypokalaemia;

• Severe hypercalcaemia.

4.4. Special warnings and precautions for use

The cessation of therapy with P-blockers (e.g. bisoprolol) should not be done abruptly unless clearly indicated. After long-term therapy - particularly in the presence of ischaemic heart disease bisoprolol fumarate/hydrochlorothiazide should be discontinued gradually (dividing in hall the dose over 7-10 days), since an abrupt withdrawal may lead to an acute deterioration of the patient's condition.

PATIENTS WITH ANY OF THE FOLLOWING SHOULD BE MONITORED CLOSELY:

• Heart failure (in patients with concomitant stable chronic heart failure the treatment has to be initiated with the monopreparation of bisoprolol fumarate using a special titration phase).

• Diabetes mellitus showing large fluctuations in blood glucose values; symptoms of giycaemia can be masked.

• Strict fasting.

• AV block of 1st degree

• Prinzmetal's angina.

• Peripheral arterial occlusive disease (intensification of the complaints might happen Hypovolaemia.

• Reduced liverfunction,

As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. This also applies lo desensitisation therapy. Adrenaline treatment may not always give the expected therapeutic effect.

Patients with psoriasis or with a history of psoriasis should only be given β-blockers (e.g. bisoprolol) after carefully balancing the benefits against the risks.

Undertreatment with β-blockers (e,g, bisoprolol) the symptoms of a thyrotoxicosis may be masked.

In patients with phaeochromocytoma β-blockers (e.g. bisoprolol) must not be administered until after alphareceptor blockade.

In patients undergoing general anaesthesia: The anaesthetist must be aware of beta-blockade. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia. Patients undergoing concomitant treatment with inhalation anaesthetics should be monitored closely.

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; therefor the dose of β 2-stimulants may have to be increased, Patients, with bronchospasms (bronchial asthma, obstructive airway diseases) should be monitored closely.

If photosensitivity reactions occur, it is recommended to protect exposed areas to the sun or to artificial UVA light. in severe cases it may be necessary to stop the treatment.

Due to the hydrochlorothiazide component the long-term, continuous administration of bisoprolol fumarate/hydrochlorothiazide may lead to disturbance of the fluid and electrolyte balance, especially to hypokalaemia and hyponatraemia, further to hypomagnesaemia and hypochloraemia, as well as hypercalcaemia Hypokalaemia facilitates the development of severe arrhythmias, particularly torsades de points, which may be fatal.

During long term-therapy with bisoprolol fumarate/hydrochlorothiazide, the serum electrolytes (especially potassium, sodium, and calcium), creatinine and urea, the serum lipids (cholesterol and triglycerides), uric acid as well as blood glucose should be monitored regular1y.

During treatment with bisoprolol fumarate/ hydrochlorothiazide patients should ensure an adequate supply of fluid and food rich in potassium (e.g. bananas, vegetables, nuts) to compensate for the increased loss of potassium. The potassium losses may be reduced or prevented by concomitant therapy with potassium-sparing diuretics.

In patients with hyperuricaemia the risk for attacks of gout may be increased.

Metabolic alkalosis may worsen due to disturbance of fluid and electrolyte haemostasis.

In patients with cholelithiasis acute cholecystitis has been reported.

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 based on the Danish National Cancer Registry. Photosensitising actions of HCTZ could act as a possible meci1anism for NMSC.

Patients taking HCTZ 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 minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma

Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours lo weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glauooma may include a history of sulfonamide or penicillin allergy.

4.5. Interaction with other medicinal products and other forms of interaction

General information

It should be considered that due to serum potassium disturbances certain medicinal products may be affected.

Contraindicated combinations

Floctafenine: Bisoprolol may inhibit compensatory cardiovascular reactions to floctafenine-induced hypotonia or shock.

Sultopride: concomitant administration with bisoprolol may lead to an increased risk for ventricular arrhythmia

Combinations not recommended

Lithium: Bisoprolol fumarate/hydrochlorothiazide may intensify the cardiotoxic and neurotoxic effect of lithium through a reduction of lithium excretion.

Calcium antagonists such as the verapamil type and the diltiazem type: Negative influence on contractility and atria-ventricular conduction. Intravenous

administration of verapamil in patients on β-blocker treatment may lead to profound hypotension and atrioventricular block.

Centrally-acting antihypertensive agents (e.g. reserpine, alpha-methyldopa, guanfacine, clonidine):

Concomitant use of centrally-acting antihypertensive agents may lead to a further reduction in heart rate and cardiac output and to vasodilatation. Abrupt withdrawal may increase the risk of 'rebound hypertension'. These must not be discontinued unless the use of bisoprolol fumarate/ hydrochiorothiazide was stopped some days before. This may be then followed by the stop-wise withdrawal of the centrallyacting anti hypertensive agent.

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

Non-antiarrhythmic medicinal products that may induce torsades de pointes: astemizole, IV erythromycin, halofantrine, pentamidine, sparfloxacin, terfenadine, vincamine. Hypokalaemia may facilitate the occurrence of torsades de pointes. In case of hypokalaemia use medicinal products that do not produce torsades de pointes.

Combinations to be used with caution

Calcium antagonists such as dihydropyridine derivatives (e.g. nifedipine): 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.

Concomitant use with other antihypertensive agents or with other medicinal products with blood pressure lowering potential may increase the risk of hypotension.

ACE inhibitors (e.g, enalapril, captopril), Angiotensin II antagonists (e.g, losartan): Risk of significant fall in blood pressure and/or acute renal failure during initiation of ACE inhibitor therapy in patients with pre-existing sodium depletion (particularly in patients with renal artery stenosis).

If prior diuretic therapy has produced sodium depletion, either stop the diuretic 3 days before starting ACE inhibitor therapy, or initiate ACE inhibitor therapy at a low dose.

Class-I antiarrhythmic agents (e.g. disopyrarr1ide, quinidine): Effect on atria-ventricular conduction time may be potentiated and negative inotropic effect increased.

Ciass-111 antiarrhythmic agents (e.g. amiodarone): Effect on atrio- ventricular conduction time may be potentiated.

Antiarrhythmic medicinal products that may produce torsades de pointes: Class IA medicinal products (quinidine, disopyramide), amiodarone, sotalo!. Prevent and, if necessary, correct hypokalaemia. Monitor

QT interval. In case of torsades de pointes do not administer antiarrhythmics (electrical pacing).

Parasympathomimetic medicinal products (including tacrine): Atrio-ventricular conduction time and the risk of bradycardia may be increased.

Topical β-blockers, including eye drops, may add to the systemic effects of bisoprolol.

Insulin and oral antidiabetic agents: intensification of blood sugar lowering effect Blockade of βadrenoceptors may mask symptoms of hypoglycaemia,

Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension.

Continuation of β-blockade reduces the risk of arrhythmia during induction and intubation. The anaesthesiologist should be informed when the patient is receiving a β-blocker (e.g. bisoprolol)

Digitalis glycosides: Prolongation of atria-ventricular conduction time, reduction in heart rate. in hypokalaemia and/or hypomagnesaemia developing during treatment with bisoprolol fumarate/ hydrochlorothiazide the myocardium may show increased sensitivity to cardiac glycosides, thus leading to a potentiation of their effects and adverse effects of the glycosides.

Prostaglandin synthetase inhibiting medicinal products: Decreased hypotensive effects. In high-dose salicylate administration the toxic offed of salicylates on the central nervous system may be potentiated.

Non-steroidal anti-Inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect

In patients developing hypovolaemia the concomitant administration of non-steroidal anti-inflammatory medicinal products (NSAID's) can trigger acute renal failure.

Beta-sympathomimetics: Combination with bisoprolol may reduce the effect of both agents.

Sympathomimetic medicinal products: Combination with bisoprolol may reduce the effect of both medicinal products. Higher doses of epinephrine may be necessary for treatment of allergic reactions.

Sympathomimetics that activate both beta- and alpha-adrenoceptors: Combination with bisoprolol may lead to blood pressure increase. Such interactions are considered to be more likely with nonselective betablockers.

The concurrent use of bisoprolol fumarate/hydrochlorothiazide and potassium-wasting agents (e.g.

glucocorticoids, ACTH, carbenoxolone, amphotericin B, furosemide or laxatives) may result in increased potassium losses.

Methyldopa: haemolysis duo to the formation of antibodies to hydrochlorothiazide has been described in isolated cases.

The effect of uric-acid-lowering medicinal products may be attenuated in concomitant administration of bisoprolol fumarate/hydrochlorothiazide.

Cholestyramine, colestipol: reduces the absorption of the hydrochlorothiazide component of bisoprolol fumarate/hydrochlorothiazide.

Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

Tricyclicantidepressants, barbiturates, phenothiazines: Increased blood pressure lowering effect.

Rifampicin: Slight reduction of the half-life of bisoprolol possible doe to the induction of hepatic medicinal product-metabolising enzymes. Normally a dosage adjustment is not necessary.

The effect of curare-type muscle relaxants may be potentiated or prolonged by bisoprolol fumarate/ hydrochlorothiazide.

Cytostatics (e.g. cyclophosphamide, fluorouracil, methotrexate): increased bone marrow toxicity is to be expected.

Other concomitant treatment that should be used with caution: oral anticoagulants (the antithrombotic effect can be reduced by the use thiazides) and probenecid (diminished diuretic action).

Combinations to be considered

Mefloquine: increased risk of bradycardia.

Corticosteroids: Reduced antihypertensive effect.

4.6. Fertility, pregnancy and lactation

Pregnancy

There is limited experience with hydrochlorothiazide or bisoprolol during pregnancy

This medicine should not be used during pregnancy unless clearly necessary.

Breast-.feeding

This medicine is not recommended in breastfeeding women.

Fertility

There are no nonclinical date with Hydrochlorothiazide and bisoprolol.

As with some other drugs used in the treatment of hypertension, clinical reports have suggested that hydrochlorothiazide and bisoprolol may occasionally induce impotence in males.

4.7. Effects on ability to drive and use machines

Bisoprolol Fumarate and Hydrochlorothiazide has no or negligible influence on the ability to drive and use machines. The ability to actively participate in driving or operating machinery may be impaired through individual different reactions to the medical product.

This should be taken into consideration especially in early treatment and upon change of medication and in combination with alcohol.

4.8. Undesirable effects

The following definitions apply to the frequency terminology used hereafter:

Very common (≥ 1/10)

Common (≥ 1/100 to 1/10)

Uncommon (≥ 1/1,000 to 1/100)

Rare (≥ 1/10,000, to 1/1,000)

Very rare (< 1/10,000) including isolated cases

Blood and lymphatic system disorders

Rare: leucopenia, thrombocytopenia

Very rare: agranulocytosis

Metabolism and nutrition disorders

Uncommon: loss of appetite, hyperglycaemia, hyperuricaemia, disturbances of fluid and electrolyte balance (in particular hypokalaemia and hyponatraemia, also hypomagnesaemia and hypochloraemia, as well as hypercalcaemia)

Very rare: metabolicalkalosis

Psychiatric disorders

Uncommon: depression, sleep disorders Rare: nightmares, hallucinations

Nervous system disorders

Common: dizziness*, headache*

Eye disorders

Rare: decreased tearflow (to be taken into consideration in patients wearing contact lenses), visual disturbances.

Very rare: conjunctivitis

Ear and labyrinth disorders

Rare: hearing disorders

Cardiac disorders

Uncommon: bradycardia, atria-ventricular conduction disorders, worsening of pre-existing heart Failure

Vascular disorders

Common: feeling of coldness or numbness in extremities

Uncommon: orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Uncommon: bronchospasm in patients with bronchial asthma or history of obstructive airways disease

Rare: allergic rhinitis

Gastrointestinal disorders

Common: gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation

Uncommon: abdominal complaints

Very rare: pancreatitis

Hepatobiliary disorders

Rare: hepatitis, jaundice

Skin and subcutaneous tissue disorders

Rare: hypersensitivity reactions such as itching, flush, rash, photodermatitis, purpura, urticaria

Very rare: alopecia, cutaneous lupus erythematosus. Beta-blockers may provoke or worsen psoriasis or induce a psoriasis-like rash, anaphylactic reactions, toxic epidermal necrolysis (Lyell's syndrome).

Musculoskeletal and connective tissue disorders

Uncommon: muscle weakness, muscle cramps

Reproductive system and breast disorders

Rare: potency disorders

General disorders and administration site conditions

Common: fatigue*

Uncommon: asthenia

Very rare: chest pain

Investigations

Uncommon: increase in amylases, reversible increase of serum creatinine and urea, increased triglyceride and cholesterol levels, glucosuria

Rare: increase in hepatic enzymes (ASAT, ALAT)

*These symptoms appear especially at the beginning of the treatment. They are generally mild and disappear most of the time within one to two weeks.

Reporting of suspected adverse reactions

Health care professionals are asked to report any suspected adverse reactions via the https://pv.pharmacyboardkenya.org

4.9. Overdose

Symptoms

The most common signs expected with overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. 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. The clinical picture in acute or chronic overdose of hydrochlorothiazide is characterised by the extent of fluid and electrolyte loss.

Most common signs are dizziness, nausea, somnolence, hypovolaemia, hypotension and hypokalaemia.

Management

In general, if overdose occurs, discontinuation of this medicine and supportive and symptomatic treatment is recommended.

Bradycardia: administer atropine intravenously. If the reaction is insufficient, isoprenaline or another agent with positive chronotropic properties may be administered cautiously. in certain cases, the insertion of a transvenous cardiac stimulator may be required.

Hypotension: vascular filling and vasopressive substances must be administered intravenously.

Atria-ventricular block (second and third degree): the patients must be monitored and treated with an isoprenaline infusion or the insertion of an intravenous cardiac stimulator.

Acute aggravation of heart failure: administer diuretics, inotropicagents, vasodilator agents via I.V.

Bronchospasm: administer a broncho-dilator treatment such as isoprenaline, beta 2 sympathomimetic substances and/or aminophylline.

Hypoglycaemia: administer glucose intravenously.

Limited data suggest that bisoprolol is hardly dialyzable. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

5. Pharmacological properties

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Selective beta blocking agent and thiazide diuretic

ATC code: C07BB07

Mechanism of action

Bisoprolol is a powerful and ß1 selective adrenergic inhibitor, devoid of intrinsic sympathomimetic activity and whict1 does not have any significant membrane stabilizing effects.

As for other P1 receptor antagonists, the mode of action of bisoprolol in hypertension is poorly known, however it has been demonstrated that this product clearly decreases plasma rennin levels and slows down the heart rate.

Hydrochlorothiazide is a thiazide diuretic that has an antihypertensive action. Its diuretic effect is due to the inhibition of Na+ active transport from the renal tubules to the blood, preventing the reabsorption of Na+

5.2. Pharmacokinetic properties

Related to Bisoprolol

Absorption: Tmax ranges from 1 to 4 hours.

Distribution: bisoprolol has a plasma protein binding of 30 % and the distribution level is high (approximately 3 I/kg), Bioavailability is high (88 %), with a very low first hepatic passage effect, and is not modified by the administration of food. The kinetics are linear for doses ranging from 5 to40 mg.

Biotransformation: 40% of bisoprolol is metabolised in the liver. The metabolites formed are inactive.

Elimination: the elimination half-life is 11 hours.

Renal and hepatic clearance are approximately equivalent and half the dose administered is found unchanged in the urine, es wall aa the metabolites. Total clearence is approximately 15l/h.

Related to Hydrochlorothiazide

Absorption: The bioavailabilily of hydrochlorothiazide varies depending on the subjects between 60 and 80 °/o. Tmax varies between 1.5 and 5 hours, the mean is at about4 hours.

Distribution: plasma protein binding is of 40 %.

Elimination: hydrochlorothiazide is not metabolised, and it is excreted almost entirely as the unaltered form by glomerular filtration and active tubular secretion. The elimination half-life of hydrochlorothiazide is approximately 8 hours.

In renal and heart failure, hydrochlorothiazide renal clearance decreases and the elimination half-life increases. The same applies to elderly subjects, with an additional increase in the maximum plasma concentration (Cmax).

There is passage into placenta and maternal milk.

5.3. Preclinical safety data

The conventional preclinical toxicity studies (chronic toxicity, mutagenicity, genotoxicity or carcinogenicity) for bisoprolol and hydrochlorothiazide have revealed no evidence of adverse effects in humans. Like other beta-blockers, bisoprolol in animal studies caused maternal (decreased food intake and decreased body weight) and embryo/fetal toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development until the end of lactation) at high doses.

Bisoprolol and hydrochlorothiazide, however, were not found to be teratogenic. Combined administration of the two components showed no increased toxicity.

6. Pharmaceutical particulars

6.1. List of excipients

Sr. No.	Name of the Ingredients	Specification
1.	Dicalcium Phosphate (Anhydrous)	BP
2	Microcrystalline Cellulose	BP
3	Crospovidone XL-10	BP
4	Colloidal anhydrous silica	BP
5	Magnesium Stearate	BP
6	Hypromellose (E-15)	BP
7	Titanium Dioxide	BP
8	Purified Talc	BP
9	Macrogol 6000	BP
10	Isopropyl alcohol	BP
11	Methylene Dichloride	BP

6.2. Incompatibilities

None reported

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store below 30°C.

Protect from direct sunlight, heat and moisture.

Keep all medicines out of reach of children.

6.5. Nature and contents of container

Blister pack of 10 tablets

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GALAXY PHARMACEUTICAL LTD

1ST FLOOR, DOCTORS' PARK, 3RD PARKLANDS AVENUE,

PO BOX 39107-00623, NAIROBI, KENYA

8. MARKETING AUTHORISATION NUMBER(S)

H2024/CTD9966/22624

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30.07.2024

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