Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

BISOCARD-5 (BISOPROLOL FUMARATE TABLETS USP 5 MG)

BISOCARD-10 (BISOPROLOL FUMARATE TABLETS USP 10 MG

2. Qualitative and quantitative composition

BISOCARD-5: Each film coated tablet contains bisoprolol Fumarate USP 5 mg

BISOCARD-10: Each film coated tablet contains bisoprolol Fumarate USP 10 mg

Excipient(s) with known effect

5 mg tablet:

Each tablet contains:

Yellow Oxide of Iron, Titanium Dioxide BP

10 mg tablet:

Each tablet contains:

Yellow Oxide of Iron, Red Oxide of Iron, Titanium Dioxide BP

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet (tablet)

5 mg tablet only:

Light yellow colored, circular shaped, biconvex film-coated tablet.

10 mg tablet only:

Brown colored, circular shaped, biconvex film-coated tablet.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of hypertension.

Treatment of chronic stable angina pectoris.

Treatment of stable chronic heart failure with reduced systolic ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides (for additional information see section 5.1).

4.2 Posology and method of administration

Posology

Treatment of hypertension and chronic stable angina pectoris

Adults

The dosage should be individually adjusted. It is recommended to start with 5 mg per day. The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day.

Patients with renal or hepatic impairment

In patients with severe renal impairment (creatinine clearance < 20 ml/min) and in patients with severe hepatic function disorders the dose should not exceed 10 mg once daily. This dosage may eventually be divided into halves.

Elderly

No dosage adjustment is normally required. It is recommended to start with the lowest possible dose.

Paediatric population

There is no experience with bisoprolol in children, therefore its use cannot be recommended for children.

Discontinuation of treatment

Treatment should not be stopped abruptly (see section 4.4). The dosage should be diminished slowly by a weekly halving of the dose.

Treatment of stable chronic heart failure

Adults

Standard treatment of CHF consists of an ACE inhibitor (or an angiotensin receptor blocker in case of intolerance to ACE inhibitors), a beta-blocking agent, diuretics, and when appropriate cardiac glycosides. Patients should be stable (without acute failure) when bisoprolol treatment is initiated.

It is recommended that the treating physician should be experienced in the management of chronic heart failure.

Titration phase

The treatment of stable chronic heart failure with bisoprolol requires a titration phase.

The treatment with bisoprolol is to be started with a gradual uptitration according to the following steps:

- 1.25 mg once daily for 1 week, if well tolerated increase to
- 2.5 mg once daily for a further week, if well tolerated increase to
- 3.75 mg once daily for a further week, if well tolerated increase to
- 5 mg once daily for the 4 following weeks, if well tolerated increase to

- 7.5 mg once daily for the 4 following weeks, if well tolerated increase to

- 10 mg once daily for the maintenance therapy.

The maximum recommended dose is **10 mg once daily.**

Transient worsening of heart failure, hypotension, or bradycardia may occur during the titration period and thereafter.

Close monitoring of vital signs (heart rate, blood pressure) and symptoms of worsening heart failure is recommended during the titration phase. Symptoms may occur within the first day after initiating the therapy.

Treatment modification

If the maximum recommended dose is not well tolerated, gradual dose reduction may be considered.

In case of transient worsening of heart failure, hypotension, or bradycardia reconsideration of the dosage of the concomitant medication is recommended. It may also be necessary to temporarily lower the dose of bisoprolol or to consider discontinuation.

The reintroduction and/or uptitration of bisoprolol should always be considered when the patient becomes stable again.

If discontinuation is considered, gradual dose decrease is recommended, since abrupt withdrawal may lead to acute deterioration of the patient's condition.

Treatment of stable chronic heart failure with bisoprolol is generally a long-term treatment.

Special populations

Hepatic or renal impairment*:*

There is no information regarding pharmacokinetics of bisoprolol in patients with chronic heart failure and with impaired hepatic or renal function. Titration of the dose in these populations should therefore be made with particular caution.

Elderly

No dosage adjustment is normally required.

Paediatric population

There is no experience with bisoprolol in children, therefore its use cannot be recommended for children.

Method of administration

For oral use.

Bisoprolol fumarate tablets should be taken in the morning and can be taken with food. They should be swallowed with liquid and should not be chewed.

4.3 Contraindications

Bisoprolol is contraindicated in patients with:

• hypersensitivity to the active substance or to any of the excipients listed in section 6.1

• acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy

• cardiogenic shock

• second- or third-degree AV block

• sick sinus syndrome

• sinoatrial block

• symptomatic bradycardia

• symptomatic hypotension

• severe bronchial asthma

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

• untreated phaeochromocytoma (see section 4.4)

• metabolic acidosis

4.4 Special warnings and precautions for use

Special warnings

Applies only to chronic heart failure:

The treatment of stable chronic heart failure with bisoprolol has to be initiated with a special titration phase (see section 4.2)

Applies to all indications:

Especially in patients with ischaemic heart disease the cessation of therapy with bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition (see section 4.2).

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'

The dosage forms contain sunset yellow (E110) that may cause allergic reactions.

Precautions

Applies only to hypertension or angina pectoris:

Bisoprolol must be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.

Applies only to chronic heart failure:

The initiation and cessation of treatment with bisoprolol necessitates regular monitoring. For the posology and method of administration please (see section 4.2).

There is no therapeutic experience of bisoprolol treatment in heart failure in patients with the following diseases and conditions:

- insulin dependent diabetes mellitus (type I)

- severely impaired renal function

- severely impaired hepatic function

- restrictive cardiomyopathy

- congenital heart disease

- haemodynamically significant organic valvular disease

- myocardial infarction within 3 months

Applies to all indications:

Bisoprolol must be used with caution in:

• bronchospasm (bronchial asthma, obstructive airways diseases)

• diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia (e.g. tachycardia, palpitations, sweating) can be masked

• strict fasting

• ongoing desensitisation therapy. As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine treatment may not always yield the expected therapeutic effect.

• first degree AV block

• Prinzmetal's angina Cases of coronary vasospasm have been observed. Despite its high beta1-selectivity, angina attacks cannot be completely excluded when bisoprolol is administered to patients with Prinzmetal's angina.

• peripheral arterial occlusive disease. Aggravation of symptoms may occur especially when starting therapy

• general anaesthesia.

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

The symptoms of thyrotoxicosis may be masked under treatment with bisoprolol.

In patients with phaeochromocytoma bisoprolol must not be administered until after alpha-receptor blockade.

In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance of beta-blockade be continued peri-operatively. The anaesthetist must be aware of beta-blockade because of the potential for interactions with other drugs, resulting in bradyarrhythmias, attenuation of reflex tachycardia, and decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

Combination of bisoprolol with calcium antagonists of the verapamil or diltiazem type, with Class I antiarrhythmic drugs and with centrally acting antihypertensive drugs is generally not recommended, for details please refer to section 4.5.

Although cardioselective (beta1) beta-blockers may have less effect on lung function than non-selective beta- blockers, as with all beta-blockers, these should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, bisoprolol may be used with caution. In patients with obstructive airways diseases, the treatment with bisoprolol should be started at the lowest possible dose and patients should be carefully monitored for new symptoms (e.g. dyspnoea, exercise intolerance, cough). In bronchial asthma or other chronic obstructive pulmonary diseases, which may cause symptoms, concomitant bronchodilating therapy is recommended. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of beta2-stimulants may have to be increased.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations not recommended:

Applies only to chronic heart failure:

• Class-I antiarrhythmic drugs (e.g. disopyramide, quinidine, lidocaine, phenytoin; flecainide, propafenone): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Applies to all indications:

• Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type: Negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrioventricular block.

• Centrally acting antihypertensive drugs (e.g. clonidine, methyldopa, moxonidine, rilmenidine): Concomitant use of centrally acting antihypertensive drugs may further decrease the central sympathetic tonus (and may thus lead to a reduction of heart rate and cardiac output, and to vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of " rebound hypertension" .

Combinations to be used with caution:

Applies only to hypertension or angina pectoris:

• Class-I antiarrhythmic drugs (e.g. disopyramide, quinidine, lidocaine, phenytoin; flecainide, propafenone): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Applies to all indications:

• Calcium antagonists of the dihydropyridine type (e.g. nifedipine, amlodipine, felodipine): Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

• Class-III antiarrhythmic drugs (e.g. amiodarone): Effect on atrio-ventricular conduction time may be potentiated.

• Topical beta-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.

• Parasympathomimetic drugs: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.

• Insulin and oral antidiabetic drugs: Increase of blood sugar lowering effect. Blockade of beta-adrenoreceptors may mask symptoms of hypoglycaemia.

• Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension (for further information on general anaesthesia see also section 4.4).

• Digitalis glycosides: Reduction of heart rate, increase of atrio-ventricular conduction time.

• Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol.

• Beta-sympathomimetic agents (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both agents.

• Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. noradrenaline, adrenaline): Combination with bisoprolol may unmask the alpha-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective beta-blockers.

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

• Concomitant use with antihypertensive agents as well as with other drugs with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.

Combinations to be considered:

• Mefloquine: increased risk of bradycardia

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Pregnancy and Lactation

Pregnancy

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. In general, β -adrenoceptor blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the fetus and newborn infant. If treatment with β -adrenoceptor blockers is necessary, β 1-selective adrenoceptor blockers are preferable.

Bisoprolol is not recommended during pregnancy unless clearly necessary. If treatment is considered necessary, monitoring of the uteroplacental blood flow and fetal growth is recommended. In case of harmful effects on pregnancy or the fetus consideration of alternative treatment is recommended. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

Lactation

There are no data on the excretion of bisoprolol in human breast milk or the safety of bisoprolol exposure in infants. Therefore, breastfeeding is not recommended during administration of bisoprolol.

4.7 Effects on ability to drive and use machines

In a study of coronary heart disease patients, bisoprolol did not impair driving performance. However, depending on the individual patient's response to treatment, the ability to drive a vehicle or to use machines may be impaired. This should be considered particularly at the start of treatment and upon change of medication or in conjunction 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)

Not known (cannot be estimated from the available data).

Psychiatric disorders:

Uncommon: sleep disorder, depression.

Rare: nightmare, hallucination.

Nervous system disorders:

Common: dizziness*, headache*.

Rare: syncope.

Eye disorders:

Rare: reduced tear flow (to be considered if the patient uses lenses).

Very rare: conjunctivitis.

Ear and labyrinth disorders:

Rare: hearing disorders.

Cardiac disorders:

Very common: bradycardia (in patients with chronic heart failure).

Common: worsening of pre-existing heart failure (in patients with chronic heart failure).

Uncommon: AV-conduction disturbances; worsening of pre-existing heart failure (in patients with hypertension or angina pectoris); bradycardia (in patients with hypertension or angina pectoris).

Vascular disorders:

Common: feeling of coldness or numbness in the extremities, hypotension especially in patients with heart failure.

Uncommon: orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:

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

Rare: allergic rhinitis.

Gastrointestinal disorders:

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

Hepatobiliary disorders:

Rare: hepatitis.

Skin and subcutaneous tissue disorders:

Rare: hypersensitivity reactions such as pruritus, flush, rash and angioedema.

Very rare: alopecia, beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash.

Musculoskeletal and connective tissue disorders:

Uncommon: muscular weakness, muscle cramps.

Reproductive system and breast disorders:

Rare: erectile dysfunction.

General disorders and administration site conditions:

Common: asthenia (in patients with chronic heart failure), fatigue*.

Uncommon: asthenia (in patients with hypertension or angina pectoris).

Investigations:

Rare: increased triglycerides, increased liver enzymes (ALAT, ASAT).

Paediatric population:

No data are available.

Applies only to hypertension or angina pectoris:

*These symptoms especially occur at the beginning of the therapy. They are generally mild and often disappear within 1 to 2 weeks.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal products. Healthcare professionals are asked to report any suspected adverse reactions via Pharmacy and Poisons Board-Pharmacovigilance Electronic Reporting System (PvERS); https://pv.pharmacyboardkenya.org

4.9 Overdose

Symptoms

With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness have been reported. In general, the most common signs expected with overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is limited experience with overdose of bisoprolol, only a few cases of overdose with bisoprolol (maximum: 2000 mg) have been reported in patients suffering from hypertension and/or coronary heart disease showing bradycardia and/or hypotension were noted, all patients recovered. There is a wide inter-individual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive. Therefore, it is mandatory to initiate the treatment of these patients with a gradual uptitration according to the scheme given in section 4.2.

Management

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

Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures may be considered when clinically warranted.

Bradycardia: Administer intravenous atropine. If the response is inadequate, isoprenaline or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.

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

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

Acute worsening of heart failure: Administer i.v. diuretics, inotropic agents, vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, beta2-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

Limited data suggest that bisoprolol is hardly dialysable.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective, ATC code: C07 AB07

Chronic heart failure:

Mechanism of action

Bisoprolol is a potent, highly beta1-selective adrenoreceptor blocking agent lacking intrinsic sympathomimetic activity and without relevant membrane stabilising activity. It only shows low affinity to the beta2-receptor of the smooth muscles of bronchi and vessels as well as to the beta2-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta2-mediated metabolic effects. Its beta1-selectivity extends beyond the therapeutic dose range.

Hypertension or angina pectoris:

Mechanism of action

Antianginal mechanism: Bisoprolol by inhibiting the cardiac beta receptors inhibits the response given to sympathetic activation. That results in the decrease of heart rate and contractility this way decreasing the oxygen demand of the cardiac muscle.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases.

Pharmacodynamic effects

Bisoprolol is used for the treatment of hypertension and angina pectoris. As with other Beta-1-blocking agents, the method of acting in hypertension is unclear. However, it is known that Bisoprolol reduces plasma renin activity markedly.

5.2 Pharmacokinetic properties

Absorption

Bisoprolol is absorbed almost completely from the gastrointestinal tract. Together with the very small first pass effect in the liver, this results in a high bioavailability of approximately 90%.

Distribution

The plasma protein binding of bisoprolol is about 30 %. The distribution volume is 3.5 l/kg. The total clearance is approximately 15 l/h.

The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage.

Biotransformation

50 % is metabolised by the liver to inactive metabolites which are then excreted by the kidneys.

Elimination

Bisoprolol is excreted from the body by two routes. 50% is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in an unmetabolised form. Since the elimination takes place in the kidneys and the liver to the same extent a dosage adjustment is not required for patients with impaired liver function or renal insufficiency.

Other special population

In patients with chronic heart failure (NYHA stage III) the plasma levels of bisoprolol are higher and the half-life is prolonged compared to healthy volunteers. Maximum plasma concentration at steady state is 64± 21 ng/ml at a daily dose of 10 mg and the half-life is 17± 5 hours.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential, toxicity to reproduction and development.

Like other beta-blockers, bisoprolol 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) at high doses but was not teratogenic.

6. Pharmaceutical Particulars

6.1 List of Excipients

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Strength	**Tablet**	**Film-coat**
5 mg tablet only:	Cellulose microcrystalline Butylhydroxyanisole Isopropyl alcohol Colloidal anhydrous silica Magnesium stearate Sodium lauril sulfate Iron oxide yellow (E172) Croscarmellose sodium	Titanium dioxide (E171) Talc Hypromellose (E464) Indigo carmine (E132) Quinoline yellow (E104) Sunset yellow (E110)
10 mg tablet only:	Cellulose microcrystalline Butylhydroxyanisole Isopropyl alcohol	Titanium dioxide (E171) Talc Hypromellose (E464) Iron oxide yellow (E172)

	Colloidal anhydrous silica Magnesium stearate Sodium lauril sulfate Iron oxide red (E172) Croscarmellose sodium	Sunset yellow (E110)

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

36 months

6.4 Special Precautions for storage

Store below 30° C.

This medicinal product does not require any special storage conditions.

6.5 Nature and Content 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 Authorization Holder

GALAXY PHARMACEUTICAL LTD

8. Marketing Authorization Number

BISOCARD-5- 22618

BISOCARD-10- 22619

9. Date of first authorization/renewal of the authorization

30/05/2024

10. Date of revision of the text

06/05/2025