

Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

BISOCARD 5 mg

Bisoprolol Fumarate film coated Tablets USP 5 mg

BISOCARD 10

Bisoprolol Fumarate film coated Tablets USP 10 mg

2. Qualitative and quantitative composition

Bisocard 5

Each film coated Bisocard 5 tablet contains:

Bisoprolol Fumarate USP 5 mg

Excipients QS

Bisocard 10

Each film coated Bisocard 10 tablet contains:

Bisoprolol Fumarate USP 10 mg

Excipients QS

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Bisocard 5

Film coated tablet.

A yellow coloured, round in Shape, biconvex, film coated tablet.

Bisocard 10

Film coated tablet.

A yellow coloured, round in Shape, biconvex, film coated tablet.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of hypertension and 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

Treatment of hypertension and chronic stable angina pectoris

Adults

For both indications the normal dosage is 1 tablet (5-10 mg) once daily as a single dose. If 5 mg is not given necessary effect, the dose may be increased to 10 mg once daily or very rarely to 20 mg once daily.

The maximum recommended dose is 20 mg once daily.

In all cases the dosage is adjusted individually, in order to avoid bradycardia.

In hypertension, Bisoprolol Fumarate Tablets could be combined with diuretics, if necessary, effect is not achieved.

Treatment of stable chronic heart failure (Long term)

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

Especially in patients with ischaemic heart disease, treatment must not be discontinued suddenly since this might lead to a transitory worsening of angina pectoris with risk of heart attack. Gradual reduction of the dosage for 1-2 weeks is recommended.

If it is thought necessary to withdraw Bisoprolol Fumarate Tablets before surgery, this should be done gradually and completed about 48 hours before operation except in certain cases, for example thyrotoxicosis and phaeochromocytoma.

Administration

Bisoprolol Fumarate Tablets are taken in the morning with or without food. They are swallowed with some liquid and not to be chewed.

Special populations

Renal or liver impairment

In patients with liver or kidney function disorders of mild to moderate severity, no dosage adjustment is normally required. In patients with severe renal impairment (creatinine clearance < 20 ml/min) and in patients with severe liver function disorders it is recommended that a daily dose of 10 mg bisoprolol fumarate is not exceeded. Experience with the use of bisoprolol in renal dialysis patients is limited; however, there is no evidence that the dosage regimen needs to be altered.

Elderly

No dosage adjustment is required.

Children

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

4.3 Contraindications

Bisoprolol is contra-indicated in patients with :

- Acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy,
- Cardiogenic shock,
- AV block of second or third degree (without a pacemaker),
- Sick sinus syndrome,
- Sino atrial block,
- Bradycardia with less than 60 beats/min before start of the treatment,
- Hypotension (systolic blood pressure less than 100 mm Hg),
- Severe bronchial asthma
- Severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome,
- Untreated phaeochromocytoma
- Metabolic acidosis.
- Hypersensitivity to bisoprolol or to any of the excipients.

4.4 Special warnings and precautions for use

Bisoprolol must be used with caution in patients with:

- hypertension or angina pectoris and accompanying heart failure.
- diabetes mellitus showing large fluctuations in blood glucose values. Symptoms of hypoglycaemia can be masked,
- strict fasting,
- ongoing desensitisation therapy.
- AV block of first degree,
- 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. Intensification of complaints may occur especially when starting therapy.

In patients undergoing the 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 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 the reflex tachycardia and the 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.

Although cardioselective (beta₁) beta-blockers may have less effect on lung function than nonselective betablockers, 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 Fumarate Tablets may be used with caution. 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, therefore the dose of beta2-stimulants may have to be increased.

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

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

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

Under treatment with bisoprolol the symptoms of a thyreotoxicosis may be masked.

The cessation of therapy with bisoprolol should not be done abruptly unless clearly indicated.

4.5 Interaction with other medicinal products and other forms of interaction

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 β -blocker treatment may lead to profound hypotension and atrio-ventricular block.

Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonidine, rilmenidine):

Concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of "rebound hypertension".

Combinations to be used with caution

Calcium antagonists of the dihydropyridine type such as felodipine and amlodipine: 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:

Intensification of blood sugar lowering effect. Blockade of beta-adrenoreceptors may mask symptoms of hypoglycaemia (for example tachycardia).

Anaesthetic agents:

Attenuation of the reflex tachycardia and increase of the risk of hypotension.

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.

 β -Sympathomimetic agents (e.g. isoprenaline, dobutamine):

Combination with bisoprolol may reduce the effect of both agents.

Sympathomimetics that activate both β - and α -adrenoceptors (e.g. noradrenaline, adrenaline):

Combination with bisoprolol may unmask the α -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 β -blockers.

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 foetus/new-born. 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 foetus and newborn infant. If treatment with β -adrenoceptor blockers is necessary, β 1-selective adrenoceptor blockers are preferable.

Bisoprolol Fumarate Tablet is not recommended during pregnancy unless clearly necessary. If treatment is considered necessary, monitoring of the uteroplacental blood flow and the foetal growth is recommended.

In case of harmful effects on pregnancy or the foetus consideration of alternative treatment is recommended.

The new-born 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. Therefore, breastfeeding is not recommended during administration of Bisoprolol Fumarate Tablets.

4.7 Effects on ability to drive and use machines

In a study with coronary heart disease patients, bisoprolol did not impair driving performance.

However, due to individual variations in reactions to the drug, the ability to drive a vehicle or to operate machinery may be impaired. This is to be considered particularly at start of treatment and upon change of medication as well as in conjunction with alcohol.

4.8 Undesirable effects

The following definitions apply to the frequency terminology used hereafter.

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Frequency not known (cannot be estimated from available data)

Investigations

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

Cardiac disorders

Uncommon: AV-conduction disturbances, worsening of pre-existing heart failure; bradycardia

Nervous system disorders

Common: dizziness*, headache*

Rare: syncope

Eye disorders

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

Very rare: conjunctivitis

Ear and labyrinth disorders

Rare: hearing disorders

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

Skin and subcutaneous tissue disorders

Rare: hypersensitivity reactions (pruritus, flush, rash and angioedema)

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

Musculoskeletal and connective tissue disorders

Uncommon: muscle weakness, muscle cramps

Vascular disorders

Common: feeling of coldness or numbness in the extremities, hypotension

General disorders

Common: fatigue

Uncommon: asthenia

Hepatobiliary disorders

Rare: hepatitis

Reproductive system and breast disorders

Rare: erectile dysfunction

Psychiatric disorders

Uncommon: depression, sleep disorder

Rare: nightmare, hallucination

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

An increased level of antinuclear antibodies (ANA) has been noticed, but the clinical relevance of this is not clear.

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 up titration according to the scheme given in section 4.2.

If overdose occurs, bisoprolol treatment should be stopped and supportive and symptomatic treatment should be provided. Limited data suggest that bisoprolol is hardly dialysable. Based on the expected pharmacologic actions and recommendations for other beta-blockers,

the following general measures should 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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective, ATC code: C07AB07

Bisoprolol is a highly beta1-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and 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.

Bisoprolol has a negative inotropic and cronotropic effect.

Bisoprolol reaches its maximal effect 3-4 hours after oral administration.

The maximal antihypertensive effect of bisoprolol is generally reached after 2 weeks.

In acute administration, bisoprolol reduces the heart rate and stroke volume, thus reducing cardiac output. In chronic administration the initially elevated peripheral resistance decreases.

5.2 Pharmacokinetic properties

Absorption

Bisoprolol is absorbed and has a biological availability of about 90% after oral administration.

Distribution

The plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg. Total clearance is approximately 15 l/h. The half-life in plasma of 10-12 hours gives a 24-hour effect after dosing once daily.

Biotransformation

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

Excretion

Bisoprolol is excreted from the body by two routes. 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.

The kinetics of bisoprolol are linear and independent of age

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of general toxicity, genotoxicity or carcinogenicity. 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

Magnesium Stearate, Purified Talc, Colloidal anhydrous silica, Crospovidone, Microcrystalline Cellulose, Polacrillin Potassium(Kyron T), Film Coat, Yellow Oxide of Iron, Iso Propyl Alcohol, Dichloromethane and Titanium Dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

36 months

6.4 Special Precautions for storage

Store below 30°C and protect from direct sunlight.

6.5 Nature and Content of container

2 x 14 pack: 14 tablets packed in Alu-Alu blister and such 2 Alu-Alu blisters are packed in single carton along with pack insert.

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing Authorization Holder

Pharma Life Science
Limited
P.o Box 38148-00623
Nairobi, kenya.

8. Marketing Authorization Number

Bisocard 5 - CTD9965
Bisocard 10 - CTD9960

9. Date of first authorization/renewal of the authorization

30/05/2024

10. Date of revision of the text

8/05/2025