Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Bisocard -10mg(bisoprolol fumarate tablets USP 10mg)

2. Qualitative and quantitative composition

Bisocard-10mg

Each film-coated tablet contains;

Bisoprolol Fumarate USP 10mg

Yellow Oxide of Iron, Red Oxide of Iron, Titanium Dioxide BP (-)

For a full list of excipients, see section 6.1.

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

3. Pharmaceutical form

Film-coated tablet.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of Hypertension

Treatment of stable chronic angina

Treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides

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.

Patient with renal impairment

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

Patients with severe hepatic impairment

No dosage adjustment is required, however careful monitoring is advised.

Elderly

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

Children

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. 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.

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

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 up titration 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.

Close monitoring of vital signs (heart rate, blood pressure) and symptoms of worsening heart failure is recommended during the titration phase. Symptoms may already 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 up titration 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 patients condition.

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

Special population

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. Up titration of the dose in these populations should therefore be made with additional caution.

Elderly

No dosage adjustment is required. Here is no experience with bisoprolol in children, therefore its use cannot be recommended for children.

Method of administration

For oral use

Bisoprolol 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 contra-indicated in chronic heart failure 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 (without a pacemaker)

- Sick sinus syndrome

- Sinoatrial block

- Symptomatic bradycardia

- Symptomatic hypotension

- Severe bronchial asthma or severe chronic obstructive pulmonary disease

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

- Untreated pheochromocytoma (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.

Applies to all indications:

Especially in patients with ischemic 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).

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 of treatment of stable chronic heart failure with bisoprolol necessitates regular monitoring. For the posology and method of administration please refer to section 4.2.

There is no therapeutic experience of bisoprolol treatment of 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). In bronchial asthma or other chronic obstructive lung diseases, which may cause symptoms, bronchodilating therapy is recommended to 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.

- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia (e.g. tachycardia, palpitations or 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 does 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

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 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.

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.

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. dyspnea, exercise intolerance, cough). 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.

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 thyrotoxicosis may be masked.

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. quinidine, disopyramide, 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 effect on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrio-ventricular 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 reduction of heart rate and cardiac output and to vasodilatation. Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase the risk of " rebound hypertension"

Combinations to be used with caution

Applies only to hypertension or angina pectoris:

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

Applies to all indications

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.

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

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

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: Increase of atrio-ventricular conduction time, reduction in heart rate.

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. norepinephrine, epinephrine): 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.

<u>Combinations to be considered</u>

Mefloquine: increased risk of bradycardia

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

Rifampicin: Slight reduction of the half-life of bisoprolol possible due to the induction of hepatic drug metabolising enzymes. Normally no dosage adjustment is necessary.

Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

4.6 Fertility, pregnancy and lactation

Pregnancy

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. In general, beta-adrenoceptor blocking agents 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 beta-adrenoceptor blocking agents is necessary, beta1-selective adrenoceptor blocking agents are preferable.

Bisoprolol is not recommended during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, the uteroplacental blood flow and fetal growth should be monitored. In case of harmful effects on pregnancy or the fetus alternative treatment should be considered. 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 with coronary heart disease patients, bisoprolol did not impair driving performance. However, depending on the individual patients response to treatment an effect on the ability to drive a vehicle or to use machines cannot be excluded. This needs to be considered particularly at start of treatment, 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 (can not be estimated from the available data)

Psychiatric disorders:

Uncommon: sleep disorders, depression.

Rare: nightmares, hallucinations.

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 patient 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 (pruritus, flush, rash and angioedema).

Very rare: betablockers may provoke or worsen psoriasis or induce psoriasislike rash, alopecia.

Musculoskeletal and connective tissue disorders:

Uncommon: muscular weakness and cramps.

Reproductive system and breast disorders:

Rare: erectile dysfunction.

General disorders:

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).

4.9 Overdose

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 have been reported. 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.

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-blocking agents, 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 temporary pacing.

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: C07AB07

Mechanism of action

Bisoprolol is a potent highly beta1-selective-adrenoceptor blocking agent, lacking intrinsic sympathomimetic 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.

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%. 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.

Distribution

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

Biotransformation and 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.

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

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity. Like other beta-blocking agents, 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

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

3.1 Incompatibilities

None reported

3.2 Shelf life

36 months

3.3 Special precautions for storage

Store below 30°C.

Protect from direct sunlight, heat and moisture. Keep all medicines out of reach of children.

3.4 Nature and contents of container

Blister pack of 10 tablets

3.5 Special precautions for disposal and other handling

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

4.Marketing authorisation holder

PHARMA LIFE SCIENCE

5.Marketing authorisation number(s)

Bisocard -10 CTD 9960

6.Date of first authorisation/renewal of the authorisation

30/05/2024

7.Date of revision of the text

5/17/2025