Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bisocor 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of bisoprolol fumarate.
Excipient with known effect: Lactose Monohydrate 131 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

The tablets are mottled beige, round and convex with the following identification markings: BI centrally above a break-line with 10 below. The tablets can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension.
Chronic stable angina pectoris.

4.2 Posology and method of administration

Posology

The dosage should be individually adjusted. It is recommended to start with the lowest possible dose. In some patients, 5 mg per day may be adequate. The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day.

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

Patients with severe liver impairment
No dosage adjustment is required, however careful monitoring is advised. In patients with severe liver function disorders a daily dose of 10mg bisoprolol should not be exceeded

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

Paediatric population:
There is no paediatric experience with this medicine, therefore itsuse cannot be recommended

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**.**

Bisocor 10 mg Tablets are for oral administration.

The tablet should be taken in the morning and be swallowed with a sufficient amount of fluid (e.g. one glass of water) .The tablet can be taken with food.

4.3 Contraindications

- 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.
- metabolic acidosis.
- untreated phaeochromocytoma (see 4.4).
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Warnings

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

Precautions

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

Bisoprolol must be used with caution in

- diabetes mellitus showing 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 may not always yield the expected therapeutic effect.

- First degree AV block.

- Prinzmetal's angina.

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

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 donegradually and completed about 48 hours before anaesthesia.

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.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Combinations not recommended

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, moxonodine, 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

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.

Calcium antagonists of the dihydropyridine type (e.g. 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-blockers (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 betaadrenoceptors 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 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.

Beta-sympathomimetics (e.g. isoprenaline, dobutamine):

Combination with bisoprolol may reduce the effect of both agents.

Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. norepinephrine, epinephrine):
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.

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 betablockers but also risk of 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, β-adrenoceptor blocking agents reduce placental perfusion,which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse reactions (e.g. hypoglycaemia, bradycardia) may occur in the fetus and newborn infant. If treatment with β-adrenoceptor blocking agents is necessary, β_1-adrenoceptor blocking agents are preferable.

Bisoprolol should not be used during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, monitoring of the uteroplacental blood flow and the foetal growth is recommendedIn case of harmful effects on pregnancy or the fetus 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.

Breast-feeding:
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 vehicleor 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

Very common (> 1/10), Common >1/100,< 1/10), Uncommon (> 1/1,000, < 1/100), Rare (> 1/10,000,< 1/1,000), Very rare (< 1/10,000).

System Order Class	Very common (> 1/10)	Common (>1/100, < 1/10)	Uncommon (> 1/1,000 to < 1/100)	Rare (> 1/10,000 to < 1/1,000)	Very Rare (< 1/10,000)
Psychiatric disorders			Depression, sleep disorders	Nightmares, hallucinations	

Nervous system disorders		Dizziness*, headache*		Syncope	
Eye disorders				Reduced tear flow (to be considered if the patient uses contact lenses)	Conjunctivitis
Ear and labyrinth disorders				Hearing disorders	
Cardiac disorders	Bradycardia (in patients with chronic heart failure)		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		Feeling of coldness or numbness in the extremities, hypotension especially in patients with heart failure			
Respiratory, thoracic and mediastinal disorders			Bronchospasm in patients with bronchial asthma or a history of obstructive airways disease	Allergic rhinitis	
Gastrointestinal disorders		Gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation			
Hepatobilary disorders				Hepatitis	
Skin and subcutaneous tissue disorders				Hypersensitivity reactions such as itching, flush, rash	Alopecia. Beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash.
Musculoskeletal and connective tissue disorders			Muscle weakness, muscle cramps		
Reproductive system and				Potency disorders	

breast disorders					
General disorders		Asthenia (patients with chronic heart failure), fatigue*	Asthenia (in patients with hypertension or angina pectoris)		
Investigations				Increased triglycerides, increased liver enzymes (ALAT, ASAT)	

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

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

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 withoverdose 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.

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 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 fumarate is a highly beta1-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity.

Pharmacodynamic effects
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 fumarate 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.

As with other beta1-blocking agents, the mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma rennin levels.

Clinical efficacy
In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol fumarate reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases. Hence bisoprolol is effective in eliminating or reducing the symptoms.

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.

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

Linearity
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 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.

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 β-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

Lactose monohydrate
Cellulose, microcrystalline E460
Magnesium stearate E572
Crospovidone E1201
Beige PB 27215 (lactose monohydrate and iron oxides red and yellow (E172))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Bisocor 10 mg tablets are presented in:
Blisters comprising of PVC/PVdC/aluminium foil, contained within a printed carton box. Each carton will contain either; 20, 28, 30, 50, 56, 60, 90 or 100 tablets. Not all pack sizes may be marketed**.**

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Unichem Laboratories Ltd
Studio 8B, Ard Gaoithe Commercial Centre
Ard Gaoithe Business Park
Cashel Road
Clonmel
Co Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22654/003/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 05 September 2010

10 DATE OF REVISION OF THE TEXT

May 2019