Summary of product characteristics.

1. Name of the medicinal product

Bisocor 5 Tablet (bisoprolol)

2. Qualitative and quantitative composition

Each tablet contains Bisoprolol Fuamarate USP 5 mg

3. Pharmaceutical form

Tablet; is a pink color pillow shaped film coated tablet having break-line on one side and other side is plain.

4. Clinical particulars

4.1 Therapeutic indications

Bisocor (Bisoprolol) is indicated in the management of hypertension and in the treatment of angina. It may be used alone or in combination with other antihypertensive agents.

4.2 Posology and method of administration

The dose of **Bisocor** must be individualized to the needs of the patient. The usual starting dose is **Bisocor** 5 mg once daily. In some patients, **Bisocor** 2.5 mg may be an appropriate starting dose. If the antihypertensive effect of **Bisocor** 5 mg is inadequate, the dose may be increased to 10 mg and then, if necessary, to 20 mg once daily.

Patients with Renal or Hepatic Impairment: In patients with hepatic impairment (hepatitis or cirrhosis) or renal dysfunction (creatinine clearance <40 mL/min), the initial daily dose should be 2.5 mg and caution should be used in dose-titration. Since limited data suggest that Bisoprolol fumarate is not dialyzable, drug replacement is not necessary in patients undergoing dialysis.

Geriatric Patients: It is not necessary to adjust the dose in the elderly, unless there is also significant renal or hepatic dysfunction.

Pediatric Patients: There is no pediatric experience with Bisoprolol.

4.3 Contraindications

Bisoprolol is contraindicated in patients with cardiogenic shock, overt cardiac failure, second- or third-degree AV block, and marked sinus bradycardia.

4.4 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 influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients on β-blocker treatment may lead to profound hypotension and atrioventricular block.

- Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonodine, 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

Applies only to hypertension or angina pectoris:

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 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: 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.

- 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.

<u>Combinations to be considered</u>

- 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.

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

- Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

4.5 Pregnancy and lactation

Pregnancy: Bisoprolol should not be used during pregnancy unless

clearly necessary. If treatment with Bisoprolol is considered necessary, the uteroplacental blood flow and the foetal growth should be monitored. In case of harmful effects on pregnancy or the foetus, 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: It is not known whether this drug is excreted in human milk. Therefore, breast-feeding is not recommended during administration of Bisoprolol.

4.6 Effects on ability to drive and use machines

Not Available

4.7 Undesirable effects

Fatigue, dizziness, headache, disturbances of the gut such as nausea, vomiting, diarrhoea, constipation or abdominal pain, cold or numb extremities, e.g. hands and feet, muscle weakness or cramps, slower than normal heart beat (bradycardia), worsening of heart failure, sleep disturbance, depression, breathing difficulties due to a narrowing of the airways (bronchospasm) in people with asthma or COPD.

4.8 Overdose

The most common signs expected with overdosage of a beta-blocker are bradycardia, hypotension, congestive heart failure, bronchospasm, and hypoglycemia. Only a few cases of overdose with Bisoprolol have been reported. Bradycardia and/or hypotension were noted. Sympathomimetic agents were given in some cases, and all patients recovered. In general, if overdose occurs, Bisoprolol therapy should be stopped and supportive and symptomatic treatment should be provided.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

5.2 Pharmacokinetic properties

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.

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

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.

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-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

Dibasic Calcium Phosphate
Microcrystalline Cellulose
(Avicel PH 102) Pregelatinized
Starch

Crospovidone
Colloidal Anhydrous Silica
(Aerosil 200) Magnesium
Stearate
Opadry II 85G54101 (Pink)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C. Protect from light and moisture. Keep out of the reach of children.

6.5 Nature and contents of container

Alu-Alu Blister pack.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorization holder and manufacturing site addresses

Marketing Authorization Holder

Square Formulations Ltd. Square Centre
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8. Marketing authorization number

H2022/CTD8423/15608

9. Date of first <registration> / renewal of the <registration>

November /15/2022.

10. Date of revision of text.

November 2022