Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Emcolol 10 mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg bisoprolol hemifumarate (equivalent to 8.4 mg bisoprolol)

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet. (Tablet)
Pale orange-light orange, heart-shaped, scored tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the management of hypertension and the management of angina pectoris.

4.2 Posology and method of administration

Route of administration:
Oral

Recommended dosage:

Adults:
The usual dose is 10mg once daily, with a maximum recommended dose of 20mg per day. In some patients 5mg per day may be adequate. In patients with final stage impairment of renal function (creatinine clearance <20ml/minute) or liver function, the dose should not exceed 10mg bisoprolol once daily. 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 normally required, but 5mg per day may be adequate. In some patients, as for others adults, dosage may have to be reduced in cases of severe renal or hepatic dysfunction.

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

In patients with ischaemic heart disease, treatment should not be withdrawn abruptly; gradual dosage reduction over 1-2 weeks is recommended.

4.3 Contraindications

Bioprolol is contra-indicated in patients with:

- 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
- Marked bradycardia (heart rate less than 60 beats/min prior to start of therapy)
- Hypotension (systolic blood pressure < 100mmHg)
- Severe bronchial asthma or severe chronic obstructive pulmonary disease
- Late stages of peripheral arterial occlusive disease and Raynaud's syndrome
- Untreated phaeochromocytoma *(see 4.4)*
- 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:

- heart failure (the treatment of stable chronic heart failure with bisoprolol has to be initiated with a special titration phase [for details, see SPC for bisoprolol indicated for the treatment of stable, chronic heart failure]).
- bronchial asthma, obstructive airways disease
- concomitant treatment with inhalation anaesthetics *(see see section 4.5)*
- diabetes mellitus with 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
- peripheral arterial occlusive disease (intensification of complaints may occur particularly during the start of therapy)

In bronchial asthma or other chronic obstructive lung diseases, which may cause symptoms, bronchodilating therapy may have to be given concomitantly. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of β2-stimulants may have to be increased.

As with other β-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 β-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.

The cessation of therapy with bisoprolol should not be done abruptly unless clearly indicated. For further information, *see section 4.2.*

4.5 Interaction with other medicinal products and other forms of interaction

<u>Combinations not recommended</u>
Calcium antagonists such as verapamil and to a lesser extent diltiazem: Negative influence on contractility and artio-ventricular conduction. Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrioventricular block.

Clonidine: Increased risk of "rebound hypertension" as well as exaggerated decrease in heart rate and cardiac conduction.

Monoamineoxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of β-blockers but also risk of hypertensive crisis.

<u>Combinations to be used with caution</u>

Calcium antagonists such as dihydropyridine derivatives (e.g. nifedipine): increased risk of hypotension. In patients with latent cardiac insufficiency, concomitant treatment with beta-blocking agents may lead to cardiac failure.

Class-I antiarrhythmic drugs (e.g. disopyramide, quinidine): Effect on atrial conduction time may be potentiated and negative inotropic effect may be increased.

Class-III antiarrhythmic drugs (e.g. amiodarone): Effect on atrial conduction time may be potentiated.
Parasympathomimetic drugs (including tacrine): Antio-ventricular conduction time may be increased.

Other β-blockers, including eye drops, have additive effects.

Insulin and oral antidiabetic drugs: Intensification of blood sugar lowering effect. Blockade of β-adrenoceptors may mask symptoms of hypoglycaemia.

Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension. Continuation of β-blockade reduces the risk of arrhythmia during induction and intubation. The anaesthesiologist should be informed when the patient is receiving bisoprolol.

Digitalis glycosides: increase of atrio-ventricular conduction time.

Prostaglandin synthetase inhibiting drugs: Decreased hypotensive effect.

Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

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.

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.

Combination to be considered
Mefloquine: increased risk of bradycardia.

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-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, β1—selective adrenoceptor blockers are preferable.

Bisoprolol should not be used during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, the uteroplacental blood flow and the 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
It is not known whether this drug is excreted in human milk. Therefore, breastfeeding is not recommended during administration of bisoprolol.

4.7 Effects on ability to drive and use machines

In the 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 should be considered particularly at start of treatment and upon change of medication as well as in conjunction with alcohol.

4.8 Undesirable effects

Common (≥ 1% and <10%)	*Circ:*	Feeling of coldness or numbness in the extremities
	CNS:	Tiredness*, exhaustion*, dizziness*, headache*
	Gl:	Nausea, vomiting, diarrhoea, constipation
Uncommon (≥ 0.1% and <1%)	*General:*	Muscular weakness and cramps
	Circ:	Bradycardia, AV-stimulus disturbances, worsening of heart failure, orthostatic hypotension
	CNS:	Sleep disturbances, depression
	Airways:	Bronchospasm in patients with bronchial asthma or history of obstructive airways disease
Rare (≥ 0.01% and <0.1%)	*CNS:*	Nightmares, hallucinations
	Skin:	hypersensitivity reactions(itching flush, rash)
	Liver:	Increased liver enzymes (ALAT, ASAT), Hepatitis
	Metabolism:	Increased triglycerides
	Urogenital:	Potency disorders
	Ear-nose-throat:	hearing impairment, allergic rhinitis
	Eyes:	reduced tear flow (to be considered if the patient uses lenses)
Single cases (< 0.01%)	*Eyes:*	conjunctivitis, visual disturbances
	Skin:	β -blockers may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia
	Circ:	chest pain

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

4.9 Overdose

The most common signs expected with overdosage of a β-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. To date a few cases of overdose (maximum: 2000 mg) with bisoprolol have been reported. Bradycardia and/or hypotension were noted. All patients recovered. There is a wide interindividual variation in sensitivity to one single high dose of bisoprolol.

In general, 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 pharmacological actions and recommendations for other β-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 vasopressor 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 bronchodilators therapy such as isoprenaline, ß2-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Bisoprolol is a potent, highly β_1-selective adrenoreceptor blocking agent devoid of intrinsic sympathomimetic activity and without relevant membrane stabilising activity.

As with other β_1-blocking agents, the mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma renin activity.

In patients with angina, the blockade of β_1-receptors reduces heart action and thus reduces oxygen demand. Hence bisoprolol is effective in eliminating or reducing the symptoms.

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 drug is cleared equally by the liver and kidney.

The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage. About 95% of the drug substance is excreted through the kidney, half of this is as unchanged bisoprolol. There are no active metabolites in man.

5.3 Preclinical safety data

N/A.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients

Colloidal anhydrous silica
Magnesium stearate
Crospovidone
Microcrystalline cellulose
Maize starch
Calcium hydrogen phosphate, anhydrous

Coating

Iron oxide yellow (E172)
Iron oxide red (E172)
Dimeticone
Macrogol 400
Titanium dioxide (E171)
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Cartons containing aluminium/PVC or aluminium/PVDC blister packs of 4, 14 or 28 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

McDermott Laboratories Limited (t/a Gerard Laboratories)
35-36 Baldoyle Industrial Estate,
Grange Road,
Dublin 13

8 MARKETING AUTHORISATION NUMBER

PA 577/38/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 January 2001

Date of last renewal: 12 January 2006

10 DATE OF REVISION OF THE TEXT

November 2007