SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bisoprolol Fumarate 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Bisoprolol fumarate 10 mg. For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet
Round, white, film-coated convex tablets with ”R6” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The management of hypertension.
The management of angina pectoris.

4.2 Posology and method of administration

Posology:

For the management of hypertension and angina pectoris:

Adults

The usual adult dose is 10mg once daily with a maximum recommended dose of 20mg per day. In some patients, 5mg per day may be adequate.

Renal or hepatic impairment

In patients with final stage impairment of renal function (creatinine clearance less than 20ml/min) or in patients with severe hepatic dysfunction, the dosage should not exceed 10mg bisoprolol once daily.

Experience of use of bisoprolol in renal dialysis patients is limited, however it is thought that bisoprolol fumarate cannot be dialysed.

Elderly

No dosage adjustment is normally required but 5mg per day may be adequate in some elderly patients; as for other adults, the dosage may have to be reduced in cases of severe renal or hepatic dysfunction.

Paediatric

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

Method of Administration:

Bisoprolol tablet should be taken in the morning and can be taken with food. They should be swallowed in liquid and should not be chewed.

4.3 Contraindications

Bisoprolol is contraindicated in patients with:
• acute heart failure or during episodes of heart failure decompensation requiring
i.v. inotropic therapy
• cardiogenic shock.
• sinoatrial block.
• second or third degree AV block (without pacemaker).
• bradycardia (heart rate less than 60 beats/min prior to start of therapy).
• severe bronchial asthma or severe chronic obstructive pulmonary disease
• sick sinus syndrome.
• hypotension (systolic blood pressure <100mmHg).
• later stages of peripheral arterial occlusive disease and Raynaud's syndrome
• untreated phaeochromocytoma (see section 4.4)
• metabolic acidosis
• hypersensitivity to the active substance(s) or to any of the excipients listed in section
6.1

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).

• bronchospasm (bronchial asthma, obstructive airways diseases):

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.

• concomitant treatment with inhalation anaesthetics (see section 4.5)

• for patients with severe renal impairment and patients with severe liver function disorders please refer to section 4.2.

• diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia can be masked.

• strict fasting.

• ongoing desensitisation therapy.

• first degree AV block.

• prinzmetal's angina.

• peripheral arterial occlusive disease (intensification of complaints might happen especially during the start of 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 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 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 or with centrally acting antihypertensive drugs or monoamine oxidase inhibitors (except MAO-B inhibitors) is generally not recommended, for details please refer to section 4.5.

• 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 thyrotoxicosis may be masked.

• Treatment with bisoprolol should not be stopped abruptly unless clearly indicated, especially in patients with ischaemic heart disease.

4.5 Interaction with other medicinal products and other forms of interaction

Calcium antagonists: Bisoprolol should be used with care with myocardial depressants or inhibitors of AV conduction such as verapamil and diltiazem, because of their negative inotropic effects on contractility, atrioventricular conduction and blood pressure. Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrio-ventricular block.

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

Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonidine, rilmenidine):
Concomitant use of centrally acting antihypertensive drugs may further decrease 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 nifedipine: 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. In patients with latent cardiac insufficiency, concomitant treatment with beta-blocking agents may lead to cardiac failure.

Class I antiarrhythmic agents, such as disopyramide and quinidine, may have a potentiating effect on atrial-conduction time and induce a negative inotropic effect when given concomitantly with beta-blockers.

Class III antiarrhythmic agents, such as amiodarone, may potentiate the effect of beta-blockers on atrial conduction time.

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.

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

Insulin and oral anti-diabetic drugs: The use of beta-blockers may intensify the blood sugar lowering effects of these drugs. Beta-blockers may also mask signs of hypoglycaemia, such as tachycardia.

Anaesthetic drugs:
Attenuation of the reflex tachycardia and increase of the risk of hypotension (for further information on general anaesthesia see also section 4.4). Continuation of β-blockade reduces the risk of arrhythmia during induction and intubation. The anaesthesiologist should be informed when the patient is receiving bisoprolol.

Alcohol may potentiate the hypotensive effects of beta-blockers.

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.

Beta-sympathomimetic agents (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both agents.

Prostaglandin synthetase inhibiting drugs: Decreased hypotensive effect.

Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. noradrenaline, adrenaline): 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. Higher doses of adrenaline 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, as well as other antihypertensive agents) may increase the risk of hypotension.

Moxisylyte: Possibly causes severe postural 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.

Combinations 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 foetus/newborn. 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, 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 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.

4.7 Effects on ability to drive and use machines

In a study of 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 the 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 (> 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)

Cardiac disorders:
Uncommon: AV-conduction disturbances, worsening of pre-existing heart failure,
bradycardia (decrease in pulse rate).

Very rare: Chest pain

Vascular disorders:
Common: feeling of coldness or numbness in the extremities.
Uncommon: Orthostatic hypotension.
Rare: Cyanosis of extremities, paraesthesia,
If you already have Raynaud's disease or intermittent claudication (pain in the legs
while walking) Bisoprolol may make these worse.

Metabolism and nutrition disorders:
Rare: Increased triglycerides.

Beta-blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia.

Psychiatric disorders:
Uncommon: sleep disorders (including vivid dreams), depression.
Rare: nightmares, hallucinations, anxiety, psychosis, confusion.

Nervous system disorders:
Common: tiredness*, exhaustion*, dizziness*, headache*.
Rare: syncope
Eye disorders:
Rare: dry eyes (to be considered if the patient uses lenses), impaired vision, reduced
tear flow.
Very rare: conjunctivitis, visual disturbances.

Ear and labyrinth disorders:
Rare: hearing impairment.

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: increased liver enzymes (ALAT, ASAT), hepatitis.

Skin and subcutaneous tissue disorders:
Common: perspiration
Rare: hypersensitivity reactions (such as itching, flush, rash and angioedema)
Very rare: beta-blockers may provoke or worsen psoriasis or induce psoriasis-like
rash, alopecia.

Musculoskeletal and connective tissue disorders:
Uncommon: muscular weakness, pain and cramps.
Rare: muscle and joint ache

Reproductive system and breast disorders:
Rare: potency disorders.

General disorders:
Common: lassitude, fatigue*, oedema
Uncommon: asthenia.

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

Reporting of suspected adverse reactions:
If you get any side effects, talk to your doctor. This includes any possible side effects
not listed in this leaflet. You can also report side effects directly via Yellow Card
scheme at : www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the
Google Play or Apple App Store. By reporting side effects you can help provide more
information on the safety of this medicine

4.9 Overdose

The most common signs expected with overdosage of a ß-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 ß-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, ß2-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C07A B07

Bisoprolol is a potent, highly β1-selective-adrenoreceptor blocking agent devoid of intrinsic sympathomimetic activity and without relevant membrane stabilising activity.

In patients with hypertension, the mode of action of bisoprolol is not quite clear but it is known to have a negative inotropic effect, to reduce cardiac output and to depress plasma renin activity.

In patients with angina, the blockade of β1-receptors reduces heart action and thus reduces oxygen demand. Hence bisoprolol is effective in eliminating or reducing the symptoms of angina pectoris.

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

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Microcrystalline cellulose (E460)
Magnesium stearate (E572)
Croscarmellose sodium

Coating ingredients:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 6000

6.2 Incompatibilities

None stated.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Blister:	Do not store above 25°C. Keep container in the outer carton.
Plastic container (bottle):	Do not store above 30°C. Store in the original container

6.5 Nature and contents of container

The tablets are packaged in thermoformed PVC/PVdC colourless foils laminated with aluminium foils or in polyethylene bottles with polyethylene snap-on closure caps supplied with tamper-evident ring.

The blister strips are packed into cardboard cartons

Pack sizes: 20, 28, 30, 50, 56, 98, 100 and 105 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

Ennogen IP Ltd
Unit G4,

Riverside Industrial Estate,
Riverside Way,
Dartford, DA1 5BS,
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 55612/0092

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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