SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bisoprolol 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg bisoprolol fumarate (2:1)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

Ivory coloured, scored, film-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Management of hypertension
2. Management of angina pectoris

4.2 Posology and method of administration

Adults: The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day. In some patients 5 mg per day may be adequate. In patients with final stage impairment of renal function (creatinine clearance < 20 ml/min) or liver function, the dose should not exceed 10 mg bisoprolol once daily.

Elderly: No dosage adjustment is normally required, but 5 mg per day may be adequate in some patients; as for other adults, dosage may have to be reduced

in cases of severe renal or hepatic dysfunction.
Children and adolescents under 18: There is no paediatric experience with bisoprolol, therefore its use cannot be recommended for children.

Route of administration: Oral

4.3 Contraindications

Bisoprolol is contra-indicated in chronic heart failure 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
- sick sinus syndrome
- sinoatrial block
- symptomatic bradycardia
- symptomatic
- severe bronchial asthma
- severe forms of peripheral arterial occlusive disease and Raynaud's syndrome
- untreated phaeochromocytoma~~)~~ (see section 4.4)
- metabolic acidosis
- hypersensitivity to bisoprolol or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

The treatment of stable chronic heart failure with bisoprolol has to be initiated with a special
titration phase.

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.

The initiation and cessation of treatment with bisoprolol necessitates regular monitoring.
There is no therapeutic experience of bisoprolol treatment of heart failure in patients with the
following diseases and conditions:

There is no therapeutic experience of bisoprolol treatment in heart failure in patients with the following diseases and conditions:

- insulin dependent diabetes mellitus (type I)

- severely impaired renal function impaired ~~liver~~ hepatic function
- restrictive cardiomyopathy
- congenital heart disease
- haemodynamically significant organic valvular disease
- myocardial infarction within 3 months

Bisoprolol must be used with caution in:

- bronchospasm (bronchial asthma, obstructive airways diseases)
- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia 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
- 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 postoperative
  period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthesist 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 antiarrhytmic drugs and with centrally acting antihypertensive drugs is generally not
recommended, for details please refer to section 4.5.

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, Cardicor 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 ß$_2$-stimulants may have to be increased.

Patients with psoriasis or with a history of psoriasis should only be given ß-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

Calcium antagonists such as verapamil and to a lesser extent of the diltiazem type: Negative influence on contractility~~,~~ and atrio-ventricular conduction.~~.~~ Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrioventricular block.

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.

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

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 atrial 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: Intensification of blood sugar lowering effect. Blockade of ß-adrenoceptors 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.). Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol.

Digitalis glycosides: Reduction of heart rate, increase of atrio-ventricular conduction time.

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-mediatedvasoconstrictor 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.

Combinations to be considered

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.

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.

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 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Frequency not known (cannot be estimated from available data)

Immune system disorders:
Unknown: Hypersensitivity reactions (such as itching, flush, rash and angioedema).

Cardiac disorders:
Very common: bradycardia.
Common: worsening of heart failure.
Uncommon: AV-conduction disturbances.

Investigations:
Rare: increased triglycerides, increased liver enzymes (ALAT, ASAT).

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.

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.

Skin and subcutaneous tissue disorders:
Rare: hypersensitivity reactions (itching, flush, rash).

Very rare: alopecia. Beta-blockers may provoke or worsen psoriasis or induce psoriasislike
Rash

Musculoskeletal and connective tissue disorders:
Uncommon: muscular weakness and cramps.

Vascular disorders:
Common: feeling of coldness or numbness in the extremities, hypotension.
Uncommon: orthostatic hypotension.

General disorders:
Common: asthenia, fatigue.

Hepatobiliary disorders:
Rare: hepatitis.

Reproductive system and breast disorders:
Rare: potency disorders.

Psychiatric disorders:
Uncommon: sleep disorders, depression.
Rare: nightmares, hallucinations.

Reporting of suspected adverse reactions
Reporting 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 the Yellow Card Scheme, website www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms
With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness have been reported.. In general the most common signs expected with overdosage of a-beta-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 in patients suffering from hypertension and/or coronary heart disease showing bradycardia and/or hypotension; all patients recovered. There is a wide interindividual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive. Therefore it is mandatory to initiate the treatment of these patients with a gradual uptitration according to the scheme given in section 4.2.

Management

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 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, ß$_2$-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective
ATC Code: C07AB07
Mechanism of action
Bisoprolol is a highly- beta$_1$-selective-adrenoceptor blocking agent, lacking intrinsic stimulation and relevant membrane stabilizing activity. It only shows low affinity to the ~~ß2~~ beta$_2$-receptor of the smooth muscles of bronchi and vessels as well as to the ~~ß2~~ beta$_2$-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and ~~ß2~~ beta$_2$-mediated metabolic effects. Its ~~ß1~~ beta$_1$-selectivity extends beyond the therapeutic dose range.

Clinical efficacy and safety

In total 2647 patients were included in the CIBIS II trial. 83% (n = 2202) were in NYHA class III and 17% (n = 445) were in NYHA class IV. They had stable symptomatic systolic heart failure (ejection fraction ≤ 35%, based on echocardiography). Total mortality was reduced from 17.3% to 11.8% (relative reduction 34%). A decrease in sudden death (3.6% vs. 6.3%, relative reduction 44%) and a reduced number of heart failure episodes requiring hospital admission (12% vs. 17.6%, relative reduction 36%) was observed. Finally, a significant improvement of the functional status according to NYHA classification has been shown. During the initiation and titration of bisoprolol hospital admissions due to bradycardia (0.53%), Hypotension (0.23%), and acute decompensation (4.97%) were observed, but they were not more frequent than in the placebo-group (0%, 0.3% and 6.74%). The numbers of fatal and disabling strokes during the total study period were 20 in the bisoprolol group and 15 in the placebo group.

The CIBIS III trial investigated 1010 patients aged ≥65 years with mild to moderate chronic
heart failure (CHF; NYHA class II or III) and left ventricular ejection fraction ≤35%, who had

not been treated previously with ACE inhibitors, beta-blockers, or angiotensin receptor
blockers. Patients were treated with a combination of bisoprolol and enalapril for 6 to 24
months after an initial 6 months treatment with either bisoprolol or enalapril.
There was a trend toward higher frequency of chronic heart failure worsening when bisoprolol was used as the initial 6 months treatment. Non inferiority of bisoprolol-first versus
enalapril-first treatment was not proven in the per-protocol analysis, although the two strategies for initiation of CHF treatment showed a similar rate of the primary combined
endpoint death and hospitalization at study end (32.4% in the bisoprolol-first group vs. 33.1
% in the enalapril-first group, per-protocol population). The study shows that bisoprolol can
also be used in elderly chronic heart failure patients with mild to moderate disease.

Bisoprolol is also used for the treatment of hypertension and angina.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases.

5.2 Pharmacokinetic properties

Absorption

Bisoprolol is absorbed and has a biological availability of about 90% after oral administration.
Distribution
The distribution volume is 3.5 l/kg. The plasma protein binding of bisoprolol is about 30%.

Linarity
The kinetics of bisoprolol are linear and independent of age.

Special population
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. The pharmacokinetics in patients with stable chronic heart failure and with impaired liver or renal function has not been studied. 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

Tablet core:
Maize starch
Microcrystalline cellulose
Crospovidone
Anhydrous calcium hydrogen phosphate
Magnesium stearate
Colloidal anhydrous silica.

Film-coating:
Hypromellose
Titanium dioxide (E171)
Macrogol 6000
Dimeticone 350
Iron oxide yellow (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life for this product is 3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blister packs of aluminium foil and PVC/PVDC in cartons.

Pack size: 28 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 43870/0029

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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