Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bisoprolol Fumarate 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains bisoprolol fumarate 5 mg

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Pale yellow round biconvex, with 'BIS' over '5' on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Bisoprolol fumarate can be used for the management of hypertension and the management of angina pectoris.

4.2 Posology and method of administration

For hypertension and angina pectoris the usual dosage ranges from 5 to 20 mg of bisoprolol fumarate.

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 (creatinine clearance, 20 ml/min) or liver function, the dose should not exceed 10 mg bisoprolol once daily. Experience of 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 5 mg per day may be adequate in some patients; as for other adults, doses 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In patients with ischaemic heart disease, treatment should not be withdrawn abruptly; gradual dosage reduction over 1-2 weeks is recommended.

Administration
Oral use.

Tablets should be taken in the morning and can be taken with food or with water.

4.3 Contraindications

- Acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- Cardiogenic shock
- AV block of second or third degree (without a pacemaker)
- Sick sinus syndrome
- Sinoatrial block
- Bradycardia with less than 60 beats/min before start of therapy
- Hypotension (systolic blood pressure less than 100 mm Hg)
- Severe bronchial asthma or severe chronic obstructive pulmonary disease
- Late stages of peripheral arterial occlusive disease and Raynaud's syndrome
- Untreated phaeochromocytoma (see section 4.4 Special warnings and precautions for use)
- Metabolic acidosis
- Hypersensitivity to bisoprolol or to any of the excipients

4.4 Special warnings and precautions for use

β-adrenergic blocking agents have been used safely and efficaciously in elderly patients. However, elderly patients may be more susceptible to some adverse effects of these agents. Elderly patients are more likely to have age-related peripheral vascular disease, which may require caution in patients receiving β-adrenergic blocking agents. In addition the risk of β-blocker-induced hypothermia may be increased in elderly patients.

Other formulations of bisoprolol containing medicinal products are used in the treatment of chronic heart failure. The use of β-blocking agents in this indication needs a very cautious approach and should be started with a very strict titration phase. In this phase increments are necessary all of which are not possible with the current medicinal product. This product should therefore not be used in the treatment of chronic heart failure.

Bisoprolol must be used with caution in:

- 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.
- Diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia can be masked. β-adrenergic blocking agents may mask tachycardia associated with hypoglycemia, but not dizziness and sweating; β -adrenergic blocking agents may adversely affect recovery from hypoglycemia and impair peripheral circulation; these effects may theoretically be more likely with the noncardioselective agents and less likely with labetalol and cardioselective agents.
- Strict fasting
- Ongoing desensitisation therapy
- AV block of first degree
- Prinzmetal's angina
- Peripheral arterial occlusive disease (intensification of complaints might happen especially during the start of therapy) Raynaud’s syndrome and other peripheral vascular diseases (β-adrenergic blocking agents may reduce peripheral circulation and worsen these conditions).
- 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 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.

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 a thyreotoxicosis may be masked.

Hepatic function impairment: Metabolism of β-adrenergic blocking agents that undergo hepatic metabolism may be decreased; patients with impaired hepatic function may require lower doses of β-adrenergic blocking-agents.

Myasthenia gravis: β-adrenergic blocking agents may potentiate a myasthenic condition, including muscle weakness and double vision.

Renal function impairment: May impair β-adrenergic blocking agent clearance; risk of reduced renal blood flow; patients with impaired renal function may require reduced doses of β-adrenergic blocking agents.

Hyperthyroidism: β-adrenergic blocking agents may mask tachycardia symptoms; abrupt withdrawal may intensify symptoms.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations not recommended

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.

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.

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-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 atrio-ventricular conduction time may be potentiated.

Parasympathomimetic drugs: Atrio-ventricular conduction time may be increased.

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

Insulin and oral antidiabetic drugs: Intensification 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. 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: Reduction of heart rate, 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.

Tricyclic antidepressants, barbiturates, phenothiazines as well as other antihypertensive agents: Increased blood pressure lowering effect.

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 Pregnancy and lactation

Pregnancy:

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, beta-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 beta-adrenoceptor blockers is necessary, beta1-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 bisoprolol is secreted into breast milk, 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, 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 the treatment and upon change of medication as well as in conjunction with alcohol.

4.8 Undesirable effects

The following data results from post-marketing experience with bisoprolol:
Common (>1% and <10%), uncommon (>0.1% and <1%), rare (>0.01% and <0.1%), very rare (<0.01%), single cases.

Cardiac disorders:
Uncommon: bradycardia, AV-stimulus disturbances, worsening of heart failure.

Ear and labyrinth disorders:
Rare: hearing impairment.

Eye disorders:
Rare: reduced tear flow (to be considered if the patient uses lenses).
Very rare: conjunctivitis.

Gastrointestinal disorders:
Common: Nausea, vomiting, diarrhoea, constipation.

General disorders:
Uncommon: Muscular weakness and cramps.

Hepatobiliary disorders:
Rare: increased liver enzymes (ALAT, ASAT), hepatitis.

Metabolism and nutrition disorders:
Rare: Increased triglycerides.

Nervous system disorders:
Common: Tiredness*, exhaustion*, dizziness*, headache*.
Uncommon: Sleep disturbances, depression.
Rare: Nightmares, hallucinations.

Reproductive system and breast disorders:
Rare: Potency disorders.

Respiratory, thoracic and mediastinal disorders:
Uncommon: Bronchospasm in patients with bronchial asthma or a history of obstructive airways disease.
Rare: allergic rhinitis.

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

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

*These symptoms especially occur at the beginning of the therapy. They are generally mild and usually 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.

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 pharmacologic actions and recommendations for other beta-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, beta2-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective

ATC code: C07AB07

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

As with other β1-blocking agents, the mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma renin levels.

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.

5.2 Pharmacokinetic properties

Following oral administration of bisoprolol fumarate, 90% of bisoprolol is absorbed from the gastrointestinal tract. Peak plasma concentrations are achieved after 3 hours, 40µg/l after a 10 mg dose, and appear not to be affected by concomitant food intake or fasting. The systemic bioavailability of bisoprolol, given as fumarate, is 90%, and hence pre-systemic metabolism is below 10%.

There are only small intra- and interindividual variations in the plasma levels of the drug. The mean plasma half-life of 10 to 20 hours is long compared to that of other β-blockers. About 50% of bisoprolol is excreted unchanged in the urine, and other 50% is biotransformed in the liver with subsequent elimination of pharmacologically inactive metabolites via the kidneys. The renal clearance is 160 ml/min and the non-renal clearance 150 ml/min. The pharmacokinetic properties of bisoprolol are not dependent on age or dose in the range 2.5-100mg.
The pharmacokinetics of bisoprolol is not altered in patients with febrile infectious diseases. Bisoprolol is slowly distributed throughout the body, with an apparent distribution volume of 3 l/kg.
In animal experiment bisoprolol has been found in the lung, kidneys, brain and the heart after oral and intravenous administration. In plasma about 30% of bisoprolol is protein bound. Information about concentrations of bisoprolol in the cerebrospinal fluid, the cerebrospinal fluid/plasma ratio, the concentration in the breast milk, and its placental transfer, in man is not available.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline
Mannitol (E421)
Croscarmellose sodium
Magnesium stearate

Film Coating
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

2 years

6.4 Special precautions for storage

For blister packs: Do not store above 25°C.
Store in original package.

For plastic container: Do not store above 30°C.
Store in original container.

6.5 Nature and contents of container

White round high density polyethylene tamper proof container with polyethylene cap and tamper evident ring.
Thermoformed transparent PVC/PVdC – aluminium blister strips (PVC foil 250 µm thick, PVdC coating 23 µm, and aluminium foil 20 µm thick)
Pack sizes - 14, 20, 28, 30, 50, 56, 98, 100, 105 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

Pinewood Laboratories Ltd., Trading as: ***Pinewood Healthcare***
Ballymacarbry
Clonmel
County Tipperary

8 MARKETING AUTHORISATION NUMBER

PA0281/095/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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May 2007