IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1328/135/002
Case No: 2079104

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

B & S Healthcare

Unit 4, Bradfield Road, **Ruislip**, **Middlesex**, **HA4 0NU**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Emcor 10mg Film-coated Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **04/06/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Emcor 10mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10mg film-coated tablet contains 10mg Bisoprolol fumerate.
For full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet
Product imported from Spain
Pale orange-light orange, heart-shaped, scored and film-coated tablet.

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In patients with ischaemic heart disease, treatment should not be withdrawn abruptly; gradual dosage reduction over 1-2 weeks is recommended.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

Bisoprolol 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.

- 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.
- 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.

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.
- 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).
- 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 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.

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 beta-2-stimulants may have to be increased.

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 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

Combinations not recommended: Calcium antagonists such as verapamil and to a lesser extent diltiazem: 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.

Centrally-acting antihypertensive drugs (e.g. clonidine methyldopa, moxonodine, rilmenidine): Concomitant use of centrally-acting antihypertensive drugs may lead to reduction of heart rate and cardiac output and to vasodilation.

Abrupt withdrawal may increase the 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.

Class-I antiarrhythmic drugs (e.g. disopyramide, quinidine):
Effect on atrio-ventricular 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: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.

Topical beta-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.

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

Concomitant use with antihypertensive agents as well as with other medicines with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.

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.

ß-sympathomimetics (e.g. isoprenaline, dobutamine): combination with bisoprolol may reduce the effect of both agents.

Sympathomimetics that activate ß- and α- adrenoceptors: 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 non-selective ß- blockers.

Sympathomimetic agents: Combination with bisoprolol may reduce the effect of both agents. Higher doses of epinephrine may be necessary for treatment of allergic reactions.

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- 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, beta-1-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 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 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:

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.

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: beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia.

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: fatigue*
Uncommon: asthenia.

Hepatobiliary disorders:
Rare: hepatitis.

Reproductive system and breast disorders:
Rare: potency disorders.

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

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

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4.9 Overdose

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. Bradycardia and/or hypotension were noted. All patients recovered. There is a wide interindividual variation in sensitivity to one single high dose of bisoprolol; patients with heart failure are probably particularly sensitive.

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 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, $ß_2$-sympathomimetic drugs and/or aminophylline.
Hypoglycaemia: Administer i.v. glucose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ß-blocking agents, selective (C07AB07)

Bisoprolol is a potent, highly beta-1-selective adrenoreceptor blocking agent devoid of intrinsic sympathomimetic activity and without relevant membrane stabilising activity.

As with other beta-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 beta-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

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients
Silica colloidal anhydrous
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

The shelf-life expiry date of this product shall be the date shown on the blister strip and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

This medicinal product does not require any special storage requirements.

6.5 Nature and contents of container

Cartons containing blister packs of 30 or 60 tablets.

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 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1328/135/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th June 2010

10 DATE OF REVISION OF THE TEXT