IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PPA1151/048/003
Case No: 2069197

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

Imbat Limited

Unit L2, **North Ring Business Park**, **Santry**, **Dublin 9**

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

Cardicor, 3.75 Milligram

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 **26/08/2009**.

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

Cardicor 3.75mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film-Coated Tablet contains 3.75mg bisoprolol hemifumarate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-Coated Tablet.

Product imported from Italy and the UK:
Each tablet is off-white, heart-shaped, scored and Film-Coated.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of stable chronic moderate to severe heart failure with reduced systolic ventricular function (ejection fraction ≤35%, based on echocardiography) in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides (for additional information see section 5.1).

4.2 Posology and method of administration

The patients should have stable chronic heart failure without acute failure during the past six weeks and a mainly unchanged basic therapy during the past two weeks. They should be treated at optimal dose with an ACE inhibitor (or other vasodilator in case of intolerance to ACE inhibitors) and a diuretic, and optionally cardiac glycosides, prior to the administration of bisoprolol.

It is recommended that the treating physician should be experienced in the management of chronic heart failure.

Warning: The treatment of stable chronic heart failure with bisoprolol has to be initiated with a titration phase as given in the description below.

The treatment with bisoprolol is to be started with a gradual uptitration according to the following steps:

- 1.25 mg once daily for 1 week, if well tolerated increase to

- 2.5 mg once daily for a further week, if well tolerated increase to

- 3.75 mg once daily for a further week, if well tolerated increase to

- 5 mg once daily for the 4 following weeks, if well tolerated increase to

- 7.5 mg once daily for the 4 following weeks, if well tolerated increase to

- 10 mg once daily for the maintenance therapy.

After initiation of treatment with 1.25 mg, the patients should be observed over a period of approximately 4 hours (especially as regards blood pressure, heart rate, conduction disturbances, signs of worsening of heart failure).

The maximum recommended dose is 10 mg once daily.

Occurrence of adverse events may prevent all patients being treated with the maximum recommended dose. If necessary, the dose reached can also be decreased step by step. The treatment may be interrupted if necessary and reintroduced as appropriate. During the titration phase, in case of worsening of the heart failure or intolerance, it is recommended first to reduce the dose of bisoprolol, or to stop immediately if necessary (in case of severe hypotension, worsening of heart failure with acute pulmonary oedema, cardiogenic shock, symptomatic bradycardia or AV block).

Treatment of stable chronic heart failure with bisoprolol is generally a long-term treatment.

The treatment with bisoprolol is not recommended to be stopped abruptly since this might lead to a transitory worsening of heart failure. If discontinuation is necessary, the dose should be gradually decreased divided into halves weekly.

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

Renal or liver insufficiency

There is no information regarding pharmacokinetics of bisoprolol in patients with chronic heart failure and with impaired liver or renal function. Uptitration of the dose in these populations should therefore be made with additional caution.

Elderly
No dosage adjustment is required.

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

4.3 Contraindications

Bisoprolol is contraindicated in chronic heart failure patients with:

- 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 the 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 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:
- 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
- AV block of first degree
- 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 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.

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

- NYHA class II heart failure
- insulin dependent diabetes mellitus (type I)
- impaired renal function (serum creatinine>300 micromol/l)
- impaired liver function
- patients older than 80 years
- restrictive cardiomyopathy
- congenital heart disease
- haemodynamically significant organic valvular disease
- myocardial infarction within 3 months

Combination of bisoprolol with calcium antagonists of the verapamil and diltiazem type, with Class I antiarrhythmic drugs and with centrally acting antihypertensive drugs is generally not recommended, for details please refer to section 4.5.

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.

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 initiation of treatment with bisoprolol necessitates regular monitoring. For the posology and method of administration please refer to section 4.2.
The cessation of therapy with bisoprolol should not be done abruptly unless clearly indicated. For further information please refer to section 4.2.

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.

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 atrio-ventricular 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 beta-adrenoreceptors 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.).

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.

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-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 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 Pregnancy and lactation

Pregnancy:
Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/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 fetus 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 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

Clinical trial data
The table below shows incidences of adverse events reported from both the placebo and the bisoprolol cohort of the CIBIS II trial. Regardless of causal relationship all adverse events are included. Each patient is only counted once for each adverse event occurring in at least 5% of the study population.

Preferred Term WHO	Placebo (n=1321)		Bisoprolol (n=1328)	
	Pat. with AE	% Pat. With AE	Pat. with AE	Pat. with AE
Cardiac Failure	301	22.8	244	18.4
Dyspnoea	224	17.0	183	13.8
Dizziness	126	9.5	177	133
Cardiomyopathy	132	10.0	141	10.6
Bradycardia	60	4.5	202	15.2
Hypotension	96	7.3	152	11.4
Tachycardia	144	10.9	79	5.9
Fatigue	94	7.1	123	9.3
Viral infection	75	5.7	86	6.5
Pneumonia	69	5.2	65	4.9

AE = Adverse Events

Post-marketing data
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

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.

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 highly beta1-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows low affinity to the beta2-receptor of the smooth muscles of bronchi and vessels as well as to the beta2-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta2-mediated metabolic effects. Its beta1-selectivity extends beyond the therapeutic dose range.

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 admission 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.

Bisoprolol is already 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

Bisoprolol is absorbed and has a biological availability of about 90% after oral administration. The plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg. Total clearance is approximately 15 l/h. The half-life in plasma of 10-12 hours gives a 24 hour effect after dosing once daily.

Bisoprolol is excreted from the body by two routes. 50% is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in an unmetabolised form. 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.

The kinetics of bisoprolol are linear and independent of age.

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

Silica, colloidal anhydrous
Magnesium stearate
Crospovidone
Maize starch
Microcrystalline cellulose
Calcium hydrogen phosphate, anhydrous.
Dimeticone
Macrogol 400
Titanium dioxide (E171)
Iron oxide yellow (E172)
Hypromellose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

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

6.4 Special precautions for storage

Do not store above 25^{o}C.

6.5 Nature and contents of container

Cardboard outer containing blister strips
Pack size 28

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

Imbat Limited
Unit L2
North Ring Business Park
Santry
Dublin 9

8 Parallel Product Authorisation Number

PPA 1151/48/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation 2nd May 2008

10 DATE OF REVISION OF THE TEXT

August 2009