Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bellimcor 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of bisoprolol fumarate.
Excipients: also includes lactose monohydrate 65.6 mg per tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

The tablets are pale yellow mottled in colour, round and convex with the following identification markings:
"BI" centrally above a break-line with "5" below. The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension
Chronic stable angina pectoris

4.2 Posology and method of administration

Bellimcor 5mg tablets are for oral administration.

The dosage should be individually adjusted. It is recommended to start with the lowest possible dose. In some patients, 5 mg per day may be adequate. The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day.

Patients with kidney impairment
In patients with severe renal impairment, (creatinine clearance < 20ml/min) the dose should not exceed 10 mg once daily. This dosage may eventually be divided into halves.

Patients with severe liver impairment
No dosage adjustment is required, however careful monitoring is advised.

Elderly:
No dosage adjustment is normally required. It is recommended to start with the lowest possible dose.

Children under 12 years and adolescents:
There is no paediatric experience with this medicine, therefore its use cannot be recommended.

Discontinuation of treatment
Treatment should not be stopped abruptly (see section 4.4 Special warnings and precautions for use). The dosage should be diminished slowly by a weekly halving of the dose**.**

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
- Symptomatic bradycardia with less than 60 beats/min before start of therapy
- Symptomatic hypotension (systolic blood pressure less than 100 mm Hg)
- Severe bronchial asthma or severe chronic obstructive pulmonary disease
- Severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome
- Metabolic acidosis
- Hypersensitivity to bisoprolol fumarate or to any of the excipients listed
- Untreated phaeochromocytoma *(see 4.4)*
- Combinations with floctafenine and sultopride *(see also section 4.5)*

4.4 Special warnings and precautions for use

Other formulations of bisoprolol fumarate 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.

The cessation of therapy with bisoprolol fumarate should not be done abruptly unless clearly indicated. There is a risk of myocardial infarction and sudden death if the treatment is suddenly discontinued in patients with ischaemic heart disease. For more information please refer to section 4.2.

Bisoprolol fumarate must be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.

Bisoprolol fumarate must be used with caution in:

- Diabetes mellitus showing large fluctuations in blood glucose values; symptoms of hypoglycaemia (e.g. tachycardia, palpitations or sweating) may be masked. Blood glucose levels should be monitored during treatment with bisoprolol fumarate
- Strict fasting
- Ongoing desensitisation therapy. As with other ß-blocking agents bisoprolol fumarate may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine treatment does not always give the expected therapeutic effect.
- AV block of first degree
- Printzmetal’s angina: ß-blocking agents may increase the number and duration of anginal attacks in patients with Printzmetal’s angina. The use of ß-1 selective adrenoceptor blocking agents is possible in cases of mild forms and only in combination with a vasodilating agent.
- Peripheral circulatory disorders, such as Raynaud’s phenomena and intermittent claudication: intensification of complaints might happen especially during start of therapy.

In patients with phaeochromocytoma (see section 4.3), bisoprolol fumarate must not be administered until after α-receptor blockade.

Patients with psoriasis or with a history of psoriasis should only be given beta-blockers (e.g. bisoprolol fumarate) after a careful balancing of benefits against risks.

Thyrotoxicosis, adrenergic symptoms may be masked under treatment with bisoprolol fumarate.

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 reflex tachycardia, and 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.

The initiation of treatment with bisoprolol fumarate necessitates regular monitoring, especially when treating elderly patients.

Bronchospasm (bronchial asthma, obstructive airways disease): In bronchial asthma or other chronic obstructive airway 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. It is recommended to have a functional respiratory test done before the initiating of treatment.

The combination with amiodarone is not recommended considering the risk of contractility automatism and conduction disorders (suppression of compensatory sympathetic reactions).
This medicinal product contains 65.6 mg lactose monohydrate.
Patients with rare hereditary conditions such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not use this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations contra-indicated
Floctafenine: beta blockers may impede the compensatory cardiovascular reactions associated with hypotension or shock that may be induced by floctafenine.
Sultopride: bisoprolol fumarate should not be concomitantly administered with sultopride since there is an increase risk of ventricular arrhythmia.

Combinations not recommended

- Calcium antagonists of the verapamil type and to a lesser extend of the diltiazem type (bepridil): negative influence on contractility and atrio-ventricular conduction and blood pressure. Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrio-ventricular block
- Centrally- acting antihypertensive drugs (e.g. Clonidine, methyldopa, moxonodine, rilmenidine): Concomitant use of centrally-acting antihypertensive drugs may further decrease the central sympathetic tonus and may thus lead to reduction of heart rate and cardiac output and to vasodilatation. Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase the risk of 'rebound hypertension'.

Combinations to be used with caution:
- 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.
- Class III antiarrhythmic drugs (e.g. amiodarone): effect on atrial conduction time may be potentiated.
- Calcium antagonists of the dihydropyridine derivatives (e.g.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..
- Parasympathomimetic drugs (including tacrine): atrio-ventricular conduction time and the risk of bradycardia may be increased.
- Topical beta-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol fumarate.
- Insulin and oral anti-diabetic drugs: intensification of blood sugar lowering effect. Blockade of ß-adrenoreceptor may mask symptoms of hypoglycaemia.
- Anaesthetic agents: attentuation of the reflex tachycardia and increase of the risk of hypotension. Continuation of ß-blockade reduces the risk of arrhythmia during induction and intubation. The anaesthesiologist should be informed when the patient is receiving bisoprolol fumarate.

- Digitalis glycosides: reduction of heart rate, increase of atrio-ventricular conduction time.
- Non-steroidal anti-inflammatory drugs (NSAIDs): decreased hypotensive effect of bisoprolol fumarate.
- Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. norepinephrine, epinephrine): Combination with bisoprolol fumarate 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
- 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: increased blood pressure lowering effect.
- Baclofene: increased antihypertensive activity.
- Iodated contrast products: Beta-blockers may impede the compensatory cardiovascular reactions associated with hypotension or shock induced by iodated contrast products.
- Beta-sympathomimetics (e.g. isoprenaline, dobutamine): Combination with bisoprolol fumarate may reduce the effect of both agents.

Combinations to be considered

- Mefloquine: increased risk of bradycardia.
- Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the betablockers but also risk of hypertensive crisis.
- Corticosteroids: decrease of antihypertensive effect due to water and sodium retention.
- Ergotamine derivatives: exacerbation of peripheral circulatory disturbances.
- Rifampicin: slight reduction of the half life of bisoprolol fumarate possible due to the induction of hepatic drug-metabolising enzymes. Normally no dosage adjustment is necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Bisoprolol fumarate has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. In general, β-adrenoceptor blocking agents reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse reactions (e.g. hypoglycaemia, bradycardia) may occur in the fetus and newborn infant. If treatment with β-adrenoceptor blocking agents is necessary, β_1-adrenoceptor blocking agents are preferable.
Bisoprolol fumarate should not be used during pregnancy unless clearly necessary. If treatment with bisoprolol fumarate is considered necessary, the uteroplacental blood flow and 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:
There are no data on the excretion of bisoprolol fumarate in human breast milk or the safety of bisoprolol fumarate exposure in infants. Therefore breastfeeding is not recommended during administration of bisoprolol fumarate.

4.7 Effects on ability to drive and use machines

In a study with coronary heart disease patient's bisoprolol fumarate did not impair driving performance. However, due to individual variations in reactions to the medicinal product, 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 adverse reactions considered at least possibly related to treatment are listed below by body system organ class and absolute frequency.

Frequencies are defined as: Very common (≥ 10%), common (≥ 1% and < 10%), uncommon (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%), very rare (< 0.01%))

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

Nervous system disorders
Common: dizziness*, headache*
Rare: syncope

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

Ear and labyrinth disorders
Rare: hearing disorders

Cardiac disorders
Uncommon: AV-conduction disturbances; worsening of pre-existing heart failure; bradycardia

Vascular disorders
Common: feeling of coldness or numbness in the extremities, hypotension especially in patients with heart failure

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

Hepatobilary disorders
Rare: hepatitis

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

Musculoskeletal and connective tissue disorders
Uncommon: muscle weakness, muscle cramps

Reproductive system and breast disorders
Rare: potency disorders

General disorders and administrative site conditions
Common: fatigue*
Uncommon: asthenia

Investigations
Rare: increased triglycerides, increased liver enzymes (ALAT, ASAT)
Applies only to hypertension or angina pectoris:

*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 bisoprolol fumarate are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia.

There is limited experience with overdose of bisoprolol fumarate, only a few cases of overdose with bisoprolol fumarate have been reported. Bradycardia and/or hypotension were noted. All patients recovered. There is a wide inter-individual variation in sensitivity to one single high dose of bisoprolol fumarate and patients with heart failure are probably very sensitive.
In general, if overdose occurs, discontinuation of bisoprolol fumarate treatment and supportive and symptomatic treatment is recommended.
Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures may 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 temporary pacing.
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.
Limited data suggest that bisoprolol fumarate is hardly dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective β_1-blocking agents, ATC code: C07AB07

Bisoprolol fumarate is a potent, highly β_1-selective-adrenoceptor blocking agent devoid of intrinsic sympathomimetic activity. As with other β_1-blocking agents, the mode of action in hypertension is unclear. However, it is known that bisoprolol fumarate markedly depresses plasma renin activity.

In patients with angina, the blockade of β-receptors reduces heart action and thus reduces oxygen demand.

Bisoprolol fumarate possesses similar local anaesthetic properties to propranolol.

5.2 Pharmacokinetic properties

Bisoprolol fumarate 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 plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg. The total clearance is approximately 15 l/h.
The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage.

Bisoprolol fumarate 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 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 kinetics of bisoprolol fumarate are linear and independent of age.

In patients with chronic heart failure (NYHA stage III) the plasma levels of bisoprolol fumarate 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 β-blocking agents, bisoprolol fumarate caused maternal toxicity (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

Lactose monohydrate
Cellulose, microcrystalline (E460)
Magnesium stearate (E572)
Crospovidone
Pigment Blend: Yellow PB 22812 (lactose monohydrate and iron oxide yellow (E172))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Bellimcor 5 mg tablets are presented in:
Blisters comprising of PVC/PVdC/aluminium foil, contained within a printed carton box. Each carton will contain either: 20, 28, 30, 50, 56, 60 or 100 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

Ranbaxy Ireland Ltd.
Spafield
Cork Road
Cashel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 408/54/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th June 2001
Date of last renewal: 13th September 2010

10 DATE OF REVISION OF THE TEXT

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