Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bisoprolol Fumarate 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg bisoprolol fumarate.
Excipient with known effect: 131 mg of lactose monohydrate/tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Beige mottled, round and convex, uncoated, “BI” and “10” debossed on either side of a break-line on the top side, plain on the bottom side.

The tablets can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of stable chronic heart failure with reduced systolic left ventricular function 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

Posology
Standard treatment of CHF consists of an ACE inhibitor (or an angiotensin receptor blocker in case of intolerance to ACE inhibitors, a Beta-blocking agent, diuretics, and when appropriate cardiac glycosides. Patients should be stable (without acute failure) when bisoprolol treatment is initiated.

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

Transient worsening of heart failure hypotension or bradycardia may occur during the titration period and thereafter.

Titration Phase

The treatment of stable chronic heart failure with bisoprolol requires a titration phase.

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.

The maximum recommended dose is 10 mg once daily.

Close monitoring of vital signs (heart rate, blood pressure) and symptoms of worsening heart failure is recommended during the titration phase. Symptoms may already occur within the first day after initiating therapy.

Treatment Modification

If the maximum recommended dose is not well tolerated, gradual dose reduction may be considered.

In case of transient worsening of heart failure, hypotension, or bradycardia reconsideration of the dosage of the concomitant medication is recommended. It may also be necessary to temporarily lower the dose of bisoprolol or to consider discontinuation. The reintroduction and/or uptitration of bisoprolol should always be considered when the patient becomes stable again. If discontinuation is considered, gradual dose decrease is recommended, since abrupt withdrawal may lead to acute deterioration of the patient's condition.

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

Special Population

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

Older people
No dosage adjustment is required.

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

Method of administration

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.

4.3 Contraindications

Bisoprolol is contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- 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
- symptomatic bradycardia
- symptomatic hypotension
- severe bronchial asthma or severe chronic obstructive pulmonary disease
- severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome
- untreated phaeochromocytoma (see section 4.4)
- metabolic acidosis

4.4 Special warnings and precautions for use

Warnings

The treatment of stable chronic heart failure with bisoprolol has to be initiated with a special titration phase (see section 4.2).

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 (see section 4.2).

Precautions

The initiation of treatment of stable chronic heart failure with bisoprolol necessitates regular monitoring. For the dosage and method of administration see section 4.2.

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

Bisoprolol must be used with caution in:

- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia (e.g. tachycardia, palpitations or sweating) 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 may 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.

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

The symptoms of thyrotoxicosis may be masked under treatment with bisoprolol.

In patients with phaeochromocytoma bisoprolol must not be administered until after alpha-receptor blockade.

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 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 pulmonary diseases, which may cause symptoms, concomitant bronchodilating therapy is recommended. 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.

Lactose: this medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

- **Combinations not recommended**

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.

Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type: Negative effect on contractility and atrio-ventricular conduction. 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, moxonidine, 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 vasodilation. Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase the risk of "rebound hypertension".

- **Combinations to be used with caution**

Calcium antagonists of the dihydropyridine type (e.g. felodipine and amlodipine): Concomitant use may increase the risk of hypotension, and an increase in the risk of 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.

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:
Increase of blood sugar lowering effect. Blockade of betaadrenoreceptors 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 section 4.4).

Digitalis glycosides:
Increase of atrio-ventricular conduction time, reduction in heart rate.

Non-steriodal anti-inflammatory drugs (NSAIDs):
NSAIDs may reduce the hypotensive effect of bisoprolol.

Beta-sympathomimetics (eg. isoprenaline, dobutamine):
Combination with bisoprolol may reduce the effect of both agents.

Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. norepinephrine, epinephrine):
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 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) 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 betablockers but also risk of hypertensive crisis.

Rifampicin: Slight reduction of the half-life of bisoprolol possible due to the induction of the hepatic drugmetabolising enzymes. Normally no dosage adjustment is necessary.

Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

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, 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, $beta_1$-selective adrenoceptor blockers are preferable.

Bisoprolol is not recommended during pregnancy unless clearly necessary. If treatment is considered necessary, monitoring of the uteroplacental blood flow and the foetal growth is recommended. In case of harmful effects on pregnancy or the foetus consideration of alternative treatment is recommended. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

Breast-feeding

There is no data on the excretion of bisoprolol in human breast milk or the safety of bisoprolol exposure in infants. 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, depending on the individual patients response to treatment an effect on the ability to drive a vehicle or to use machines cannot be excluded. This needs to be considered particularly at start of treatment, upon change of medication, or in conjunction with alcohol.

4.8 Undesirable effects

Very common (≥10%),
common (≥1% and < 10%),
uncommon (≥0.1% and < 1%),
rare (≥0.01% and < 0.1%),
very rare (< 0.01%).

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

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

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

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

Gastrointestinal disorders
Common: gastrointestinal complaints such as nausea, vomiting, diarrhoea, Constipation

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

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

General disorders
Common: asthenia, fatigue

Hepatobiliary disorders
Rare: hepatitis.

Reproductive system and breast disorders
Rare: potency disorders

Psychiatric disorders
Uncommon: depression, sleep disorders
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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

The most common signs expected with overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is limited experience with overdose of bisoprolol, only a few cases of overdose with bisoprolol 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 and patients with heart failure are probably very sensitive.

In general, if overdose occurs, discontinuation of bisoprolol 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 glucagons 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 bisorolol is hardly dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-blocking agents, selective
ATC code: C07_AB07

Bisoprolol is a highly $beta_1$-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows low affinity to the $beta_2$-receptor of the smooth muscles of bronchi and vessels as well as to the $beta_2$-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and $beta_2$-mediated metabolic effects. Its $beta_1$-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.

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-blocking agents, 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

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 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-blocking agents, 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

Lactose monohydrate
Cellulose, microcrystalline E460
Magnesium stearate E572
Crospovidone (Type B) E1201
Beige PB 27215 (lactose monohydrate and iron oxides red and yellow [E172])

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blisters comprising of uPVC/PVdC/aluminium foil contained within a printed cardboard carton.

Pack sizes: 10, 14, 20, 28, 30, 50, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Niche Generics Limited
1, The Cam Centre,
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8 MARKETING AUTHORISATION NUMBER

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