Public Assessment Report

Decentralised Procedure

Bisoprolol Fumarate 1.25 mg Tablets
Bisoprolol Fumarate 2.5 mg Tablets
Bisoprolol Fumarate 5 mg Tablets
Bisoprolol Fumarate 10 mg Tablets

PL 20254/0034
PL 20254/0035
PL 20254/0036
PL 20254/0037

UK/H/1817/01-04/DC

Orifarm Generics A/S
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Orifarm Generics A/S Marketing Authorisations (licences) for the medicinal products Bisoprolol Fumarate 1.25 mg, 2.5 mg, 5 mg and 10 mg Tablets (Product Licence numbers: PL 20254/0034-7). These medicines are available on prescription only.

Bisoprolol Fumarate 1.25 mg, 2.5 mg, 5 mg and 10 mg Tablets belong to a group of medicines known as beta blockers. These medicines work by affecting the body’s response to some nerve impulses, especially in the heart. As a result, bisoprolol slows down heart rate and makes the heart more efficient at pumping blood around the body.

Bisoprolol is used:
- To treat heart failure. Heart failure occurs when the heart muscle is weak and unable to pump enough blood to supply the body’s needs. It is used in combination with other medicines suitable for this condition (such as ACE inhibitors, diuretics and heart glycosides)
- In the treatment of heart disease and chest pain (angina pectoris) caused by a shortage of oxygen in the heart muscle
- In the treatment of high blood pressure (hypertension)

The data submitted in support of these applications raised no clinically significant safety concerns and it was therefore judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
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### Module 1

**Information about decentralised procedure**

| Name of the product in the Reference Member State | Bisoprolol Fumarate 1.25 mg Tablets  
Bisoprolol Fumarate 2.5 mg Tablets  
Bisoprolol Fumarate 5 mg Tablets  
Bisoprolol Fumarate 10 mg Tablets |
|--------------------------------------------------|----------------------------------------------------------------------------------|
| **Type of application (Eudratrack details)**     | Level 1 Abridged  
Level 2 Initial  
Level 3 10.1  
Level 4 Chemical substance  
Level 5 Prescription only |
| Name of the active substance (INN)               | Bisoprolol Fumarate |
| Pharmacotherapeutic classification (ATC code)    | Beta blocking agents selective (C07A B07) |
| Pharmaceutical form and strength                | Tablets 1.25mg, 2.5mg, 5mg, 10mg |
| Reference numbers for the decentralised Procedure | UK/H/1817/01-04/DC |
| Reference Member State                          | United Kingdom |
| Member States concerned                         | DK SE NO |
| Date of start of the procedure                  | 15 May 2008 |
| End date of decentralised procedure             | 8 February 2010 |
| Marketing Authorisation Number                  | PL 20254/0034-7 |
| Name and address of the authorisation holder    | Orifarm Generics A/S  
Energivej 15, 5260 Odense S  
Denmark |
Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Bisoprolol Fumarate 1.25 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 1.25 mg of bisoprolol fumarate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
White to off white round biconvex tablet

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).
- Treatment of hypertension.
- Treatment of chronic, stable angina pectoris.

4.2 Posology and method of administration
Route of Administration: Oral use
Bisoprolol Fumarate Tablets should be taken in the morning and can be taken with food. They should be swallowed with liquid and should not be chewed.

Treatment with bisoprolol is generally a long-term treatment.

 Stable chronic heart failure
Standard treatment of CHF consists of an ACE inhibitor (or an angiotensin receptor blocker in case of intolerance to ACE inhibitors), a beta-blocker, 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 fumarate requires a titration phase. The treatment with bisoprolol fumarate is to be started with a gradual up titration 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 the 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 patients condition.

**Renal or liver insufficiency:**

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

**Elderly:**

No dosage adjustment is required. It is recommended to start with the lowest possible Dose.

**Children under 12 years and adolescents:**

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

**Hypertension and Angina pectoris**
Adults: The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day. In patients with ischemic heart disease, it is recommended that withdrawal of treatment should be gradually over 1-2 weeks. In some patients 5 mg per day may be adequate. In patients with final stage impairment of renal function (creatinine clearance < 20 ml/min) or liver failure, the dose should not exceed 10 mg bisoprolol once daily.

Elderly: No dosage adjustment is normally required, but 5 mg 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 under 12 years and adolescents: There is no paediatric experience with bisoprolol, therefore its use cannot be recommended for children.

4.3 Contraindications
- hypersensitivity to bisoprolol or to any of the excipients
- untreated, acute, or uncompensated heart failure, requiring intravenous inotropic support (see 4.4)
- cardiogenic shock
- sick sinus syndrome, sino-atrial block or atrio-ventricular block of second or third degree (without a pacemaker).
- significant 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

4.4 Special warnings and precautions for use
Bisoprolol Fumarate must be used with caution in:
- stable chronic heart failure (Bisoprolol indicated for treatment after initial titration phase)
- 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 fumarate treatment of 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

Combination of bisoprolol fumarate 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 fumarate 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 fumarate ) after carefully balancing the benefits against the risks.

Under treatment with bisoprolol fumarate the symptoms of a thyrotoxicosis may be masked.

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

The initiation of treatment with bisoprolol fumarate necessitates regular monitoring. For the posology and method of administration please refer to section 4.2.

The cessation of therapy with bisoprolol fumarate 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 and blood pressure. Intravenous administration of verapamil in patients on beta-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 such as dihydropyridine derivatives with negative inotropic effect (e.g. nifedipine). Nifedipine decrease myocardial contractility by affecting the amount of calcium. Its concomitant use in patients on beta-blocker treatment may increase the risk of hypotension and reduction of the ventricular pump function with possible development of heart failure in patients with latent cardiac insufficiency. The negative inotropism of nifedipine may precipitate or exacerbate heart failure.

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 atrial 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.

Prostaglandin synthetase inhibiting drugs: Decreased hypotensive effect.
Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

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. Higher doses of ephedrine may be necessary for treatment of allergic reactions.

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.

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.

Moxisylate: Possibly causes severe postural hypotension.

**Combinations to be considered**

Mefloquine: increased risk of bradycardia

Monoamineoxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of β-blockers but also risk of hypertensive crisis.

### 4.6 Pregnancy and lactation

**Pregnancy:**
Bisoprolol Fumarate 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 fumarate.

4.7 Effects on ability to drive and use machines
In a study with coronary heart disease patients bisoprolol fumarate 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:

- Very common (≥ 1/10)
- 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:**
- Very common: bradycardia.
- Common: worsening of heart failure.
- Uncommon: AV-conduction disturbances.

**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 impairment.

**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: asthenia, fatigue.

**Hepatobiliary disorders:**
Rare: hepatitis.

**Reproductive system and breast disorders:**
Rare: potency disorders.

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

### 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 up titration according to the scheme given in section 4.2.

If overdose occurs, bisoprolol fumarate 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 fumarate 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 fumarate 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.

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-blockers, 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 already used for the treatment of hypertension and angina. As with other β1-blocking agents, the mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma rennin levels.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol fumarate reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases. Hence bisoprolol is effective in eliminating or reducing the symptoms.

### 5.2 Pharmacokinetic properties

**Absorption**

Bisoprolol fumarate is absorbed and has a biological availability of about 90% after oral administration. The half-life in plasma of 10-12 hours gives a 24 hour effect after dosing once daily.

**Distribution**

The plasma protein binding of bisoprolol fumarate is about 30%. The distribution volume is 3.5 l/kg.

**Elimination**

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 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. Total clearance is approximately 15 l/h.

**Special populations**

*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.

*Hepatic/renal Insufficiency:*

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.

*Elderly:*

The kinetics of bisoprolol fumarate are linear and independent of age.
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 fumarate 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
- Microcrystalline Cellulose
- Silica, Colloidal Anhydrous
- Croscarmellose sodium
- Sodium Starch glycolate (Type A)
- Magnesium Stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
- Blister of white PVC/PVDC/Aluminium.
- 7, 10, 20, 21, 28, 30, 98, and 100 tablets.
- Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Orifarm Generics A/S
Energivej 15, 5260 Odense S
Denmark

8 MARKETING AUTHORISATION NUMBER(S)
PL 20254/0034
1 NAME OF THE MEDICINAL PRODUCT
Bisoprolol Fumarate 2.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 2.5 mg of bisoprolol fumarate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
White to off white round biconvex tablet with a break line on one side.
The tablet can be divided into equal halves.

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).
• Treatment of hypertension.
• Treatment of chronic, stable angina pectoris.

4.2 Posology and method of administration
Route of Administration: Oral use
Bisoprolol Fumarate Tablets should be taken in the morning and can be taken with food. They should be swallowed with liquid and should not be chewed.

Treatment with bisoprolol is generally a long-term treatment.

Stable chronic heart failure
Standard treatment of CHF consists of an ACE inhibitor (or an angiotensin receptor blocker in case of intolerance to ACE inhibitors), a beta-blocker, 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 fumarate requires a titration phase.

The treatment with bisoprolol fumarate is to be started with a gradual up titration 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 the 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 patients condition.

Renal or liver insufficiency:

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

Elderly:

No dosage adjustment is required. It is recommended to start with the lowest possible Dose.
Children under 12 years and adolescents:
There is no paediatric experience with bisoprolol, therefore its use cannot be recommended for children.

Hypertension and Angina pectoris
Adults: The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day. In patients with ischemic heart disease, it is recommended that withdrawal of treatment should be gradually over 1-2 weeks. In some patients 5 mg per day may be adequate. In patients with final stage impairment of renal function (creatinine clearance < 20 ml/min) or liver failure, the dose should not exceed 10 mg bisoprolol once daily.

Elderly: No dosage adjustment is normally required, but 5 mg 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 under 12 years and adolescents: There is no paediatric experience with bisoprolol, therefore its use cannot be recommended for children.

4.3 Contraindications
- hypersensitivity to bisoprolol or to any of the excipients
- untreated, acute, or uncompensated heart failure, requiring intravenous inotropic support (see 4.4)
- cardiogenic shock
- sick sinus syndrome, sino-atrial block or atrio-ventricular block of second or third degree (without a pacemaker).
- significant 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

4.4 Special warnings and precautions for use
Bisoprolol Fumarate must be used with caution in:
- stable chronic heart failure (Bisoprolol indicated for treatment after initial titration phase)
- 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 bradycardia, 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 fumarate treatment of 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

Combination of bisoprolol fumarate 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 fumarate 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 fumarate) after carefully balancing the benefits against the risks.

Under treatment with bisoprolol fumarate the symptoms of a thyrotoxicosis may be masked.

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

The initiation of treatment with bisoprolol fumarate necessitates regular monitoring. For the posology and method of administration please refer to section 4.2.
The cessation of therapy with bisoprolol fumarate 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 and blood pressure. Intravenous administration of verapamil in patients on beta-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 such as dihydropyridine derivatives with negative inotropic effect (eg, nifedipine). Nifedipine decrease myocardial contractility by affecting the amount of calcium. Its concomitant use in patients on beta-blocker treatment may increase the risk of hypotension and reduction of the ventricular pump function with possible development of heart failure in patients with latent cardiac insufficiency. The negative inotropism of nifedipine may precipitate or exacerbate heart failure.

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 atrial 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.

Prostaglandin synthetase inhibiting drugs: Decreased hypotensive effect.

Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

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. Higher doses of ephedrine may be necessary for treatment of allergic reactions.

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.

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.

Moxisylate: Possibly causes severe postural hypotension.

Combinations to be considered
Mefloquine: increased risk of bradycardia

Monoamineoxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of β-blockers but also risk of hypertensive crisis.

4.6 Pregnancy and lactation

Pregnancy:
Bisoprolol Fumarate 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 fumarate.

4.7 **Effects on ability to drive and use machines**
In a study with coronary heart disease patients bisoprolol fumarate 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:

- **Very common** (≥ 1/10)
- **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:**
- Very common: bradycardia.
- Common: worsening of heart failure.
- Uncommon: AV-conduction disturbances.

**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 impairment.

**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).
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**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: asthenia, fatigue.

**Hepatobiliary disorders:**
Rare: hepatitis.

**Reproductive system and breast disorders:**
Rare: potency disorders.

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

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 up titration according to the scheme given in section 4.2.

If overdose occurs, bisoprolol fumarate 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 fumarate 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 fumarate 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.
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-blockers, 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 already used for the treatment of hypertension and angina. As with other β1-blocking agents, the mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma rennin levels.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol fumarate reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases. Hence bisoprolol is effective in eliminating or reducing the symptoms.

5.2 Pharmacokinetic properties

Absorption
Bisoprolol fumarate is absorbed and has a biological availability of about 90% after oral administration. The half-life in plasma of 10-12 hours gives a 24 hour effect after dosing once daily.

Distribution
The plasma protein binding of bisoprolol fumarate is about 30%. The distribution volume is 3.5 l/kg.

Elimination
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 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. Total clearance is approximately 15 l/h.

Special populations
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.
Hepatic/renal Insufficiency:
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.

Elderly:
The kinetics of bisoprolol fumarate are linear and independent of age.

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 fumarate 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
Microcrystalline Cellulose
Silica, Colloidal Anhydrous
Croscarmellose sodium
Sodium Starch glycolate (Type A)
Magnesium Stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Blister of white PVC/PVDC/Aluminium.
7, 10, 28, 30, 98, 100 and tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Orifarm Generics A/S
1 NAME OF THE MEDICINAL PRODUCT
Bisoprolol Fumarate 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5 mg of bisoprolol fumarate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet

White to off white round biconvex tablet with a break line on one side.
The tablet can be divided into equal halves.

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).
• Treatment of hypertension.
• Treatment of chronic, stable angina pectoris.

4.2 Posology and method of administration
Route of Administration: Oral use

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

Treatment with bisoprolol is generally a long-term treatment.
**Stable chronic heart failure**

Standard treatment of CHF consists of an ACE inhibitor (or an angiotensin receptor blocker in case of intolerance to ACE inhibitors), a beta-blocker, 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 fumarate requires a titration phase.

The treatment with bisoprolol fumarate is to be started with a gradual up titration 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 the 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 patients condition.

**Renal or liver insufficiency:**

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

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

**Children under 12 years and adolescents:**
There is no paediatric experience with bisoprolol, therefore its use cannot be recommended for children.

**Hypertension and Angina pectoris**
Adults: The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day. In patients with ischemic heart disease, it is recommended that withdrawal of treatment should be gradually over 1-2 weeks. In some patients 5 mg per day may be adequate. In patients with final stage impairment of renal function (creatinine clearance < 20 ml/min) or liver failure, the dose should not exceed 10 mg bisoprolol once daily.

Elderly: No dosage adjustment is normally required, but 5 mg 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 under 12 years and adolescents: There is no paediatric experience with bisoprolol, therefore its use cannot be recommended for children.

### 4.3 Contraindications
- hypersensitivity to bisoprolol or to any of the excipients
- untreated, acute, or uncompensated heart failure, requiring intravenous inotropic support (see 4.4)
- cardiogenic shock
- sick sinus syndrome, sino-atrial block or atrio-ventricular block of second or third degree (without a pacemaker).
- significant 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

### 4.4 Special warnings and precautions for use
Bisoprolol Fumarate must be used with caution in:
- stable chronic heart failure (Bisoprolol indicated for treatment after initial titration phase)
- 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 fumarate treatment of 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
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- myocardial infarction within 3 months

Combination of bisoprolol fumarate 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 fumarate 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 fumarate) after carefully balancing the benefits against the risks.

Under treatment with bisoprolol fumarate the symptoms of a thyrotoxicosis may be masked.
In patients with phaeochromocytoma bisoprolol must not be administered until after alpha-receptor blockade.

The initiation of treatment with bisoprolol fumarate necessitates regular monitoring. For the posology and method of administration please refer to section 4.2. The cessation of therapy with bisoprolol fumarate 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 and blood pressure. Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrioventricular block.

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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 such as dihydropyridine derivatives with negative inotropic effect (e.g. nifedipine). Nifedipine decrease myocardial contractility by affecting the amount of calcium. Its concomitant use in patients on beta-blocker treatment may increase the risk of hypotension and reduction of the ventricular pump function with possible development of heart failure in patients with latent cardiac insufficiency. The negative inotropism of nifedipine may precipitate or exacerbate heart failure.

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

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Combinations to be considered
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4.6 Pregnancy and lactation

Pregnancy:
Bisoprolol Fumarate 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 fumarate.

4.7 **Effects on ability to drive and use machines**
In a study with coronary heart disease patients bisoprolol fumarate 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.

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**Investigations:**
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**Eye disorders:**
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### 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 up titration according to the scheme given in section 4.2.
If overdose occurs, bisoprolol fumarate 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 fumarate 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 fumarate 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.

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-blockers, 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 already used for the treatment of hypertension and angina. As with other β1-blocking agents, the mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma rennin levels.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol fumarate reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases. Hence bisoprolol is effective in eliminating or reducing the symptoms.

5.2 Pharmacokinetic properties

Absorption
Bisoprolol fumarate is absorbed and has a biological availability of about 90% after oral administration. The half-life in plasma of 10-12 hours gives a 24 hour effect after dosing once daily.

Distribution
The plasma protein binding of bisoprolol fumarate is about 30%. The distribution volume is 3.5 l/kg.

Elimination
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 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. Total clearance is approximately 15 l/h.
Special populations

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 $64\pm21$ ng/ml at a daily dose of 10 mg and the half-life is $17\pm5$ hours.

Hepatic/renal Insufficiency:
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.

Elderly:
The kinetics of bisoprolol fumarate are linear and independent of age.

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 fumarate 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
Microcrystalline Cellulose
Silica, Colloidal Anhydrous
Crocarmellose sodium
Sodium Starch glycolate (Type A)
Magnesium Stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Blister of white PVC/PVDC/Aluminium.
7, 10, 28, 30, 98, and 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Orifarm Generics A/S
Energivej 15, 5260 Odense S
Denmark

8 MARKETING AUTHORISATION NUMBER(S)
PL 20254/0036

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/02/2010

10 DATE OF REVISION OF THE TEXT
24/02/2010

1 NAME OF THE MEDICINAL PRODUCT
Bisoprolol Fumarate 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg of bisoprolol fumarate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
White to off white round biconvex tablet with a break line on one side.
The tablet can be divided into equal halves.

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).
• Treatment of hypertension.
• Treatment of chronic, stable angina pectoris.

4.2 Posology and method of administration
Route of Administration: Oral use
Bisoprolol Fumarate Tablets should be taken in the morning and can be taken with food. They should be swallowed with liquid and should not be chewed.

Treatment with bisoprolol is generally a long-term treatment.

**Stable chronic heart failure**

Standard treatment of CHF consists of an ACE inhibitor (or an angiotensin receptor blocker in case of intolerance to ACE inhibitors), a beta-blocker, 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 fumarate requires a titration phase.

The treatment with bisoprolol fumarate is to be started with a gradual up titration 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 the 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 patients condition.

**Renal or liver insufficiency:**
There is no information regarding pharmacokinetics of bisoprolol fumarate in patients with chronic heart failure and with impaired liver or renal function. Up titration of the dose in these populations should therefore be made with additional caution.

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

**Children under 12 years and adolescents:**
There is no paediatric experience with bisoprolol, therefore its use cannot be recommended for children.

**Hypertension and Angina pectoris**
Adults: The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day. In patients with ischemic heart disease, it is recommended that withdrawal of treatment should be gradually over 1-2 weeks. In some patients 5 mg per day may be adequate. In patients with final stage impairment of renal function (creatinine clearance < 20 ml/min) or liver failure, the dose should not exceed 10 mg bisoprolol once daily.

Elderly: No dosage adjustment is normally required, but 5 mg 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 under 12 years and adolescents: There is no paediatric experience with bisoprolol, therefore its use cannot be recommended for children.

### 4.3 Contraindications
- hypersensitivity to bisoprolol or to any of the excipients
- untreated, acute, or uncompensated heart failure, requiring intravenous inotropic support (see 4.4)
- cardiogenic shock
- sick sinus syndrome, sino-atrial block or atrio-ventricular block of second or third degree (without a pacemaker).
- significant 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

### 4.4 Special warnings and precautions for use
Bisoprolol Fumarate must be used with caution in:
- stable chronic heart failure (Bisoprolol indicated for treatment after initial titration
phase)
- 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 fumarate treatment of 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

Combination of bisoprolol fumarate 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 fumarate 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 fumarate) after carefully balancing the benefits against the risks.

Under treatment with bisoprolol fumarate the symptoms of a thyrotoxicosis may be masked.

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

The initiation of treatment with bisoprolol fumarate necessitates regular monitoring. For the posology and method of administration please refer to section 4.2.

The cessation of therapy with bisoprolol fumarate 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 and blood pressure. Intravenous administration of verapamil in patients on beta-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 such as dihydropyridine derivatives with negative inotropic effect (e.g. nifedipine). Nifedipine decrease myocardial contractility by affecting the amount of calcium. Its concomitant use in patients on beta-blocker treatment may increase the risk of hypotension and reduction of the ventricular pump function with possible development of heart failure in patients with latent cardiac insufficiency. The negative inotropism of nifedipine may precipitate or exacerbate heart failure.

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 atrial 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.

Prostaglandin synthetase inhibiting drugs: Decreased hypotensive effect.

Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

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. Higher doses of ephedrine may be necessary for treatment of allergic reactions.

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.

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.

Moxisylate: Possibly causes severe postural hypotension.

Combinations to be considered

Mefloquine: increased risk of bradycardia
Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of β-blockers but also risk of hypertensive crisis.

4.6 Pregnancy and lactation

**Pregnancy:**
Bisoprolol Fumarate 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 fumarate.

4.7 Effects on ability to drive and use machines

In a study with coronary heart disease patients bisoprolol fumarate 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:

- **Very common** (≥ 1/10)
- **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:**
Very common: bradycardia.
Common: worsening of heart failure.
Uncommon: AV-conduction disturbances.

**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 impairment.

**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: asthenia, fatigue.

**Hepatobiliary disorders:**
Rare: hepatitis.

**Reproductive system and breast disorders:**
Rare: potency disorders.

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

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 up titration according to the scheme given in section 4.2.

If overdose occurs, bisoprolol fumarate 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
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ATC Code: C07AB07

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(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.

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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.

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Distribution
The plasma protein binding of bisoprolol fumarate is about 30%. The distribution volume is 3.5 l/kg.

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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 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. Total clearance is approximately 15 l/h.

**Special populations**

*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.

*Hepatic/renal Insufficiency:*
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.

*Elderly:*
The kinetics of bisoprolol fumarate are linear and independent of age.

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 fumarate 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**
- Microcrystalline Cellulose
- Silica, Colloidal Anhydrous
- Croscarmellose sodium
- Sodium Starch glycolate (Type A)
- Magnesium Stearate

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
3 years.

6.4 **Special precautions for storage**
This medicinal product does not require any special storage conditions.

6.5 **Nature and contents of container**
Blister of white PVC/PVDC/Aluminium.
7, 10, 28, 30, 98 and 100 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORITY HOLDING
Orifarm Generics A/S
Energivej 15, 5260 Odense S
Denmark

8 MARKETING AUTHORITY NUMBER(S)
PL 20254/0037

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY
24/02/2010

10 DATE OF REVISION OF THE TEXT
24/02/2010
Module 3

Product Information Leaflet

No leaflet mock ups have been provided. In accordance with the medicines legislation, the products shall not be marketed in the UK until approval of the product labelling and leaflet mock-ups has been obtained. The following text has been approved use with these products.
PACKAGE INFORMATION LEAFLET

Bisoprolol Fumarate 1.25 mg Tablets
Bisoprolol Fumarate 2.5 mg Tablets
Bisoprolol Fumarate 5 mg Tablets
Bisoprolol Fumarate 10 mg Tablets

Bisoprolol Fumarate

Read all of this leaflet carefully before you start taking this medicine

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Bisoprolol Fumarate Tablets are and what they are used for.
2. Before you take Bisoprolol Fumarate Tablets
3. How to take Bisoprolol Fumarate Tablets
4. Possible side effects
5. How to store Bisoprolol Fumarate Tablets
6. Further Information.

1. What Bisoprolol Fumarate Tablets are and what they are used for

The active substance in this medicine is Bisoprolol fumarate. Bisoprolol Fumarate belongs to a group of medicines called beta-blockers. These medicines work by affecting the body’s response to some nerve impulses, especially in the heart. As a result, bisoprolol slows down the heart rate and makes the heart more efficient at pumping blood around the body. Heart failure occurs when the heart muscle is weak and unable to pump enough blood to supply the body’s needs.

Bisoprolol is used:
- To treat stable chronic heart failure. It is used in combination with other medicines suitable for this condition (such as ACE-inhibitors, diuretics, and heart glycosides).
- In treatment of coronary heart disease and chest pain (angina pectoris) caused by shortage of oxygen in the heart muscle.
- In treatment of high blood pressure (hypertension).

2. Before you take Bisoprolol Fumarate Tablets

Do not take Bisoprolol Fumarate Tablets if one of the following conditions applies to you:
- allergic (hypersensitive) to bisoprolol fumarate or any of the other ingredients of Bisoprolol Fumarate tablets.
- severe asthma or severe chronic lung disease • severe blood circulation problems in your limbs (such as Raynaud’s syndrome), which may cause your fingers and toes to tingle or turn pale or blue • untreated phaeochromocytoa, which is a rare tumour of the adrenal gland • metabolic acidosis, which is a condition when there is too much acid in the blood.

Do not take Bisoprolol Fumarate Tablets if you have one of the following heart problems:
- acute heart failure
- worsening heart failure requiring injection of medicines into a vein, that increase the force of contraction of the heart
- slow heart rate
- low blood pressure
- certain heart conditions causing a very slow heart rate or irregular heartbeat
- cardiogenic shock, which is an acute serious heart condition causing low blood pressure and
circulatory failure.

**Take special care with Bisoprolol Fumarate Tablets:**
If you have any of the following conditions tell your doctor before taking this medicine; he or she may want to take special care (for example give additional treatment or perform more frequent checks):
- diabetes
- strict fasting
- certain heart diseases such as disturbances in heart rhythm, or severe chest pain at rest (Prinzmetal's angina)
- kidney or liver problems
- less severe blood circulation problems in your limbs
- less severe asthma or chronic lung disease
- history of a scaly skin rash (psoriasis)
- tumour of the adrenal gland (pheochromocytoma)
- thyroid disorder.

In addition, tell your doctor if you are going to have:
- desensitization therapy (for example for the prevention of hay fever), because Bisoprolol may make it more likely that you experience an allergic reaction, or such reaction may be more severe
- anaesthesia (for example for surgery), because this medicine may influence how your body reacts to this situation

**Taking other medicines:**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Do not take the following medicines with Bisoprolol Fumarate without special advice from your doctor:
- Certain medicines used to treat irregular or abnormal heartbeat (Class I antiarrhythmic medicines such as quinidine, disopyramide, lidocaine, phenytoin; flecaïnine, propafenone)
- Certain medicines used to treat high blood pressure, angina pectoris or irregular heartbeat (calcium antagonists such as verapamil and diltiazem)
- Certain medicines used to treat high blood pressure such as clonidine, methyldopa, moxonidine, rilmenidine. However, do not stop taking these medicines without checking with your doctor first.

Check with your doctor before taking the following medicines with Bisoprolol Fumarate: your doctor may need to check your condition more frequently:
- Certain medicines used to treat high blood pressure or angina pectoris (dihydropyridine-type calcium antagonists such as felodipine andamlodipine)
- Certain medicines used to treat irregular or abnormal heartbeat (Class III antiarrhythmic medicines such as amiodarone)
- Beta-blocking agents applied locally (such as timolol eye drops for glaucoma treatment)
- Certain medicines used to treat for example Alzheimer's disease or glaucoma (parasympathomimetics such as tacrine or carbachol) or medicines that are used to treat acute heart problems (sympathomimetics such as isoprenaline and dobutamine)
- Antidiabetic medicines including insulin
- Anaesthetic agents (for example during surgery)
- Digitalis, used to treat heart failure
- Non-steroidal anti-inflammatory medicines (NSAIDs) used to treat arthritis, pain or inflammation (for example ibuprofen or diclofenac)
- Any medicine, which can lower blood pressure as a desired or undesired effect such as antihypertensives, certain medicines for depression (tricyclic antidepressants such as imipramine or amitriptyline), certain medicines used to treat epilepsy or during anaesthesia (barbiturates such as phenobarbitone), or certain medicines to treat mental illness characterized by a loss of contact with reality (phenothiazines such as levomepromazine)
- Mefloquine, used for prevention or treatment of malaria
- Depression treatment medicines called monoamine oxidase inhibitors (except MAO-B inhibitors) such as moclobemide.

**Pregnancy and breast-feeding:**
You should not take Bisoprolol Fumarate Tablets if you are planning to become pregnant, pregnant or breast-feeding. Please ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines:**
Bisoprolol Fumarate Tablets may cause side effects that may affect a person's ability to drive and use machinery particularly during the first few weeks of your treatment. You may find that your reactions are
impaired, especially if you have also consumed alcohol. Examples of side effects include visual disturbances, drowsiness or dizziness. If you suffer from any of these side effects it is advisable to refrain from driving or using machinery.

3. **How to take Bisoprolol Fumarate tablets**

**Keep out of reach and sight of children**
Always take Bisoprolol Fumarate tablets exactly as your doctor has told you. You should check with your doctor or your pharmacist if you are not sure. Bisoprolol Fumarate Tablets should be taken in the morning, before, with or after breakfast. Swallow the tablet/s whole with some water and do not chew or crush them. This treatment should be initiated by a specialist in cardiology or internal medicine.

**Children under 12 years and adolescents**: Bisoprolol Fumarate Tablet/s is/are not recommended for use in children

**Stable chronic heart failure**
Adults including the elderly: Treatment with bisoprolol must be started at a low dose and increased gradually. Your doctor will decide how to increase the dose, and this will normally be done in the following way:
- 1.25 mg bisoprolol once daily for one week
- 2.5 mg bisoprolol once daily for one week
- 5.75 mg bisoprolol once daily for one week
- 5 mg bisoprolol once daily for four weeks
- 7.5 mg bisoprolol once daily for four weeks
- 10 mg bisoprolol once daily for maintenance (on-going) therapy.

The maximum recommended daily dose is 10 mg bisoprolol. Depending on how well you tolerate the medicine, your doctor may also decide to lengthen the time between dose increases. If your condition gets worse or you no longer tolerate the drug, it may be necessary to reduce the dose again or to interrupt treatment. In some patients a maintenance dose lower than 10 mg bisoprolol may be sufficient. Your doctor will tell you what to do. If you have to stop treatment entirely, your doctor will usually advise you to reduce the dose gradually, as otherwise your condition may become worse.

**Renal or liver disease**: The dosage should be increased very gradually and cautiously in patients with severe kidney or liver problems

**Hypertension and angina**
Adults and the elderly: The usual dose for adults is one tablet (10 mg) daily. Your doctor may decide to increase or decrease this dose.

**Renal or liver disease**: The dosage should not exceed 10 mg once daily in patients with severe kidney or liver problems.

**If you take more Bisoprolol Fumarate Tablets than you should**
Contact your doctor or local emergency ward immediately. Take this leaflet and any tablets you still have with you. You may feel dizzy or extremely tired or notice tinnitus (ringing in your ears).

**For Spain only**: En caso de sobredosis o ingestión accidental, consulte inmediatamente a su médico o farmacéutico o llame al Servicio de Información Toxicológica, teléfono 91 562 04 20 indicando el medicamento y la cantidad ingerida.

**If you forget to take Bisoprolol Fumarate Tablets**:
If you forget to take a dose, take it as soon as you remember it unless it is nearly time for your next dose. Do not take a double dose to make up for a forgotten dose.

**If you stop taking Bisoprolol Fumarate Tablets**:
Do not stop treatment suddenly or change the recommended dose without talking to your doctor first. If you need to stop treatment, it must be done gradually, to avoid side effects.
If you have any further questions on the use of this product, ask you doctor or pharmacist.

4. **Possible side effects**
Like all medicines, Bisoprolol Fumarate Tablets can cause side effects, although not everybody gets them.

To prevent serious reactions, speak to a doctor immediately if a side effect is severe, occurred suddenly or gets worse rapidly. The most serious side effects are related to the heart function:

- slowing of heart rate (affects more than 1 person in 10)
- worsening of heart failure (affects less than 1 person in 10)
- slow or irregular heartbeat (affects less than 1 person in 100)

If you feel dizzy or weak, or have breathing difficulties please contact your doctor as soon as possible.

Further side effects are listed below according to how frequently they may occur:

**Common** (affects less than 1 person in 10):
- tiredness, feeling weak, dizziness, headache
- feeling of coldness or numbness in hands or feet
- low blood pressure
- stomach or intestine problems such as nausea, vomiting, diarrhoea, or constipation.

**Uncommon** (affects less than 1 person in 100):
- sleep disturbances
- depression
- dizziness when standing up
- breathing problems in patients with asthma or chronic lung disease
- muscle weakness, muscle cramps.

**Rare** (affects less than 1 person in 1,000):
- hearing problems
- allergic runny nose
- reduced tear flow
- inflammation of the liver which can cause yellowing of the skin or whites of the eyes
- certain blood test results for liver function or fat levels differing from normal
- allergy-like reactions such as itching, flush, rash
- impaired erection
- nightmares, hallucinations
- fainting

**Very rare** (affects less than 1 person in 10,000):
- irritation and redness of the eye (conjunctivitis)
- hair loss
- appearance or worsening of scaly skin rash (psoriasis); psoriasis-like rash.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. **How to store Bisoprolol Fumarate tablets**

**Keep out of the reach and sight of children**

Do not use Bisoprolol Fumarate Tablets after the expiry date which is stated on the blister and the carton. The expiry date refers to the last day of that month. This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **Further Information**

**What Bisoprolol Fumarate Tablets contain**
The active substance is bisoprolol fumarate. Each 1.25 mg tablet contains 1.25 mg bisoprolol fumarate. Each 2.5 mg tablet contains 2.5 mg bisoprolol fumarate. Each 5 mg tablet contains 5 mg bisoprolol fumarate. Each 10 mg tablet contains 10 mg bisoprolol fumarate.
The other ingredients are microcrystalline cellulose, silica colloidal anhydrous, croscarmellose sodium, sodium starch glycolate (type A) and magnesium stearate.

**What Bisoprolol Fumarate Tablets look like and contents of the pack:**
1.25 mg: White to off white round biconvex tablets.
2.5 mg: White to off white round biconvex tablets with a break line on one side.
5 mg: White to off white round biconvex tablets with a break line on one side.
10 mg: White to off white round biconvex tablets with a break line on one side.

Bisoprolol Fumarate 2.5 mg, 5 mg and 10 mg Tablets only: The tablets can be divided into equal halves.

Pack sizes of 7, 10, 20, 21, 28, 30, 98 and 100 tablets. Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**
The marketing authorisation holder is [To be completed nationally]
For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder [To be completed nationally]

**Manufacturer:**
Chanelle Medical, Loughrea, Co Galway, Ireland

**This leaflet was last approved in:** MM/YYYY
Module 4

Labelling

No label mock ups have been provided. In accordance with the medicines legislation, the products shall not be marketed in the UK until approval of the product labelling and leaflet mock-ups has been obtained. The following text has been approved use with these products.
PARTICULARS TO APPEAR ON THE OUTER PACKAGING BOX

1. NAME OF THE MEDICINAL PRODUCT

Bisoprolol Fumarate 1.25/2.5/5/10 mg tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1.25/2.5/5/10 mg of bisoprolol fumarate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet
- 7 tablets
- 10 tablets
- 20 tablets
- 21 tablets
- 28 tablets
- 30 tablets
- 98 tablets
- 100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

None

8. EXPIRY DATE

EXP.:
9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE.**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION**

Orifarm Generics A/S, Energivej 15, 5260 Odense S, Denmark

12. **MARKETING AUTHORISATION NUMBER(S)**

13. **BATCH NUMBER**

Lot:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS FOR USE**

16. **INFORMATION IN BRAILLE**

Bisoprolol Fumarate 1.25 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

1. **NAME OF THE MEDICINAL PRODUCT**

Bisoprolol Fumarate 1.25, 2.5, 5, 10 mg tablets

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

Orifarm Generics

3. **EXPIRY DATE**

EXP.:

4. **BATCH NUMBER**

Lot:

5. **OTHER**
Module 5

Scientific discussion during initial procedure

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considers that the applications for Bisoprolol Fumarate 1.25 mg, 2.5 mg, 5 mg and 10 mg Tablets is approvable for the following:

- 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).
- Treatment of hypertension.
- Treatment of chronic, stable angina pectoris.

EXECUTIVE SUMMARY

About the product
Bisoprolol is a highly beta₁-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity.

The originator product is Emcor 10mg tablets by E Merck Ltd, Denmark, registered since 11 February 1988.

The UK reference product is Cardicor 1.25 mg film-coated tablets (PL 00493/0179), licensed to E Merck Ltd.

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. Peak plasma concentrations are reached 2 to 4 hours after oral doses. The half-life in plasma of 10-12 hours gives a 24 hour effect after dosing once daily.

Bisoprolol is a racemic mixture with the levorotatory form S(-) enantiomer possessing 30 to 80 times the greater β blocking activity than the dextrorotatory form. Data have been provided to assure that no stereo selective disposition occurs (Dutta 1994).

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. The kinetics of bisoprolol are linear and independent of age.

General comments on the submitted dossier
The applicant summarizes the grounds and evidence used for demonstrating that the medicinal product is essentially similar to an authorised medicinal product, based on a pharmacokinetic bioequivalence study using the 10mg strength tablets, comparative dissolution and impurity profiles. A biowaver has been requested for the 1.25 mg, 2.5 mg, and 5mg strengths. Critical assessment of these data is summarised later in this report.
With UK as the Reference Member State in this Decentralized Procedure, Orifarm Generics A/S is applying for a Marketing Authorisations for Bisoprolol Fumarate 1.25 mg, 2.5 mg, 5 mg and 10 mg Tablets in the Denmark, Sweden and Norway.

**General comments on compliance with GMP, GLP, GCP and agreed ethical principles.**
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS has been assured that acceptable standards of GCP were in place for the bioequivalence study. Copies of signed documents were provided to support ethical approval.

**SCIENTIFIC OVERVIEW AND DISCUSSION**

**Quality aspects**

**Drug substance**
The chemical-pharmaceutical documentation and Expert Report in relation to bisoprolol fumarate are of sufficient quality in view of the present European regulatory requirements. The active substance, bisoprolol fumarate, which is the subject of a Ph. Eur. monograph, is controlled by appropriate drug substance specifications. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. An adequate re-test period has been defined based on conducted stability studies.

**Drug Product**
The development of the products has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations data supporting the analytical methods have been presented. The batch analysis results show that the finished products meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for the drug products are adequately drawn up. The proposed shelf-life of 3 years is acceptable. This medicinal product does not require any special storage conditions.

**NON CLINICAL ASPECTS**
Specific non-clinical studies have not been performed, which is acceptable for this application for a generic product. The non-clinical overview provides a review of the known pharmacological, pharmacokinetic and toxicological properties of bisoprolol fumarate.
The lack of an environmental risk assessment is justified since the products are generic versions of an already approved one and it is not likely to change the total market of bisoprolol fumarate.

CLINICAL ASPECTS

Pharmacokinetics
To support the application, the applicant has submitted as a report, one bioequivalence study using the 10mg strength tablets. The bioequivalence study was an open label, balanced, randomised, analyst blind, two treatments, two period, two-sequence, cross over single dose, bioequivalence study in healthy male human subjects under fasting conditions with a wash out period of nine days between periods.

The applicant has requested a biowaiver for the 1.25mg, 2.5mg and 5mg strengths of the test product on the basis of the Note for guidance of on investigation of bioavailability and bioequivalence noting that the pharmacokinetics are linear from 2.5 mg to 100 mg, the concentration of active is <5%, the ratio of active to excipients is similar and in vitro dissolution data are similar for the different strengths. This is acceptable.

Test product
Bisoprolol fumarate 10mg

Reference product
Cardicor 10mg Bisoprolol fumarate 10mg, Merck Pharmaceuticals UK

Methods
The study recruited healthy, adult, male, human subjects, aged between 18 and 55 years. All 28 volunteers complying with the requirements of the protocol were enrolled in the study. All 28 subjects completed both periods of the study successfully. There were some protocol deviations: one subject smoked 5-7 cigarettes per day and three subjects deviated from restrictions on certain drinks 2 days before dosing. There were nine deviations on late sampling times: however, the impact was considered as minimal by the applicant as Kel could be defined for these subjects.

The subjects fasted for at least 10 hours prior to administration of the study drug. They were provided with lunch 4 hours post-dose. They were not allowed access to drinking water from 1 hour pre-dose till 2 hours post dose administration, except during administration of the dose. A dose of 10 mg of bisoprolol fumarate tablets test or reference product was orally administered as a single dose followed by 240 ml of water at ambient temperature in both periods.

Concentration of bisoprolol was measured in plasma samples of the subjects. Sampling was done pre-dose (0h00) and up to and 72h00 hours post dose. The plasma samples of subjects were analyzed by an HPLC method. The bioanalytical method used in the biostudy has been adequately validated.

Results
The In-transformed least square means and 90% Confidence Interval based on least square mean obtained from ANOVA and ratio of test and reference formulations for the pharmacokinetic parameters Cmax, AUC0-t and AUC0-inf, for bisoprolol are summarised in the following table:

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) Bisoprolol plasma concentrations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC0-t</th>
<th>AUC0-∞</th>
<th>Cmax</th>
<th>tmax</th>
<th>T1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ng/ml/h</td>
<td>ng/ml/h</td>
<td>ng/ml</td>
<td>h</td>
<td>h</td>
</tr>
<tr>
<td>Test</td>
<td>582.91(120.29)</td>
<td>630.78(119.02)</td>
<td>43.86(6.84)</td>
<td>2.32(0.9)</td>
<td>10.07 (0.9)</td>
</tr>
<tr>
<td>Reference</td>
<td>571.56(111.81)</td>
<td>622.43(110.58)</td>
<td>43.77(7.07)</td>
<td>2.26(0.88)</td>
<td>9.74(2.54)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>101.97(98.44-105.62)</td>
<td>101.29(97.94-104.75)</td>
<td>100.30(96.69-104.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV (%)</td>
<td>7.73%</td>
<td>7.39%</td>
<td>8.04%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AUC0-t: area under the plasma concentration-time curve from time zero to t hours
AUC0-∞: area under the plasma concentration-time curve from time zero to infinity
Cmax: maximum plasma concentration
Tmax: time for maximum concentration
T1/2: half-life

*In-transformed values

The 90% confidence intervals, for the geometric mean ratios of drug formulations of Cmax, AUC0-t and AUC0-inf for bisoprolol meet the prespecified bioequivalence criteria.

Pharmacodynamics
No new data have been submitted or are required.

Clinical efficacy
No new data have been submitted or are required.

Clinical safety
No new data have been submitted or are required.

Pharmacovigilance system
The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan
Bisoprolol Fumarate 1.25 mg, 2.5 mg, 5 mg and 10 mg Tablets are generic products. As with the reference medicinal product, no special important risks or potential risks have been identified which require additional risk minimization activities other than the global pharmacovigilance system.
Product literature
All product literature (SPC, PIL and labelling) is satisfactory. The package leaflet was submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

BENEFIT RISK ASSESSMENT
Bioequivalence to the originator has been established. Approval is recommended.