Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

BISOPROLOL FUMARATE 1.25MG 2.5MG AND 3.75MG TABLETS

UK/H/1458/001-3/DC
UK Licence No: PL 11204/0206-8

STADA ARZNEIMITTEL AG

LAY SUMMARY

On 23rd February 2010, the UK granted Stada Arzneimittel AG Marketing Authorisations (licences) for the prescription only medicinal products Bisoprolol Fumarate 1.25mg, 2.5mg and 3.75mg Tablets (PL 11204/0206-8; UK/H/1458/001-3/DC).

Bisoprolol fumarate belongs to a group of medicines called beta-blockers.

Bisoprolol works 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).

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Bisoprolol Fumarate 1.25mg, 2.5mg and 3.75mg Tablets outweigh the risks; hence these Marketing Authorisations have been granted.

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Module 1

Product Name	Bisoprolol Fumarate 1.25mg, 2.5mg and 3.75mg Tablets
Type of Application	Generic, Article 10.1
Active Substance	Bisoprolol Fumarate
Form	Tablets
Strength	1.25mg, 2.5mg and 3.75mg
MA Holder	STADA Arzneimittel AG Stadastraβe 2-18, D-61118 Bad Vilbel Germany
Reference Member State (RMS)	UK
CMS	France, Germany, Italy, The Netherlands, Sweden
Procedure Number	UK/H/1458/001-3/DC
End of Procedure	Day 210 – 8th February 2010

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Bisoprolol Fumarate 1.25 mg Tablets

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

3 PHARMACEUTICAL FORM
Tablet
Bisoprolol Fumarate 1.25 mg Tablet is a white to off white round biconvex tablet

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

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

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

The treatment with bisoprolol fumarate is to be started with a gradual uptitration according to the following steps:
- 1.25 mg once daily for 1 week, if well tolerated increase to
- 2.5 mg once daily for a further week, if well tolerated increase to
- 3.75 mg once daily for a further week, if well tolerated increase to
- 5 mg once daily for the 4 following weeks, if well tolerated increase to
- 7.5 mg once daily for the 4 following weeks, if well tolerated increase to
- 10 mg once daily for the maintenance therapy.

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

The maximum recommended dose is 10 mg once daily.

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

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

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

Bisoprolol 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.

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. Uptitration of the dose in these populations should therefore be made with additional caution.

Elderly:
No dosage adjustment is required.

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

4.3 Contraindications

Bisoprolol Fumarate is contraindicated in chronic heart failure patients with:
- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock
- AV block of second or third degree (without a pacemaker)
- sick sinus syndrome
- sinoatrial block
- bradycardia with less than 60 beats/min before the start of therapy
- hypotension (systolic blood pressure less than 100 mm Hg)
- severe bronchial asthma or severe chronic obstructive pulmonary disease
- late stages of peripheral arterial occlusive disease and Raynaud's syndrome
- untreated phaeochromocytoma (see 4.4)
- metabolic acidosis
- hypersensitivity to bisoprolol or to any of the excipients

4.4 Special warnings and precautions for use

Bisoprolol Fumarate must be used with caution in:
- bronchospasm (bronchial asthma, obstructive airways diseases)
- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia can be masked
- strict fasting
- ongoing desensitisation therapy
- AV block of first degree
- Prinzmetal's angina
- peripheral arterial occlusive disease (intensification of complaints might happen especially during the start of therapy)
- General anaesthesia

In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthetist must be aware of beta-blockade because of the potential for interactions with other drugs, resulting in bradyarrhythmias, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

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

- NYHA class II heart failure
- insulin dependent diabetes mellitus (type I)
- impaired renal function (serum creatinine>300 micromol/l)
- impaired liver function
- patients older than 80 years

- restrictive cardiomyopathy
- congenital heart disease
- haemodynamically significant organic valvular disease
- myocardial infarction within 3 months

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

Under treatment with bisoprolol fumarate the symptoms of a thyreotoxicosis may be masked.
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. Intravenous administration of verapamil in patients on β-blocker treatment may lead to profound hypotension and atrioventricular block.

Class I antiarrhythmic drugs (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide, propafenone): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonodine, rilmenidine): Concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of "rebound hypertension".

Combinations to be used with caution

Calcium antagonists of the dihydropyridine type such as felodipine and amlodipine: Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Class-III antiarrhythmic drugs (e.g. amiodarone): Effect on atrio- conduction time may be potentiated.

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

Parasympathomimetic drugs: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.

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

Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension (for further information on general anaesthesia see also section 4.4.).

Digitalis glycosides: Reduction of heart rate, increase of atrio-ventricular conduction time.

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

β-Sympathomimetic agents (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both agents.

Sympathomimetics that activate both β- and α-adrenoceptors (e.g. noradrenaline, adrenaline): Combination with bisoprolol may unmask the α-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective β-blockers.

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

Combinations to be considered
Mefloquine: increased risk of bradycardia

Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the beta-blockers but also risk for hypertensive crisis.

4.6 Pregnancy and lactation

Pregnancy:
Bisoprolol 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

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

Preferred Term WHO	Placebo (n=1321)		Bisoprolol (n=1328)	
	Pat. With AE	% Pat. With AE	Pat. With AE	% Pat. With AE

Cardiac failure	301	22.8	244	18.4
Dyspnoea	224	17.0	183	13.8
Dizziness	126	9.5	177	13.3
Cardiomyopathy	132	10.0	141	10.6
Bradycardia	60	4.5	202	15.2
Hypotension	96	7.3	152	11.4
Tachycardia	144	10.9	79	5.9
Fatigue	94	7.1	123	9.3
Viral infection	75	5.7	86	6.5
Pneumonia	69	5.2	65	4.9

AE = Adverse Events

Post-marketing data
The following data results from post-marketing experience with bisoprolol fumarate:
Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10000, < 1/1000); very rare (< 1/10000).

Cardiac disorders:
Uncommon: bradycardia, AV-stimulus disturbances, worsening of heart failure.

Nervous system disorders:
Common: Tiredness*, exhaustion*, dizziness*, headache*.
Uncommon: Sleep disturbances, depression.
Rare: Nightmares, hallucinations.

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: 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.

Metabolism and nutrition disorders:
Rare: Increased triglycerides.

Vascular disorders:
Common: Feeling of coldness or numbness in the extremities.
Uncommon: orthostatic hypotension.

*These symptoms especially occur at the beginning of the therapy. They are generally mild and usually disappear within 1-2 weeks.
General disorders:
Uncommon: Muscular weakness and cramps.

Hepatobiliary disorders:
Rare: increased liver enzymes (ALAT, ASAT), hepatitis.

Reproductive system and breast disorders:
Rare: Potency disorders.

4.9 Overdose

With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness have been reported. In general the most common signs expected with overdosage of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. To date a few cases of overdose (maximum: 2000 mg) with bisoprolol have been reported in patients suffering from hypertension and/or coronary heart disease showing bradycardia and/or hypotension; all patients recovered. There is a wide interindividual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive. Therefore it is mandatory to initiate the treatment of these patients with a gradual uptitration according to the scheme given in section 4.2.

If overdose occurs, bisoprolol 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.

Bisoprolol fumarate is already used for the treatment of hypertension and angina.

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.

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.

Linearity/non-linearity

The kinetics of bisoprolol fumarate are linear and independent of age.
The pharmacokinetics in patients with stable chronic heart failure and with impaired liver or renal function has not been studied.

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
Colloidal Silicon Dioxide
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 250 / 60 sealed with 20 um Aluminium foil. Cartons of 20, 28, 30, 50, 56, 60, 90 and 100 (not all pack sizes may be marketed).

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
STADA Arzneimittel AG
Stadastraße 2-18, D-61118 Bad Vilbel
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 11204/0206

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/02/2010

10 DATE OF REVISION OF THE TEXT
23/02/2010

1 NAME OF THE MEDICINAL PRODUCT

Bisoprolol Fumarate 2.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Bisoprolol Fumarate 2.5 mg: Each tablet contains 2.5 mg of bisoprolol fumarate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Bisoprolol Fumarate 2.5 mg Tablet is a white to off white round biconvex tablet with a break line on one side
Bisoprolol Fumarate 2.5 mg Tablets only: The tablets can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Oral use

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

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

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

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

- 1.25 mg once daily for 1 week, if well tolerated increase to
- 2.5 mg once daily for a further week, if well tolerated increase to
- 3.75 mg once daily for a further week, if well tolerated increase to
- 5 mg once daily for the 4 following weeks, if well tolerated increase to
- 7.5 mg once daily for the 4 following weeks, if well tolerated increase to
- 10 mg once daily for the maintenance therapy.

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

The maximum recommended dose is 10 mg once daily.

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

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

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

Bisoprolol 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.

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. Uptitration of the dose in these populations should therefore be made with additional caution.

Elderly:
No dosage adjustment is required.

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

4.3 Contraindications

Bisoprolol Fumarate is contraindicated in chronic heart failure patients with:
- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock
- AV block of second or third degree (without a pacemaker)
- sick sinus syndrome
- sinoatrial block
- bradycardia with less than 60 beats/min before the start of therapy
- hypotension (systolic blood pressure less than 100 mm Hg)
- severe bronchial asthma or severe chronic obstructive pulmonary disease
- late stages of peripheral arterial occlusive disease and Raynaud's syndrome
- untreated phaeochromocytoma (see 4.4)
- metabolic acidosis
- hypersensitivity to bisoprolol or to any of the excipients

4.4 Special warnings and precautions for use

Bisoprolol Fumarate must be used with caution in:
- bronchospasm (bronchial asthma, obstructive airways diseases)
- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia can be masked
- strict fasting
- ongoing desensitisation therapy
- AV block of first degree
- Prinzmetal's angina
- peripheral arterial occlusive disease (intensification of complaints might happen especially during the start of therapy)
- General anaesthesia

In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthetist must be aware of beta-blockade because of the potential for interactions with other drugs, resulting in bradyarrhythmias, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

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

- NYHA class II heart failure

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

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

Under treatment with bisoprolol fumarate the symptoms of a thyreotoxicosis may be masked.
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. Intravenous administration of verapamil in patients on β-blocker treatment may lead to profound hypotension and atrioventricular block.

Class I antiarrhythmic drugs (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide, propafenone): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonodine, rilmenidine): Concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of "rebound hypertension".
Combinations to be used with caution
Calcium antagonists of the dihydropyridine type such as felodipine and amlodipine: Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Class-III antiarrhythmic drugs (e.g. amiodarone): Effect on atrio- conduction time may be potentiated.

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

Parasympathomimetic drugs: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.

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

Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension (for further information on general anaesthesia see also section 4.4.).

Digitalis glycosides: Reduction of heart rate, increase of atrio-ventricular conduction time.

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

β-Sympathomimetic agents (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both agents.

Sympathomimetics that activate both β- and α-adrenoceptors (e.g. noradrenaline, adrenaline): Combination with bisoprolol may unmask the α-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective β-blockers.

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

Combinations to be considered
Mefloquine: increased risk of bradycardia

Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the beta-blockers but also risk for hypertensive crisis.

4.6 Pregnancy and lactation

Pregnancy:
Bisoprolol 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

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

Preferred Term WHO	Placebo (n=1321)	Bisoprolol (n=1328)

	Pat. with AE	% Pat. with AE	Pat. with AE	% Pat. with AE
Cardiac failure	301	22.8	244	18.4
Dyspnoea	224	17.0	183	13.8
Dizziness	126	9.5	177	13.3
Cardiomyopathy	132	10.0	141	10.6
Bradycardia	60	4.5	202	15.2
Hypotension	96	7.3	152	11.4
Tachycardia	144	10.9	79	5.9
Fatigue	94	7.1	123	9.3
Viral infection	75	5.7	86	6.5
Pneumonia	69	5.2	65	4.9

AE = Adverse Events

Post-marketing data
The following data results from post-marketing experience with bisoprolol fumarate:
Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10000, < 1/1000); very rare (< 1/10000).

Cardiac disorders:
Uncommon: bradycardia, AV-stimulus disturbances, worsening of heart failure.

Nervous system disorders:
Common: Tiredness*, exhaustion*, dizziness*, headache*.
Uncommon: Sleep disturbances, depression.
Rare: Nightmares, hallucinations.

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: 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.

Metabolism and nutrition disorders:
Rare: Increased triglycerides.

Vascular disorders:
Common: Feeling of coldness or numbness in the extremities.
Uncommon: orthostatic hypotension.

*These symptoms especially occur at the beginning of the therapy. They are generally mild and usually disappear within 1-2 weeks.
General disorders:
Uncommon: Muscular weakness and cramps.

Hepatobiliary disorders:
Rare: increased liver enzymes (ALAT, ASAT), hepatitis.

Reproductive system and breast disorders:
Rare: Potency disorders.

4.9 Overdose

With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness have been reported. In general the most common signs expected with overdosage of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. To date a few cases of overdose (maximum: 2000 mg) with bisoprolol have been reported in patients suffering from hypertension and/or coronary heart disease showing bradycardia and/or hypotension; all patients recovered. There is a wide interindividual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive. Therefore it is mandatory to initiate the treatment of these patients with a gradual uptitration according to the scheme given in section 4.2.

If overdose occurs, bisoprolol 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.

Bisoprolol fumarate is already used for the treatment of hypertension and angina.

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.

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.

Linearity/non-linearity

The kinetics of bisoprolol fumarate are linear and independent of age.
The pharmacokinetics in patients with stable chronic heart failure and with impaired liver or renal function has not been studied.

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
Colloidal Silicon Dioxide
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 250 / 60 sealed with 20 um Aluminium foil. Cartons of 10, 20, 28, 30, 50, 56, 60, 90 and 100 (not all pack sizes may be marketed).

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
STADA Arzneimittel AG
Stadastraße 2-18, D-61118 Bad Vilbel
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 11204/0207

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/02/2010

10 DATE OF REVISION OF THE TEXT
23/02/2010

1 NAME OF THE MEDICINAL PRODUCT

Bisoprolol Fumarate 3.75 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Bisoprolol Fumarate 3.75 mg:
Each tablet contains 3.75 mg of bisoprolol fumarate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Bisoprolol Fumarate 3.75 mg Tablet is a white to off white round biconvex tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

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

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

The treatment with bisoprolol fumarate is to be started with a gradual uptitration according to the following steps:
- 1.25 mg once daily for 1 week, if well tolerated increase to
- 2.5 mg once daily for a further week, if well tolerated increase to
- 3.75 mg once daily for a further week, if well tolerated increase to
- 5 mg once daily for the 4 following weeks, if well tolerated increase to
- 7.5 mg once daily for the 4 following weeks, if well tolerated increase to
- 10 mg once daily for the maintenance therapy.

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

The maximum recommended dose is 10 mg once daily.

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

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

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

Bisoprolol 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.

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. Uptitration of the dose in these populations should therefore be made with additional caution.

Elderly:
No dosage adjustment is required.

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

4.3 Contraindications

Bisoprolol Fumarate is contraindicated in chronic heart failure patients with:
- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock
- AV block of second or third degree (without a pacemaker)
- sick sinus syndrome
- sinoatrial block
- bradycardia with less than 60 beats/min before the start of therapy
- hypotension (systolic blood pressure less than 100 mm Hg)
- severe bronchial asthma or severe chronic obstructive pulmonary disease
- late stages of peripheral arterial occlusive disease and Raynaud's syndrome
- untreated phaeochromocytoma (see 4.4)
- metabolic acidosis
- hypersensitivity to bisoprolol or to any of the excipients

4.4 Special warnings and precautions for use

Bisoprolol Fumarate must be used with caution in:
- bronchospasm (bronchial asthma, obstructive airways diseases)
- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia can be masked
- strict fasting
- ongoing desensitisation therapy
- AV block of first degree
- Prinzmetal's angina
- peripheral arterial occlusive disease (intensification of complaints might happen especially during the start of therapy)
- General anaesthesia

In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthetist must be aware of beta-blockade because of the potential for interactions with other drugs, resulting in bradyarrhythmias, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

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

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

- myocardial infarction within 3 months

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

Under treatment with bisoprolol fumarate the symptoms of a thyreotoxicosis may be masked.
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. Intravenous administration of verapamil in patients on β-blocker treatment may lead to profound hypotension and atrioventricular block.

Class I antiarrhythmic drugs (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide, propafenone): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonodine, rilmenidine): Concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of "rebound hypertension".
Combinations to be used with caution
Calcium antagonists of the dihydropyridine type such as felodipine and amlodipine: Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Class-III antiarrhythmic drugs (e.g. amiodarone): Effect on atrio- conduction time may be potentiated.

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

Parasympathomimetic drugs: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.

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

Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension (for further information on general anaesthesia see also section 4.4.).

Digitalis glycosides: Reduction of heart rate, increase of atrio-ventricular conduction time.

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

β-Sympathomimetic agents (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both agents.

Sympathomimetics that activate both β- and α-adrenoceptors (e.g. noradrenaline, adrenaline): Combination with bisoprolol may unmask the α-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective β-blockers.

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

Combinations to be considered
Mefloquine: increased risk of bradycardia

Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the beta-blockers but also risk for hypertensive crisis.

4.6 Pregnancy and lactation

Pregnancy:
Bisoprolol 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

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

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AE = Adverse Events

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Cardiac disorders:
Uncommon: bradycardia, AV-stimulus disturbances, worsening of heart failure.

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Common: Tiredness*, exhaustion*, dizziness*, headache*.
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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:
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Vascular disorders:
Common: Feeling of coldness or numbness in the extremities.
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*These symptoms especially occur at the beginning of the therapy. They are generally mild and usually disappear within 1-2 weeks.
General disorders:
Uncommon: Muscular weakness and cramps.

Hepatobiliary disorders:
Rare: increased liver enzymes (ALAT, ASAT), hepatitis.

Reproductive system and breast disorders:
Rare: Potency disorders.

4.9 Overdose

With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness have been reported. In general the most common signs expected with overdosage of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. To date a few cases of overdose (maximum: 2000 mg) with bisoprolol have been reported in patients suffering from hypertension and/or coronary heart disease showing bradycardia and/or hypotension; all patients recovered. There is a wide interindividual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive. Therefore it is mandatory to initiate the treatment of these patients with a gradual uptitration according to the scheme given in section 4.2.

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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

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ATC Code: C07AB07

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The kinetics of bisoprolol fumarate are linear and independent of age.
The pharmacokinetics in patients with stable chronic heart failure and with impaired liver or renal function has not been studied.

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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.

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

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Colloidal Silicon Dioxide
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 250 / 60 sealed with 20 um Aluminium foil. Cartons of 20, 28, 30, 50, 56, 60, 90 and 100 (not all pack sizes may be marketed).

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
STADA Arzneimittel AG
Stadastraße 2-18, D-61118 Bad Vilbel
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 11204/0208

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/02/2010

10 DATE OF REVISION OF THE TEXT
23/02/2010

Module 3
Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Bisoprolol Fumarate 1.25 mg Tablets
Bisoprolol Fumarate 2.5 mg Tablets
Bisoprolol Fumarate 3.75 mg Tablets

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 your 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 your pharmacist.

In this leaflet:

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

[Bisoprolol Fumarate]belongs to a group of medicines called beta-blocking agents. 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 Fumarate 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).

2. Before you take Bisoprolol Fumarate Tablets

Do not 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 phaeochromocytoma, 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 (phaeochromocytoma)
- 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
- anaesthesia (for example for surgery), because Bisoprolol 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; flecainide, 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, moxonodine, 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 and amlodipine)
• 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 phenobarbital), 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.

Taking [Bisoprolol Fumarate] Tablets with food and drink
[Bisoprolol Fumarate] Tablets should be taken in the morning, before, with or after breakfast. They should be swallowed whole with liquid and should not be chewed or crushed.
Avoid drinking excessive alcohol, since it may increase the blood pressure-lowering effect of Bisoprolol. Avoid drinking alcohol altogether, if it makes you more dizzy or more light-headed than usual.

Pregnancy and breast-feeding:
There is a risk that use of [Bisoprolol Fumarate] during pregnancy may harm the baby. If you are pregnant or planning to become pregnant, tell your doctor. He or she will decide whether you can take this medicine during pregnancy. It is not known whether bisoprolol passes into human breast milk. Therefore, breastfeeding is not recommended during therapy with Bisoprolol Fumarate.

Driving and using machines:

Your ability to drive or use machinery may be affected depending on how well you tolerate the medicine. Please be especially cautious at the start of treatment, when the dose is increased or the medication is changed, as well as in combination with alcohol.

3. How to take [Bisoprolol Fumarate] tablets

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. Always take [Bisoprolol Fumarate] tablets in the morning, before, with, or after breakfast. Swallow the tablet/s whole with some water and do not chew or crush them.

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
• 3.75 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.

Children: [Bisoprolol Fumarate] Tablet/s is/are not recommended for use in children

Renal or liver disease: The dosage should be increased very gradually and cautiously 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. Your doctor will decide what measures are necessary. Symptoms of an overdose may include slowed heart rate, severe difficulty in breathing feeling dizzy, or trembling (due to decreased blood sugar).
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:

Very common:	**affects more than 1 user in 10**
Common:	**affects 1 to 10 users in 100**
Uncommon:	**affects 1 to 10 users in 1,000**

Rare:	**affects 1 to 10 users in 10,000**
Very rare:	**affects less than 1 user in 10,000**

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 3.75 mg tablet contains 3.75 mg bisoprolol fumarate.

The other ingredients are microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, sodium starch glycolate (type A) and magnesium stearate.

What [Bisoprolol Fumarate] Tablets look like and contents of the pack:
[Bisoprolol Fumarate] 1.25 mg tablets are white to off white round biconvex tablets.
[Bisoprolol Fumarate] 2.5 mg tablets are white to off white round biconvex tablets with a break line on one side.
[Bisoprolol Fumarate] 3.75 mg tablets are white to off white round biconvex tablets.

They come in packs of 10, 20, 28, 30, 50, 56, 60, 90 and 100 tablets (not all pack sizes may be marketed).

Marketing Authorisation Holder and Manufacturer:
The marketing authorisation holder is [to be completed nationally]

The manufacturer is Chanelle Medical, Loughrea, Co. Galway, Ireland.

This medicinal product is authorised in the Member States of the EEA under the following names:

United Kingdom :	**Bisoprolol Fumarate Tablets**
Austria:	**Bisostad Tabletten**
Beligium:	**Bisoprolol EG**
Germany:	**Bisoprolol STADA Tabletten**
France:	**BISOPROLOL EG comprimé pelliculé**
Italy:	**BISOPROLOLO EUROGENERICI compresse**
Luxembourg:	**Bisoprolol EG**
The Netherlands:	**Bisoprololfumaraat CF tabletten**
Sweden:	**Bisostad filmdragerade tabletter**

This leaflet was last approved in: MM/YYYY

Module 4
Labelling

PARTICULARS TO APPEAR ON THE <OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>

Carton

1. NAME OF THE MEDICINAL PRODUCT

Bisoprolol Fumarate 1.25mg, 2.5mg & 3.75mg Tablets

Austria:	**Bisostad Tabletten**
Beligium:	**Bisoprolol EG**
Germany:	**Bisoprolol STADA Tabletten**
France:	**BISOPROLOL EG comprimé pelliculé**
Italy:	**BISOPROLOLO EUROGENERICI compresse**
Luxembourg:	**Bisoprolol EG**
The Netherlands:	**Bisoprololfumaraat CF tabletten**
Sweden:	**Bisostad filmdragerade tabletter**

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1.25mg/2.5mg/3.75mg of bisoprolol fumarate

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet
10 tablets
20 tablets
28 tablets
30 tablets
50 tablets
56 tablets
60 tablets
90 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

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

[to be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[to be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS FOR USE

16. INFORMATION IN BRAILLE

Bisoprolol Fumarate 1.25 mg, 2.5mg & 3.75mg Tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Bisoprolol Fumarate 1.25mg, 2.5mg & 3.75mg Tablets in UK

United Kingdom :	**Bisoprolol Fumarate Tablets**
Austria:	**Bisostad Tabletten**
Beligium:	**Bisoprolol EG**
Germany:	**Bisoprolol STADA Tabletten**
France:	**BISOPROLOL EG comprimé pelliculé**
Italy:	**BISOPROLOLO EUROGENERICI compresse**
Luxembourg:	**Bisoprolol EG**
The Netherlands:	**Bisoprololfumaraat CF tabletten**
Sweden:	**Bisostad filmdragerade tabletter**

Bisoprolol Fumarate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[to be completed nationally]

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch

5. OTHER

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, France, Germany, Italy, The Netherlands, Sweden and the UK considered that the applications for Bisoprolol Fumarate 1.25mg, 2.5mg and 3.75mg Tablets could be approved. These products are prescription only medicines (POM) and are indicated in adults for the treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides.

These applications for Bisoprolol Fumarate 1.25mg, 2.5mg and 3.75mg Tablets are submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal product to Emcor 10mg Tablets, first authorised in the UK to E. Merck Limited in February 1988. The UK reference products are Cardicor 1.25mg, 2.5mg, 3.75mg film-coated Tablets. In both formulations, the active component is Bisoprolol fumarate.

Bisoprolol fumarate is a long acting selective beta-1 adrenergic blocker without either intrinsic agonist or membrane stabilising action. Its use in hypertension and treatment of angina pectoris is well established for a number of years.

Bisoprolol is absorbed well (90% bioavailable) with little first pass metabolism. It has the advantage of having a dual excretion/elimination pathway (50% renal and 50% liver) and therefore offers certain advantages.

No new preclinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies with the exception of the bioequivalence study have been performed and none are required for these applications as the pharmacology of bisoprolol fumarate is well-established.

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 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.

The marketing authorisation holder has provided adequate justification for not submitting a risk management plan (RMP).

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Bisoprolol Fumarate 1.25mg, 2.5mg and 3.75mg Tablets
Name(s) of the active substance(s) (INN)	Bisoprolol Fumarate
Pharmacotherapeutic classification (ATC code)	Beta blocking agents, selective (C07AB07)
Pharmaceutical form and strength(s)	1.25mg, 2.5mg and 3.75mg Tablets
Reference numbers for the Decentralised Procedure	UK/H/1458/001-3/DC
Reference Member State	United Kingdom
Member States concerned	France, Germany, Italy, The Netherlands, Sweden
Marketing Authorisation Number(s)	PL 11204/0206-8
Name and address of the authorisation holder	STADA Arzneimittel AG Stadastraβe 2-18, D-61118 Bad Vilbel Germany

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

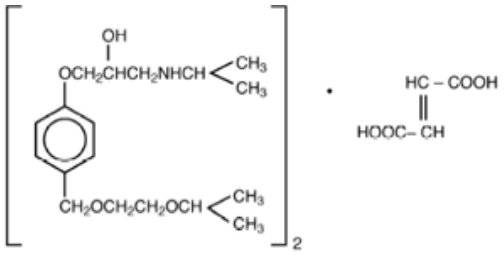
INN/Ph.Eur name: Bisoprolol Fumarate
Chemical name: Bisoprolol Hemifumarate

(R,S)1-[4-[[2-(1-Methylethoxy)ethoxy]methyl]phenoxy]-3 [(1methylethyl)amino]-2-propanol hemifumarate

(±)-1-(4-((2-(1-Methyl-ethoxy)ethoxy)methyl)phenoxy)-3-((1-methylethyl)amino)-2-propanol(E)-2-butenedioate (2:1) salt.

(±)-1-[[α-(2-Isopropoxyethoxy)-*p*-tolyl]oxy]-3-(Isopropylamino)-2-propanol fumarate (2:1) salt.

Structural formula:



Molecular formula: $(C_{18}H_{31}NO_4)_2\ C_4H_4O_4$

Appearance: White or almost white powder, slightly hygroscopic powder
Solubility: Very soluble in water and freely soluble in methanol.
Molecular weight: 767.0

Bisoprolol fumarate complies with in-house specifications.

An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance bisoprolol fumarate.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance bisoprolol fumarate, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, sodium starch glycolate (Type A) and magnesium stearate.

All excipients comply with their relevant European Pharmacopoeia monographs.

None of the excipients used contain material of animal or human origin. The magnesium stearate contained in this product is sourced from vegetable origin and therefore no European Pharmacopoeia Certificates of suitability for TSE is required.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to produce products that could be considered generic medicinal products of Emcor and Cardicor Tablets (E. Merck Limited).

The reference product used in the bioequivalence study is the UK reference product.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished products versus the reference products.

Comparative *in vitro* dissolution profiles and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on two batches per strength have been provided.

Finished Product Specification

The finished product specification proposed for the products is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for any working standards used.

Container-Closure System
These products are packaged in blisters composed of white polyvinyl chloride (PVC), polyvinylidene chloride (PVDC) 250/60 and sealed with 20um aluminium foil.
The products come in pack sizes of 20, 28, 30, 50, 56, 60, 90 and 100 tablets.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 3 years with no special storage instructions.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPCs, PILs and labelling are pharmaceutically acceptable.

User testing results have been submitted for typical PILs for these products. The results indicate that the PILs are 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.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

III.2 PRE-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of bisoprolol fumarate are well-known. As bisoprolol fumarate is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required.

The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

The marketing authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment.

III.3 CLINICAL ASPECTS

1. Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. For more details, the reader should refer to the company's clinical overview and summary and to the clinical file.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

2. Clinical study reports

To support these applications, the marketing authorisation holder has submitted one single dose bioequivalence study.

A comparative, randomised, single-dose, two-period, two-sequence, two-way cross-over open label study to determine the bioequivalence of Bisoprolol Fumarate 10mg Tablets versus Cardicor (bisoprolol fumarate) 10mg Tablets in normal, healthy, male subjects under fasting conditions.

All subjects were in a fasted state before dosing. Blood sampling was performed at baseline and up to 72 hours post dose in each treatment period. The washout period between phases was 7 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as non-transformed values:

Treatment	AUC_{0-t} (ng/ml/h)	$AUC_{0-\infty}$ (ng/ml/h)	C_{max} (ng/ml)
Bisoprolol Fumarate:			
Test	504.33 ± 116.85	521.97 ± 124.43	34.99 ± 7.57
Reference	476.94 ± 85.85	491.47 ± 91.22	31.94 ± 5.87
Ratio (90% CI)	104.96 (100.63– 109.47)	105.44 (101.17 – 109.90)	108.81 (103.21 – 114.70)

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for bisoprolol fumarate lie within 80-125% boundaries.

As the 10mg strength product meets all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 10mg strength can be extrapolated to Bisoprolol Fumarate 1.25mg, 2.5mg and 3.75mg Tablets.

3. Post marketing experience

Bisoprolol fumarate has a well-recognised efficacy and an acceptable level of safety in the indications approved for Emcor Tablets and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisations is supported.

4. Benefit-Risk assessment

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with bisoprolol

fumarate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

5. Conclusions

The grant of marketing authorisations for Bisoprolol Fumarate 1.25mg, 2.5mg and 3.75mg Tablets is recommended from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Bisoprolol Fumarate 1.25mg, 2.5mg and 3.75mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Bisoprolol Fumarate 1.25mg, 2.5mg and 3.75mg Tablets and the originator products.

No new or unexpected safety concerns arise from these applications.

The SPCs, PILs and labelling are satisfactory and consistent with that for the innovator products.

RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with bisoprolol fumarate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome