Public Assessment Report

Decentralised Procedure

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

(bisoprolol fumarate)

UK/H/1188/001-003/DC
UK licence numbers: PL 15773/0674-0676

ratiopharm GmbH
On 26th November 2009, the MHRA granted ratiopharm GmbH Marketing Authorisations (licences) for the medicinal products Bisprolol Fumarate 1.25mg, 2.5mg, and 3.75mg Tablets (PL 15773/0674-0676, UK/H/1188/001-003/DC). These are prescription-only medicines (POM).

Bisprolol 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).

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Bisprolol Fumarate 1.25mg, 2.5mg, and 3.75mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.
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# Module 1

## Information about Initial Procedure

| **Product Name** | Bisoprolol Fumarate 1.25mg tablets  
|                 | Bisoprolol Fumarate 2.5mg tablets  
|                 | Bisoprolol Fumarate 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** | ratiopharm GmbH, Graf-Arco-Str.3, D-89079 Ulm, Germany |
| **Reference Member State (RMS)** | UK |
| **Concerned Member State / s (CMS)** | UK/H/1188/001/DC (1.25mg) - FR, SE  
|                 | UK/H/1188/002/DC (2.5mg) - FI, FR, NL, SE  
|                 | UK/H/1188/003/DC (3.75mg) - FR |
| **Procedure Number** | UK/H/1188/001-003/DC |
| **Timetable** | Day 210 – 29th October 2009 |
Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Bisoprolol Fumarate 1.25mg, 2.5mg, and 3.75mg Tablets (PL 15773/0674-0676) is as follows – Differences are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1.25 / 2.5 / 3.75 mg bisoprolol fumarate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

For 1.25mg and 3.75mg strengths:
Tablet
White to off white round biconvex tablet

For 2.5mg strength:
Tablet
White to off white round biconvex tablet with a break line on one side

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides (for additional information see section 5.1).

4.2 Posology and method of administration

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

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

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

Titration phase

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

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

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

The maximum recommended dose is 10 mg once daily.

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

**Treatment modification**

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

In case of transient worsening of heart failure, hypotension, or bradycardia reconsideration of the dosage of the concomitant medication is recommended. It may also be necessary to temporarily lower the dose of bisoprolol or to consider discontinuation.

The reintroduction and/or uptitration of bisoprolol should always be considered when the patient becomes stable again.

If discontinuation is considered, gradual dose decrease is recommended, since abrupt withdrawal may lead to acute deterioration of the patients condition.

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

**Administration**

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.

**Special population**

**Renal or liver impairment:**
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 under 12 years and adolescents**
Bisoprolol Fumarate is not recommended for use in children due to a lack of experience in children.

**4.3 Contraindications**

Bisoprolol Fumarate is contraindicated in chronic heart failure patients with:

- hypersensitivity to bisoprolol or to any of the excipients
- untreated acute or uncompensated heart failure requiring intravenous inotropic support (see 4.4)
- cardiogenic shock
- Atrio-ventricular block of second or third degree (without a pacemaker)
- sick sinus syndrome
- sino-atrial 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
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 medicinal products, resulting in bradycardia, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

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

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

Combination of bisoprolol fumarate with calcium antagonists of the verapamil and diltiazem type, with Class I antiarrhythmic medicinal products and with centrally acting antihypertensive medicinal products 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-blocking agents 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-blocking agents (e.g. bisoprolol fumarate) after carefully balancing the benefits against the risks.

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

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

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

The cessation of therapy with bisoprolol fumarate should not be done abruptly unless clearly indicated. For further information please refer to section 4.2.
4.5 Interaction with other medicinal products and other forms of interaction

Combinations not recommended

Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type: Negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrioventricular block.

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

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

Combinations to be used with caution

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

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

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

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

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

Insulin and oral antidiabetic medicinal products: 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. Higher doses of adrenaline may be considered for treatment of allergic reactions.

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

Moxixylate: Possibly causes severe postural hypertension

Combinations to be considered

Mefloquine: increased risk of bradycardia
Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the beta-blocking agents 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 reactions (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

Bisoprolol Fumarate Tablets has negligible influence on the ability to drive and use machines.

In a study with coronary heart disease patients bisoprolol fumarate did not impair driving performance. However, due to individual variations in reactions to the drug, the ability to drive a vehicle or to operate machinery may be impaired. This should be considered particularly at start of treatment and upon change of medication as well as in conjunction with alcohol.

4.8 Undesirable effects

The following terminologies have been used in order to classify the occurrence of undesirable effects:

Very common (≥1/10)
Common (≥1/100 to < 1/10)
Uncommon (≥1/1,000 to < 1/100)
Rare (≥1/10,000 to < 1/1,000)
Very rare (<1/10,000)

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

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

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

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

Ear and labyrinth disorders:
Rare: hearing impairment.

Respiratory, thoracic and mediastinal disorders:
Uncommon: bronchospasm in patients with bronchial asthma or a history of obstructive airways disease.
Rare: allergic rhinitis.
**Gastrointestinal disorders:**
Common: gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation.

**Skin and subcutaneous tissue disorders:**
Rare: hypersensitivity reactions (itching, flush, rash).
Very rare: Beta-blocking agents may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia.

**Musculoskeletal and connective tissue disorders:**
Uncommon: muscular weakness and cramps.

**Vascular disorders:**
Common: feeling of coldness or numbness in the extremities, hypotension.
Uncommon: orthostatic hypotension.

**General disorders:**
Common: asthenia, fatigue.

**Hepatobiliary disorders:**
Rare: hepatitis.

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

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

### 4.9 Overdose

With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness have been reported. In general the most common signs expected with overdose of a beta-blocking agent 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-blocking agents, the following general measures should be considered when clinically warranted.

Bradycardia: Atropine should be administered intravenously. 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: Bronchodilator therapy such as isoprenaline, beta2-sympathomimetic medicinal products and/or aminophylline should be administered.

Hypoglycaemia: I.v. glucose should be administered.
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 \( \leq 35\% \), based on echocardiography). Total mortality was reduced from 17.3% to 11.8% (relative reduction 34%). A decrease in sudden death (3.6% vs 6.3%, relative reduction 44%) and a reduced number of heart failure episodes requiring hospital admission (12% vs 17.6%, relative reduction 36%) was observed. Finally, a significant improvement of the functional status according to NYHA classification has been shown. During the initiation and titration of bisoprolol hospital admission due to bradycardia (0.53%), hypotension (0.23%), and acute decompensation (4.97%) were observed, but they were not more frequent than in the placebo-group (0%, 0.3% and 6.74%). The numbers of fatal and disabling strokes during the total study period were 20 in the bisoprolol group and 15 in the placebo group.

The CIBIS III trial investigated 1010 patients aged \( \geq 65 \) years with mild to moderate chronic heart failure (CHF; NYHA class II or III) and left ventricular ejection fraction \( \leq 35 \), who had not been treated previously with ACE inhibitors, Beta-blocking agents, or angiotensin receptor blockers. Patients were treated with a combination of bisoprolol and enalapril for 6 to 24 months after an initial 6 months treatment with either bisoprolol or enalapril.

There was a trend toward higher frequency of chronic heart failure worsening when bisoprolol was used as the initial 6 months treatment. Non inferiority of bisoprolol-first versus enalapril-first treatment was not proven in the per-protocol analysis, although the two strategies for initiation of CHF treatment showed a similar rate of the primary combined endpoint death and hospitalization at study end (32.4% in the bisoprolol-first group vs. 33.1% in the enalapril-first group, per-protocol population). The study shows that bisoprolol can also be used in elderly chronic heart failure patients with mild to moderate disease.

Bisoprolol fumarate is already used for the treatment of hypertension and angina. As with other \( \beta \)-blocking agents, the mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma renin levels.

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

5.2 Pharmacokinetic properties

Bisoprolol is absorbed and has a biological availability of about 90% after oral administration. The plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg. Total clearance is approximately 15 l/h. The half-life in plasma of 10-12 hours gives a 24 hour effect after dosing once daily. Bisoprolol is excreted from the body by two routes. 50% is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in an unmetabolised form. Since the elimination takes place in the kidneys and the liver to the same extent a dosage adjustment is not required for patients with impaired liver function or renal insufficiency. The pharmacokinetics in patients with stable chronic heart failure and with impaired liver or renal function has not been studied.

The kinetics of bisoprolol are linear and independent of age.
In patients with chronic heart failure (NYHA stage III) the plasma levels of bisoprolol are higher and the half-life is prolonged compared to healthy volunteers. Maximum plasma concentration at steady state is 64+21 ng/ml at a daily dose of 10 mg and the half-life is 17±5 hours.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity. Like other Beta-blocking agents, 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
Cellulose, Microcrystalline
Silica, colloidal anhydrous
Crocarmellose sodium
Sodium Starch glycolate (Type A)
Magnesium Stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

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

6.5 Nature and contents of container
Blister of white PVC/PVDC/Aluminium
Packsizes of 20, 21, 28, 30, 50, 56, 60, 90 and 100
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
ratiopharm GmbH, Graf-Arco-Str.3, D-89079 Ulm, Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 15773/0674
PL 15773/0675
PL 15773/0676

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
26/11/2009

10 DATE OF REVISION OF THE TEXT
26/11/2009
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, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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

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

The active substance in this medicine is Bisoprolol fumarate. Bisoprolol Fumarate belongs to a group of medicines called beta-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 (pheochromocytoma)
- thyroid disorder.

In addition, tell your doctor if you are going to have:

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

Taking other medicines:

Please tell your doctor or pharmacist if you are taking or have recently taken any other
medicines, including medicines obtained without a prescription. Do not take the following
medicines with Bisoprolol Fumarate without special advice from your doctor:

- Certain medicines used to treat irregular or abnormal heart beat (Class I antiarrhythmic
  medicines such as quinidine, disopyramide, lidocaine, phenytin; flecainide, propafenone)
- Certain medicines used to treat high blood pressure, angina pectoris or irregular heart beat
  (calcium antagonists such as verapamil and diltiazem)
- Certain medicines used to treat high blood pressure such as clonidine, methyldopa, 
  moxonidine, rilmenidine. However, do not stop taking these medicines without checking
  with your doctor first.

Check with your doctor before taking the following medicines with Bisoprolol Fumarate; your
doctor may need to check your condition more frequently:

- Certain medicines used to treat high blood pressure or angina or abnormal heart beat
  (diuretics and calcium antagonists such as nifedipine)
- Certain medicines used to treat high blood pressure or angina pectoris (diuretics and other
  medicines such as felodipine and amiodipine)
- Certain medicines used to treat irregular or abnormal heart beat (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)
- Digoxin, 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)
- Moxisylyte, used for treatment raynauds disease (poor circulation which makes toes and
  fingers numb and pale)
- 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.

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. This treatment should be initiated by a specialist in cardiology or internal medicines.

**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 (ongoing) 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 under 12 years and adolescents:** Bisoprolol Fumarate Tablets 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.

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 cellulose microcrystalline, silica colloidal anhydrous, croscarmellose sodium, sodium starch glycolate (type A) and magnesium stearate.

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

Bisoprolol Fumarate 2.5 mg Tablet only: The tablet can be divided into equal halves.

Pack sizes of 20, 21, 28, 30, 50, 56, 60, 90 and 100 tablets (not all pack sizes may be marketed).

Marketing Authorisation Holder: The marketing authorisation holder is ratiopharm GmbH,
Graf-Arco-Str. 3, D-89079 Ulm, Germany.

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

For a large print, audio, Braille or CD-rom version of this patient information leaflet, phone 02392 313592.

This leaflet was last approved in: November 2009.
Module 4

Labelling

Bisoprolol Fumarate 1.25mg tablets

Blister carton - pack size 28 tablets

Braille translation

Blistert foil
Bisoprolol Fumarate 2.5mg tablets
Blister carton - pack size 28 tablets

Braille translation

Blister foil
Bisoprolol Fumarate 3.75mg tablets

Blister carton - pack size 28 tablets

**Braille translation**

**Blister foil**
Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted ratiopharm GmbH Marketing Authorisations for the medicinal products Bisprolol Fumarate 1.25mg, 2.5mg, and 3.75mg Tablets (PL 15773/0674-0676, UK/H/1188/001-003/DC) on 26th November 2009. The products are prescription-only medicines.

These are abridged applications for Bisprolol Fumarate 1.25mg, 2.5mg, and 3.75mg Tablets, three strengths of bisprolol fumarate, submitted under Article 10.1 of 2001/83 EC, as amended. The applications refer to the UK reference products, Cardicor 1.25mg, 2.5mg, and 3.75mg film-coated Tablets (PL 00493/0179-0181 respectively), authorised to E Merck Limited (trading as Merck Pharmaceuticals) on 24th December 1999. The reference medicinal product in the EEA is Detensiel containing 10 mg bisoprolol fumarate first authorised to Merck Lipha Sante in France on 05/12/1986. The period of data exclusivity has expired. With UK as the Reference Member State in this Decentralised Procedure, ratiopharm GmbH applied for Marketing Authorisations for Bisprolol fumarate 1.25mg, 2.5mg, and 3.75mg Tablets in FI, FR, NL, and SE.

Bisprolol fumarate tablets are indicated in the treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides.

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

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

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.

Bisoprolol is absorbed and has a biological availability of about 90% after oral administration. The plasma protein binding of bisoprolol is about 30%. Total clearance is approximately 15 l/h. Bisoprolol is excreted from the body by two routes. 50% is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in an unmetabolised form. Since the elimination takes place in the kidneys and the liver to the same extent a dosage adjustment is not required for patients with impaired liver function or renal insufficiency. The kinetics of bisoprolol are linear and independent of age.
No new preclinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The applications are supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Bisoprolol Fumarate 10mg Tablets, to that of the reference product, Cardicor 10mg film-coated Tablets (Merck UK). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. 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 fulfills 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 an Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. The marketing authorisation holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is a well established.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Bisoprolol Fumarate 1.25mg tablets  
Bisoprolol Fumarate 2.5mg tablets  
Bisoprolol Fumarate 3.75mg tablets |
| Name(s) of the active substance(s) (INN) | Bisoprolol fumarate |
| Pharmacotherapeutic classification (ATC code) | Beta blocking agents  
(C07A B07) |
| Pharmaceutical form and strength(s) | Tablets  
1.25mg, 2.5mg, and 3.75mg |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1188/001-003/DC |
| Reference Member State | United Kingdom |
| Member States concerned | UK/H/1188/001/DC (1.25mg) - FR, SE  
UK/H/1188/002/DC (2.5mg) - FI, FR, NL, SE  
UK/H/1188/003/DC (3.75mg) - FR |
| Marketing Authorisation Number(s) | PL 15773/0674-0676 |
| Name and address of the authorisation holder | ratiopharm GmbH,  
Graf-Arco-Str.3,  
D-89079 Ulm,  
Germany |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Bisoprolol fumarate

Nomenclature:

INN: Bisoprolol fumarate

Chemical name:

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

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

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

Structure:

\[
\text{Molecular formula: } (\text{C}_{18}\text{H}_{31}\text{NO}_{4})_{2} \cdot \text{C}_{4}\text{H}_{4}\text{O}_{4}
\]

Molecular weight: 767.0 g/mol

CAS No: 104344-23-2

Physical form: White or almost white powder


The active substance, bisoprolol fumarate, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

An appropriate specification has been provided for the active substance. 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 Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. It is packed in a transparent polyethylene bag, which in turn is covered by an outer grey polyethylene bag. Both bags are separately sealed by means of a cable tie. The external container is a fibreboard cylinder with
galvanized metal lid. Specifications and Certificates of Analysis have been provided for the packaging materials used. The polyethylene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in packaging representative of the proposed commercial packaging. These data demonstrate the stability of the active substance and support a shelf-life of 5 years, when the active is kept closed in the original containers and protected from light.

**DRUG PRODUCT**

**Description and Composition**

The drug products are presented as round, biconvex, white to off-white tablets, each containing 1.25mg, 2.5mg, or 3.75mg of the active ingredient bisoprolol fumarate. The 2.5mg strength tablets have a break-line on one side and can be divided into equal halves.

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, sodium starch glycolate, and magnesium stearate. Appropriate justification for the inclusion of each excipient has been provided.

The excipients are all controlled to the requirements of their current European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate is of vegetable origin. The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product.

There were no novel excipients used and no overages.

**Dissolution profiles**

Comparative dissolution data were provided for each strength (plus 5mg and 10mg strengths) of the proposed generic bisoprolol fumarate tablets against appropriate reference tablet formulations. The dissolution profiles were found to be similar and were satisfactory.

**Pharmaceutical development**

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted on two production scale batches for each of the strengths.

**Finished product specification**

The finished product specifications include tests and criteria to apply for both release and end of shelf life testing and are satisfactory; they provide an assurance of the quality and consistency of the finished products. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been
provided for two production scale batches of each of the strengths and they comply with the release specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**

The finished products are licensed for marketing in PVC (polyvinylchloride) / PVDC (polyvinylidene chloride) / aluminium foil blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The tablets are packaged in pack sizes of 20, 21, 28, 30, 50, 56, 60, 90 and 100 tablets. The MA Holder has stated that not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided and are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. These medicinal products do not require any special storage conditions.

**Bioequivalence Study**

A bioequivalence study was presented comparing the test product, Bisoprolol Fumarate 10mg Tablets, to the reference product, Cardicor 10mg film-coated Tablets (Merck UK).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

**Expert Report**

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

**Product Information**

The approved SmPCs, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling have been provided. The labelling fulfils the statutory requirements for Braille.

**Conclusion**

The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant’s claim that Bisoprolol Fumarate 10mg Tablets is a generic medicinal product of Cardicor 10mg film-coated Tablets (Merck UK) appears justified.

As the product range, Bisoprolol fumarate 1.25mg, 2.5mg, 3.75mg, 5mg, and 10mg Tablets, meet the criteria 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 the 1.25mg, 2.5mg, and 3.75mg strength tablets.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. Marketing Authorisations were, therefore, granted.
III.2 PRE-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for these applications for generic versions of products that have been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of bisoprolol fumarate, which is a widely used and well-known active substance.

A satisfactory non-clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

III.3 CLINICAL ASPECTS

INDICATIONS

Bisprolol fumarate tablets are indicated in the treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides.

The indications are consistent with those for the reference products and are satisfactory. Several other agents in this class have been in clinical use for treatment of various conditions including hypertension, angina pectoris and heart failure. Here the applicant seeks only the heart failure indication in the named CMS.

POSOLOGY AND METHOD OF ADMINISTRATION

The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY

No new data have been submitted and none are required for these types of application.

CLINICAL PHARMACOLOGY

The clinical pharmacology of bisoprolol fumarate is well known. No novel pharmacodynamic data are supplied or required for this application.

Pharmacokinetics – bioequivalence study

The application is supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profiles of Bisprolol Fumarate 10mg Tablets (test) and Cardicor 10mg film-coated Tablets - Merck Pharmaceuticals UK (reference). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). The use of the 10mg strength tablet for the bioequivalence study has been adequately justified.

This was a randomised, two-treatment, two-period, two-sequence, open-label, single dose crossover bioavailability and bioequivalence study conducted in 28 healthy adult human subjects under fasting conditions. A single dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 7 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 72.0 hours after administration of test or reference product. The drug concentration levels in plasma were determined by a validated LC/MS/MS method.
The primary pharmacokinetic parameters for this study were \( C_{\text{max}} \), AUC\(_{0-t} \), and AUC\(_{0-\infty} \). Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed \( C_{\text{max}} \), AUC\(_{0-t} \), and AUC\(_{0-\infty} \).

Results:
All twenty-eight subjects were used in the statistical analysis. There were no deaths or serious adverse events.

The summary of the results of the bioequivalence study are tabulated below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( C_{\text{max}} ) ng/ml</th>
<th>AUC(_{0-t} ) ng/ml/h</th>
<th>AUC(_{0-\infty} ) ng/ml/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>34.99</td>
<td>504.33</td>
<td>521.97</td>
</tr>
<tr>
<td>Reference</td>
<td>31.94</td>
<td>476.94</td>
<td>491.47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ratio (90% CI)</th>
<th>( C_{\text{max}} )</th>
<th>( AUC_{0-t} )</th>
<th>( AUC_{0-\infty} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point estimate</td>
<td>108.81 (103.21 – 114.70)</td>
<td>104.96 (100.63 – 109.47)</td>
<td>105.44 (101.17 – 109.90)</td>
</tr>
</tbody>
</table>

Conclusion on Bioequivalence
The results of the bioequivalence study show that the test product and reference product are bioequivalent, under fasting conditions, as the confidence intervals for \( C_{\text{max}} \), AUC\(_{0-t} \), and AUC\(_{0-\infty} \) fall within the acceptance criteria ranges of 80-125% in line with current CHMP guidelines.

Satisfactory justification is provided for a bio-waiver for Bisprolol Fumarate 1.25mg, 2.5mg, 3.75mg, and 5mg Tablets. As Bisprolol Fumarate 1.25mg, 2.5mg, 3.75mg, 5mg, and 10mg Tablets meet the criteria 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 the 1.25mg, 2.5mg, and 3.75mg strength tablets.

Clinical efficacy
No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of bisoprolol fumarate is well-established from its extensive use in clinical practice.

Clinical safety
No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of bisoprolol fumarate is well-known.
PRODUCT INFORMATION:
Summary of Product Characteristics (SmPC)
The approved SmPCs are consistent with those for the reference products, and are acceptable.

Patient Information Leaflet
The final PIL is in line with the approved SmPCs and is satisfactory.

Labelling
The labelling is satisfactory.

Expert report
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

CONCLUSIONS
All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Bisoprolol Fumarate 10mg Tablets, ratiopharm GmbH) and reference (Cardicor 10mg film-coated Tablets, Merck Pharmaceuticals UK) products within acceptance limits. The results and conclusions of the bioequivalence study on the 10mg strength were extrapolated to the 1.25mg, 2.5mg, and 3.75mg strength tablets.

Sufficient clinical information has been submitted to support these applications. Marketing Authorisations were, therefore, granted on medical grounds.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Bisprolol 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 Bisprolol Fumarate 10mg Tablets, and the reference product, Cardicor 10mg film-coated Tablets (Merck Pharmaceuticals UK).

As the product range, Bisprolol Fumarate 1.25mg, 2.5mg, 3.75mg, 5mg, and 10mg Tablets, meet the criteria 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 were extrapolated to the 1.25mg, 2.5mg, and 3.75mg strength products, and omission of further bioequivalence studies on the other strengths can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The testing shows that the patients/users are able to act upon the information that the leaflet contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant’s products and their respective reference products are interchangeable. Extensive clinical experience with bisprolol fumarate is considered to have demonstrated the therapeutic value of the active substance. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

There have been no variation applications submitted after approval of the initial procedure.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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