Public Assessment Report

Decentralised Procedure

BISOPROLOL FUMARATE 2.5 MG TABLETS
BISOPROLOL FUMARATE 5 MG TABLETS
BISOPROLOL FUMARATE 10 MG TABLETS

(Bisoprolol fumarate)

Procedure No: UK/H/4301/001-3/DC


IVOWEN LIMITED
LAY SUMMARY

On 27 July 2011, France, Italy and the UK agreed to grant Marketing Authorisations to Ivowen Limited for the medicinal products Bisoprolol Fumarate 2.5 mg, 5 mg and 10 mg Tablets (PL 20154/0017-9; UK/H/4301 /001-3/DC). These licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 25 August 2011.

Bisoprolol belongs to a group of medicines called beta-blockers. Bisoprolol slows down the heart rate and makes the heart more efficient at pumping blood around the body.

These are prescription-only medicines (POM) used to treat stable heart failure.

Heart failure occurs when the heart muscle is weak and unable to pump enough blood around the circulation. This results in breathlessness and swelling.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Bisoprolol Fumarate 2.5 mg, 5 mg and 10 mg Tablets outweigh the risks.
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## Module 1

| **Product Name** | Bisoprolol Fumarate 2.5 mg Tablets  
|                 | Bisoprolol Fumarate 5 mg Tablets  
|                 | Bisoprolol Fumarate 10 mg Tablets |
| **Type of Application** | Generic, Article 10.1 |
| **Active Substances** | Bisoprolol fumarate |
| **Form** | Tablet |
| **Strength** | 2.5 mg, 5 mg and 10 mg |
| **MA Holder** | Ivowen Limited, 3 Anglesea Street, Clonmel, Co. Tipperary, Ireland |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | UK/H/4301/001/DC: France and Italy  
| | UK/H/4301/002-3/DC: France |
| **Procedure Number** | UK/H/4301/001-3/DC |
| **Timetable** | Day 210 – 27 July 2011 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Bisoprolol Fumarate 2.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 2.5 mg bisoprolol fumarate
Excipients: 69 mg lactose monohydrate
For excipients, see section 6.1.

3 PHARMACEUTICAL FORM
2.5 mg tablets: white, oblong, uncoated, break-line on both top and bottom sides, “BI” and “2.5” debossed on either side of the break-line on the top. 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 chronic heart failure (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.
The 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 chronic stable heart failure with bisoprolol requires a titration phase.
The treatment with bisoprolol is to be started with a gradual uptitration according to the following steps:

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

The maximum recommended dose is 10 mg once daily.

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

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

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

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

**Administration**

For oral use

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

**Special population**

*Renal or hepatic impairment*

There is no information regarding pharmacokinetics of bisoprolol 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 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
- second or third degree AV block (without a pacemaker)
- sick sinus syndrome
- sinoatrial block
- symptomatic bradycardia
- symptomatic hypotension
- severe bronchial asthma or severe chronic obstructive pulmonary disease
- severe forms of peripheral arterial occlusive disease and severe forms of 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**

**Warnings**

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

- Especially in patients with ischaemic heart disease the cessation of therapy with bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition (see section 4.2).

**Precautions**

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

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

- insulin dependent diabetes mellitus (type I)
- severely impaired renal function
- severely impaired hepatic function
- restrictive cardiomyopathy
• congenital heart disease
• haemodynamically significant organic valvular disease
• myocardial infarction within 3 months

Bisoprolol must be used with caution in:

• diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia (e.g. tachycardia, palpitations or sweating) can be masked
• strict fasting
• ongoing desensitisation therapy. As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine treatment may not always yield the expected therapeutic effect
• first degree AV block
• Prinzmetal's angina
• peripheral arterial occlusive disease. Aggravation of symptoms may occur especially when starting therapy.

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

The symptoms of thyrotoxicosis may be masked under treatment with bisoprolol

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

In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance 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 bradycardias, attenuation of the reflex tachycardia and decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocking agent therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

In bronchial asthma or other chronic obstructive pulmonary disease, which may cause symptoms, concomitant bronchodilating therapy is recommended. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of beta₂-stimulants may have to be increased.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Combination not recommended

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

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

• Centrally-acting antihypertensive drugs (e.g. clonidine methylpda, moxonidine, rilmenidine): concomitant use of centrally-acting antihypertensive drugs may further decrease the central sympathetic tonus and may thus lead to reduction of heart rate and cardiac output and to vasodilation. Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase the risk of ”rebound hypertension”.

Combination 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-ventricular conduction time may be potentiated.
- Parasympathomimetic drugs: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.
- Topical beta-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.
- Insulin and oral antidiabetic drugs: Increase of blood sugar lowering effect. Blockade of 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).
- Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol.
- Beta-Sympathomimetic agents (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both agents.
- Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. noradrenaline, adrenaline): Combination with bisoprolol may unmask the alpha-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective beta-blockers.
- Concomitant use with antihypertensive agents as well as with other drugs with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.

**Combinations to be considered**
- Mefloquine: increased risk of bradycardia
- Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the beta-blockers but also risk for hypertensive crisis
- Rifampicin: Slight reduction of the half-life of bisoprolol possible due to the induction of hepatic drug-metabolising enzymes. Normally no dosage adjustment is necessary.
- Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

### 4.6 Fertility, Pregnancy and Lactation

#### Pregnancy
Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. In general, beta-adrenoreceptor 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-adrenoreceptor blockers is necessary, beta₁-selective adrenoceptor blockers are preferable. Bisoprolol is not recommended 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, breast feeding is not recommended during therapy with bisoprolol.

### 4.7 Effects on ability to drive and use machines
In a study with coronary heart disease patients, bisoprolol did not impair driving performance. However, depending on the individual patients response to treatment an effect on the ability to drive a vehicle or to use machines cannot be excluded. This needs to be considered particularly at start of treatment, upon change of medication, or in conjunction with alcohol.

### 4.8 Undesirable effects
The following definitions apply to the frequency terminology used hereafter:

- **Very common** (≥ 1/10),
- **Common** (≥ 1/100 and < 1/10)
- **Uncommon** (≥ 1/1000 and < 1/100)
- **Rare** (≥ 1/10,000 and < 1/1,000)
Very rare (< 1/10,000)

Cardiac disorders:
Very common: bradycardia
common: worsening of pre-existing 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 disorders

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, diarrhea, constipation

Skin and subcutaneous tissue disorders:
Rare: hypersensitivity reactions (itching, flush, rash)
Very rare: beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia

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

Vascular disorders:
Common: feeling of coldness or numbness in the extremities, 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
The most common signs expected with overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is limited experience with overdose of bisoprolol, only a few cases of overdose with bisoprolol have been reported. Bradycardia and/or hypotension were noted. All patients recovered. There is a wide inter-individual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive.

In general, if overdose occurs, discontinuation of bisoprolol treatment and supportive and symptomatic treatment is recommended.
Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures should be considered when clinically warranted.

**Bradydcardia:** Administer intravenous atropine. If the response is inadequate, isoprenaline or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.

**Hypotension:** Intravenous fluids and vasopressors should be administered. Intravenous glucagon may be useful.

**AV block (second or third degree):** Patients should be carefully monitored and treated with isoprenaline infusion or temporary pacing.

**Acute worsening of heart failure:** Administer i.v. diuretics, inotropic agents, vasodilating agents.

**Bronchospasm:** Administer bronchodilator therapy such as isoprenaline, beta₂-sympathomimetic drugs and/or aminophylline.

**Hypoglycaemia:** Administer i.v. glucose

Limited data suggest that bisoprolol is hardly dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective

ATC Code: C07AB07

Bisoprolol is a highly beta₁-selective-adrenoceptor blocking agent, lacking intrinsic stimulating activity and without 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 is generally not to be expected to influence the airway resistance and beta₂-mediated metabolic effects. Its beta₁-selectivity extends beyond the therapeutic dose range.

In total 2647 patients were included in the CIBIS II trial. 83% (n = 2202) were in NYHA class III and 17% (n = 445) were in NYHA class IV. They had stable symptomatic systolic heart failure (ejection fraction <35%, based on echocardiography). Total mortality was reduced from 17.3% to 11.8% (relative reduction 34%). A decrease in sudden death (3.6% vs 6.3%, relative reduction 44%) and a reduced number of heart failure episodes requiring hospital admission (12% vs 17.6%, relative reduction 36%) was observed. Finally, a significant improvement of the functional status according to NYHA classification has been shown. During the initiation and titration of bisoprolol hospital admission due to bradycardia (0.53%), hypotension (0.23%), and acute decompensation (4.97%) were observed, but they were not more frequent than in the placebo-group (0%, 0.3% and 6.74%). The numbers of fatal and disabling strokes during the total study period were 20 in the bisoprolol group and 15 in the placebo group.

The CIBIS III trial investigated 1010 patients aged ≥65 years with mild to moderate chronic heart failure (CHF; NYHA class II or III) and left ventricular ejection fraction 35%, who had not been treated previously with ACE inhibitors, beta-blockers, or angiotensin receptor blockers. Patients were treated with a combination of bisoprolol and enalapril for 6 to 24 months after an initial 6 months treatment with either bisoprolol or enalapril. There was a trend toward higher frequency of chronic heart failure worsening when bisoprolol was used as the initial 6 months treatment. Non inferiority of bisoprolol-first versus enalapril-first treatment was not proven in the per-protocol analysis, although the two strategies for initiation of CHF treatment showed a similar rate of the primary combined endpoint death and hospitalization at study end (32.4% in the bisoprolol-first group vs. 33.1% in the enalapril-first group, per-protocol population). The study shows that bisoprolol can also be used in elderly chronic heart failure patients with mild to moderate disease.

Bisoprolol is also used for the treatment of hypertension and angina.
In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases.

5.2 Pharmacokinetic properties
Bisoprolol is absorbed and has a biological availability of about 90% after oral administration. The plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg. Total clearance is approximately 15 l/h. The half-life in plasma of 10-12 hours gives a 24 hour effect after dosing once daily.

Bisoprolol is excreted from the body by two routes. 50% is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in an unmetabolised form. Since 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-blockers, bisoprolol caused maternal (decreased food intake and decreased body weight) and embryo/fetal toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development) at high doses but was not teratogenic.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
- microcrystalline cellulose
- lactose monohydrate
- magnesium stearate
- crospovidone

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
Blisters comprising PVC/PVdC/aluminium foil
Pack sizes: 28, 30 or 90 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Ivoven Limited, 3 Anglesea Street, Clonmel, Co. Tipperary, Ireland.

8 MARKETING AUTHORISATION NUMBER(S)
PL 20154/0017

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/08/2011
DATE OF REVISION OF THE TEXT
25/08/2011
1 NAME OF THE MEDICINAL PRODUCT
Bisoprolol Fumarate 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5 mg bisoprolol fumarate
Excipients: 136 mg lactose monohydrate

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM
5 mg tablets: pale yellow mottled, normal convex tablet embossed with BI, break-line and 5 on one side and plain on the reverse. 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 chronic heart failure (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.
The 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 chronic stable heart failure with bisoprolol requires a titration phase.
The treatment with bisoprolol is to be started with a gradual uptitration according to the following steps:

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

The maximum recommended dose is 10 mg once daily.

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

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

In case of transient worsening of heart failure, hypotension, or bradycardia reconsideration of the dosage of the concomitant medication is recommended. It may also be necessary to temporarily lower the dose of bisopropol 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**
For oral use
Bisoprolol tablets should be taken in the morning and can be taken with food. They should be swallowed with liquid and should not be chewed.

**Special population**

*Renal or hepatic impairment*
There is no information regarding pharmacokinetics of bisoprolol 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 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
- second or third degree AV block (without a pacemaker)
- sick sinus syndrome
- sinoatrial block
- symptomatic bradycardia
- symptomatic hypotension
- severe bronchial asthma or severe chronic obstructive pulmonary disease
- severe forms of peripheral arterial occlusive disease and severe forms of 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**

**Warnings**
- The treatment of stable chronic heart failure with bisoprolol has to be initiated with a special titration phase (see section 4.2).
- Especially in patients with ischaemic heart disease the cessation of therapy with bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition (see section 4.2).

**Precautions**
The initiation of treatment of stable chronic heart failure with bisoprolol necessitates regular monitoring. For the posology and method of administration please refer to section 4.2.

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

- insulin dependent diabetes mellitus (type I)
- severely impaired renal function
- severely impaired hepatic function
- restrictive cardiomyopathy
- congenital heart disease
- haemodynamically significant organic valvular disease
• myocardial infarction within 3 months

Bisoprolol must be used with caution in:
• diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia (e.g. tachycardia, palpitations or sweating) can be masked
• strict fasting
• ongoing desensitisation therapy. As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine treatment may not always yield the expected therapeutic effect
• first degree AV block
• Prinzmetal's angina
• peripheral arterial occlusive disease. Aggravation of symptoms may occur especially when starting therapy.

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

The symptoms of thyrotoxicosis may be masked under treatment with bisoprolol

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

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

In bronchial asthma or other chronic obstructive pulmonary disease, which may cause symptoms, concomitant bronchodilating therapy is recommended. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of beta₂-stimulants may have to be increased.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations not recommended

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

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

• Centrally-acting antihypertensive drugs (e.g. clonidine methyldopa, moxonidine, rilmenidine): concomitant use of centrally-acting antihypertensive drugs may further decrease the central sympathetic tonus and may thus lead to reduction of heart rate and cardiac output and to vasodilatation. Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase the risk of "rebound hypertension".

Combinations to be used with caution

• Calcium antagonists of the dihydropyridine type 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-ventricular conduction time may be potentiated.
• Parasympathomimetic drugs: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.
• Topical beta-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.
• Insulin and oral antidiabetic drugs: Increase of blood sugar lowering effect. Blockade of beta-adrenoceptors 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.
• Beta-Sympathomimetic agents (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both agents.
• Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. noradrenaline, adrenaline): Combination with bisoprolol may unmask the alpha-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective beta-blockers.
• Concomitant use with antihypertensive agents as well as with other drugs with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.

Combinations to be considered
• Mefloquine: increased risk of bradycardia
• Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the beta-blockers but also risk for hypertensive crisis
• Rifampicin: Slight reduction of the half-life of bisoprolol possible due to the induction of hepatic drug-metabolising enzymes. Normally no dosage adjustment is necessary.
• Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

4.6 Fertility, Pregnancy and Lactation

Pregnancy
Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the 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 is not recommended 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, breast feeding is not recommended during therapy with bisoprolol.

4.7 Effects on ability to drive and use machines
In a study with coronary heart disease patients, bisoprolol did not impair driving performance. However, depending on the individual patients response to treatment an effect on the ability to drive a vehicle or to use machines cannot be excluded. This needs to be considered particularly at start of treatment, upon change of medication, or in conjunction with alcohol.

4.8 Undesirable effects
The following definitions apply to the frequency terminology used hereafter:

Very common (≥ 1/10),
Common (≥ 1/100 and < 1/10)
Uncommon (≥ 1/1000 and < 1/100)
Rare (≥ 1/10,000 and < 1/1,000)
Very rare (< 1/10,000)
Cardiac disorders:
Very common: bradycardia
common: worsening of pre-existing 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 disorders

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, diarrhea, constipation

Skin and subcutaneous tissue disorders:
Rare: hypersensitivity reactions (itching, flush, rash)
Very rare: beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia

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

Vascular disorders:
Common: feeling of coldness or numbness in the extremities, 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
The most common signs expected with overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is limited experience with overdose of bisoprolol, only a few cases of overdose with bisoprolol have been reported. Bradycardia and/or hypotension were noted. All patients recovered. There is a wide inter-individual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive.

In general, if overdose occurs, discontinuation of bisoprolol treatment and supportive and symptomatic treatment is recommended.

Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures 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 glucagons may be useful.

**AV block (second or third degree):** Patients should be carefully monitored and treated with isoprenaline infusion or temporary pacing.

**Acute worsening of heart failure:** Administer i.v. diuretics, inotropic agents, vasodilating agents.

**Bronchospasm:** Administer bronchodilator therapy such as isoprenaline, beta-2-sympathomimetic drugs and/or aminophylline.

**Hypoglycaemia:** Administer i.v. glucose

Limited data suggest that bisoprolol is hardly dialysable.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective

ATC Code: C07AB07

Bisoprolol is a highly beta1-selective-adrenoceptor blocking agent, lacking intrinsic stimulating activity and without 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 is generally not to be expected to influence the airway resistance and beta2-mediated metabolic effects. Its beta1-selectivity extends beyond the therapeutic dose range.

In total 2647 patients were included in the CIBIS II trial. 83% (n = 2202) were in NYHA class III and 17% (n = 445) were in NYHA class IV. They had stable symptomatic systolic heart failure (ejection fraction <35%, based on echocardiography). Total mortality was reduced from 17.3% to 11.8% (relative reduction 34%). A decrease in sudden death (3.6% vs 6.3%, relative reduction 44%) and a reduced number of heart failure episodes requiring hospital admission (12% vs 17.6%, relative reduction 36%) was observed. Finally, a significant improvement of the functional status according to NYHA classification has been shown. During the initiation and titration of bisoprolol hospital admission due to bradycardia (0.53%), hypotension (0.23%), and acute decompensation (4.97%) were observed, but they were not more frequent than in the placebo-group (0%, 0.3% and 6.74%). The numbers of fatal and disabling strokes during the total study period were 20 in the bisoprolol group and 15 in the placebo group.

The CIBIS III trial investigated 1010 patients aged ≥65 years with mild to moderate chronic heart failure (CHF; NYHA class II or III) and left ventricular ejection fraction 35%, who had not been treated previously with ACE inhibitors, beta-blockers, or angiotensin receptor blockers. Patients were treated with a combination of bisoprolol and enalapril for 6 to 24 months after an initial 6 months treatment with either bisoprolol or enalapril. There was a trend toward higher frequency of chronic heart failure worsening when bisoprolol was used as the initial 6 months treatment. Non inferiority of bisoprolol-first versus enalapril-first treatment was not proven in the per-protocol analysis, although the two strategies for initiation of CHF treatment showed a similar rate of the primary combined endpoint death and hospitalization at study end (32.4% in the bisoprolol-first group vs. 33.1 % in the enalapril-first group, per-protocol population). The study shows that bisoprolol can also be used in elderly chronic heart failure patients with mild to moderate disease.

Bisoprolol is also used for the treatment of hypertension and angina.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases.
5.2 Pharmacokinetic properties

Bisoprolol is absorbed and has a biological availability of about 90% after oral administration. The plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg. Total clearance is approximately 15 l/h. The half-life in plasma of 10-12 hours gives a 24 hour effect after dosing once daily.

Bisoprolol is excreted from the body by two routes. 50% is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in an unmetabolised form. Since 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-blockers, bisoprolol caused maternal (decreased food intake and decreased body weight) and embryo/fetal toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development) at high doses but was not teratogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- microcrystalline cellulose
- lactose monohydrate
- magnesium stearate
- crospovidone
- Yellow PB 22812 (Iron oxide yellow (E172), lactose monohydrate)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blisters comprising PVC/PVdC/aluminium foil
Pack sizes: 28, 30 or 90 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ivowen Limited, 3 Anglesea Street, Clonmel, Co. Tipperary, Ireland.

8 MARKETING AUTHORISATION NUMBER(S)

PL 20154/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/08/2011

10 DATE OF REVISION OF THE TEXT

25/08/2011
1 **NAME OF THE MEDICINAL PRODUCT**

Bisoprolol Fumarate 10 mg Tablets

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 10 mg bisoprolol fumarate

Excipients: 131 mg lactose monohydrate

For excipients, see section 6.1.

3 **PHARMACEUTICAL FORM**

10 mg tablets: mottled, beige, round normal convex tablet embossed with BI, break-line and 10 on one side and plain on the reverse. 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 chronic heart failure (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.

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

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

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

The maximum recommended dose is 10 mg once daily.

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

**Treatment modification**

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

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

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

If discontinuation is considered, gradual dose decrease is recommended, since abrupt withdrawal may lead to acute deterioration of the patients condition.
Treatment of stable chronic heart failure with bisoprolol is generally a long-term treatment.

Administration
For oral use
Bisoprolol tablets should be taken in the morning and can be taken with food. They should be swallowed with liquid and should not be chewed.

Special population
Renal or hepatic impairment
There is no information regarding pharmacokinetics of bisoprolol 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 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
- second or third degree AV block (without a pacemaker)
- sick sinus syndrome
- sinoatrial block
- symptomatic bradycardia
- symptomatic hypotension
- severe bronchial asthma or severe chronic obstructive pulmonary disease
- severe forms of peripheral arterial occlusive disease and severe forms of 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

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

Especially in patients with ischaemic heart disease the cessation of therapy with bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition (see section 4.2).

Precautions
The initiation of treatment of stable chronic heart failure with bisoprolol necessitates regular monitoring. For the posology and method of administration please refer to section 4.2.

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

- insulin dependent diabetes mellitus (type I)
- severely impaired renal function
- severely impaired hepatic function
- restrictive cardiomyopathy
- congenital heart disease
- haemodynamically significant organic valvular disease
myocardial infarction within 3 months

Bisoprolol must be used with caution in:

- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia (e.g. tachycardia, palpitations or sweating) can be masked
- strict fasting
- ongoing desensitisation therapy. As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine treatment may not always yield the expected therapeutic effect
- first degree AV block
- Prinzmetal's angina
- peripheral arterial occlusive disease. Aggravation of symptoms may occur especially when starting therapy.

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

The symptoms of thyrotoxicosis may be masked under treatment with bisoprolol

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

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

In bronchial asthma or other chronic obstructive pulmonary disease, which may cause symptoms, concomitant bronchodilating therapy is recommended. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of beta2-stimulants may have to be increased.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

**Combinations not recommended**

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

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

- Centrally-acting antihypertensive drugs (e.g. clonidine, methyldopa, moxonidine, rilmenidine): concomitant use of centrally-acting antihypertensive drugs may further decrease the central sympathetic tonus and may thus lead to reduction of heart rate and cardiac output and to vasodilatation. Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase the risk of "rebound hypertension".

**Combinations to be used with caution**

- Calcium antagonists of the dihydropyridine type 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-ventricular conduction time may be potentiated.
• Parasympathomimetic drugs: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.
• Topical beta-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.
• Insulin and oral antidiabetic drugs: Increase of blood sugar lowering effect. Blockade of 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.
• Beta-Sympathomimetic agents (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both agents.
• Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. noradrenaline, adrenaline): Combination with bisoprolol may unmask the alpha-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective beta-blockers.
• Concomitant use with antihypertensive agents as well as with other drugs with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.

Combinations to be considered
• Mefloquine: increased risk of bradycardia
• Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the beta-blockers but also risk for hypertensive crisis
• Rifampicin: Slight reduction of the half-life of bisoprolol possible due to the induction of hepatic drug-metabolising enzymes. Normally no dosage adjustment is necessary.
• Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

4.6 Fertility, Pregnancy and Lactation’

Pregnancy
Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. In general, beta-adrenocceptor 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-adrenocceptor blockers is necessary, beta-1-selective adrenoceptor blockers are preferable.
Bisoprolol is not recommended 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, breast feeding is not recommended during therapy with bisoprolol

4.7 Effects on ability to drive and use machines
In a study with coronary heart disease patients, bisoprolol did not impair driving performance. However, depending on the individual patients response to treatment an effect on the ability to drive a vehicle or to use machines cannot be excluded. This needs to be considered particularly at start of treatment, upon change of medication, or in conjunction with alcohol.

4.8 Undesirable effects
The following definitions apply to the frequency terminology used hereafter:

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Very rare: beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia

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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
The most common signs expected with overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is limited experience with overdose of bisoprolol, only a few cases of overdose with bisoprolol have been reported. Bradycardia and/or hypotension were noted. All patients recovered. There is a wide inter-individual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive.

In general, if overdose occurs, discontinuation of bisoprolol treatment and supportive and symptomatic treatment is recommended.

Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures 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 glucagons may be useful.

AV block (second or third degree): Patients should be carefully monitored and treated with isoprenaline infusion or temporary pacing.

Acute worsening of heart failure: Administer i.v. diuretics, inotropic agents, vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, beta-2-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose

Limited data suggest that bisoprolol is hardly dialysable.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective

ATC Code: C07AB07

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Bisoprolol is also used for the treatment of hypertension and angina.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases.
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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-blockers, bisoprolol caused maternal (decreased food intake and decreased body weight) and embryo/fetal toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development) at high doses but was not teratogenic.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
- microcrystalline cellulose
- lactose monohydrate
- magnesium stearate
- crospovidone
- Biege PB 27215 (Iron oxide yellow (E172), Iron oxide red (E172), lactose monohydrate)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Do not store above 30ºC.

6.5 Nature and contents of container
Blisters comprising PVC/PVdC/aluminium foil
Pack sizes: 28, 30 or 90 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Ivowen Limited, 3 Anglesea Street, Clonmel, Co. Tipperary, Ireland.

8 MARKETING AUTHORISATION NUMBER(S)
PL 20154/0019

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/08/2011

10 DATE OF REVISION OF THE TEXT
25/08/2011
Module 3

Bisoprolol Fumarate 2.5mg, 5mg and 10mg 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 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 gets 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 is and what it is used for
2. Before you take bisoprolol
3. How to take bisoprolol
4. Possible side effects
5. How to store bisoprolol
6. Further information

1. WHAT BISOPROLOL IS AND WHAT IT IS USED FOR

The active substance in Bisoprolol Fumarate 2.5mg, 5mg and 10mg Tablets is bisoprolol. Bisoprolol belongs to a group of medicines called beta-blockers.
Bisoprolol is used to treat stable heart failure.

Heart failure occurs when the heart muscle is weak and unable to pump enough blood around the circulation. This results in breathlessness and swelling. Bisoprolol slows down the heart rate and makes the heart work more efficiently at pumping blood around the body.

2. BEFORE YOU TAKE BISOPROLOL

Do not take bisoprolol
Do not take bisoprolol if you:
- are allergic (hypersensitivity) to bisoprolol or to any of the other ingredients (see section 6 What other ingredients are in this medicine).
- have severe asthma or severe chronic lung disease
- have severe blood circulation problems in your limbs (such as Raynaud’s syndrome), that may cause your fingers and toes to tingle or turn pale or blue.
- have an untreated phaeochromocytoma, a rare tumour of the adrenal gland
- have metabolic acidosis, a condition when there is too much acid in the blood
- have heart failure that suddenly becomes worse and / or that may require hospital treatment
- have a slow or irregular heart rate: ask your doctor if you are not sure
- have very low blood pressure

Take special care with bisoprolol:
If you have any of the following conditions tell your doctor before taking bisoprolol: he or she may want to take special care (for example give additional treatment or perform more frequent checks):
- diabetes (bisoprolol can hide the symptoms of low blood sugar)
- strict fasting
- kidney or liver problems
- any blood circulation problems in your limbs
- asthma or chronic lung disease
- porphyria, rare or in the past
- tumors of the adrenal gland (phaeochromocytomas)

Thyroid disoder (Bisoprolol can hide the symptoms of an overactive thyroid).

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.
- angiodema (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 without special advice from your doctor:
- Medicines for controlling the blood pressure or medicines for heart problems (such as amiodarone, atenolol, diltiazem, digoxin, enalapril, felodipine, filosulphite, labetalol, metoprolol, mexiletine, pindolol, propafenone, quinidine, sotalol, verapamil)
- Medicines for depression e.g. imipramine, amitriptyline, maprotiline
- Medicines to treat mental illness e.g. phenothiazines such as levomepromazine
- Medicines used for anaesthesia during an operation (see also: "Take special care with bisoprolol")
- Medicines used to treat epilepsy e.g. barbiturates such as phenobarbital
- Certain pain killers (for instance acetyl salicylic acid, diclofenac, indomethacin, ibuprofen, naproxen)
- Medicines for asthma or medicines used for a blocked nose
- Medicines used for certain eye disorders such as glaucoma (increased pressure in the eye) or used to widen the pupil of the eye.
- Certain medicines to treat clinical shock e.g. adrenaline, dobutamine, noradrenaline
- Metformin, a medicine for diabetes.

All the above medicines as well as bisoprolol may affect blood pressure and / or heart function.
It is also especially important to speak with your doctor if you are taking:
- Insulin or other products for diabetes. The ability to lower blood glucose may be enhanced. Symptoms of low blood glucose level can be masked.

Taking bisoprolol with food and drink
Take the tablet with some water in the morning, with or without food. Do not crush or chew the tablet.

Pregnancy and breast-feeding

There is a risk that use of bisoprolol 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 bisoprolol during pregnancy. It is not known whether bisoprolol passes into human breast milk. Therefore, breast-feeding is not recommended during therapy with bisoprolol.

Driving and using machines

Your ability to drive or use machinery may be affected depending on how well you tolerate this 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.

Important information about some of the ingredients of Bisoprolol Fumarate Tablets

Bisoprolol Fumarate Tablets contain milk sugar (lactose). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medican.

3. HOW TO TAKE BISOPROLOL

Before you start using Bisoprolol Fumarate 2.5mg, 5mg and 10mg Tablets, you should already be taking other medicines for heart failure including an ACE-inhibitor, a diuretic and (as an added option) a cardiac glycoside.
Always take bisoprolol exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Treatment with bisoprolol requires regular monitoring by your doctor. This is particularly necessary at the start of treatment and during dose increase.
Take the tablet with some water in the morning, with or without food. Do not crush or chew the tablet.

Treatment with bisoprolol is usually long-term.

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 two weeks
- 7.5 mg bisoprolol once daily for four weeks
- 10 mg bisoprolol once daily for maintenance (on-going) therapy.

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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, or otherwise your condition may become worse.

Children
Bisoprolol is not recommended for use in children.

If you take more bisoprolol 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:
- dizziness, light-headedness, fatigue
- breathing difficulties
- slowed heart rate, low blood pressure
- feelings of hunger, sweating and palpitations (caused by low blood sugar).

If you forget to take bisoprolol
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
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 your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, bisoprolol can cause side effects, although not everybody gets them.

The following side effects are important and will require immediate action if you experience them. You should stop taking bisoprolol and see your doctor immediately if the following symptoms occur:

Common effects (affects less than 1 person in 10):
- Worsening of heart failure causing increased breathlessness and / or retention of fluid.

Frequency not stated:
- Worsening of symptoms of blockage of the main blood vessels to the legs, especially at the start of treatment.

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

Very Common (affects more than 1 person in 10):
- Slow heart beat

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
- nausea, vomiting, diarrhoea, or constipation.

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

Rare (affects less than 1 person in 1,000):
- hearing problems
- allergic runny nose
- reduced tear flow (important if you use contact lenses)
- inflammation of the liver which can cause yellowing of the skin or whites of the eyes
- changes in blood test results
- allergy-like reactions such as itching, flush, rash
- reduced sexual potency
- nightmares, hallucinations
- fainting.

Very rare (affects less than 1 person in 10,000):
- irritation and redness of the eye (conjunctivitis)
- hair loss
- cause or worsen a skin rash similar to psoriasis.

Tell your doctor or your pharmacist if you notice any of the side effects listed above or any other unwanted or unexpected effects.

5. HOW TO STORE BISOPROLOL
Keep out of the reach and sight of children. Do not use bisoprolol after the expiry date which is stated on the blister and the carton after EXP. The expiry date refers to the last date of that month. Do not store above 30°C.

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 2.5mg, 5mg and 10mg Tablets contain
The active substance is bisoprolol fumarate:
Each 2.5mg tablet contains 2.5mg of bisoprolol fumarate. Each 5mg tablet contains 5mg of bisoprolol fumarate. Each 10mg tablet contains 10mg of bisoprolol fumarate.

The other ingredients are:
- microcrystalline cellulose, lactose monohydrate, magnesium stearate, crospovidone.
- Bisoprolol Fumarate 5 mg Tablets additionally contain:
- Yellow PB 22812 (Iron oxide yellow (E172), lactose monohydrate).
- Bisoprolol Fumarate 10 mg Tablets additionally contain:
- White, oblong uncoated, break-line on both top and bottom sides, “B” and “10” debossed on either side of the break-line on the top. The tablet can be divided into equal halves.

What Bisoprolol Fumarate 2.5mg, 5mg and 10mg Tablets look like and contents of the pack
Bisoprolol Fumarate 2.5 mg Tablets: White, oblong uncoated, break-line on both top and bottom sides, “B” and “2.5” debossed on either side of the break-line on the top. The tablet can be divided into equal halves.

Bisoprolol Fumarate 5 mg Tablets: pale yellow motiled, normal convex tablet embossed with B1, break-line and 5 on one side and plain on the reverse. The tablet can be divided into equal halves.

Bisoprolol Fumarate 10 mg Tablets: motiled, biege, round normal convex tablet embossed with B1, break-line and 10 on one side and plain on the reverse. The tablet can be divided into equal halves.

Each pack contains 28, 30, or 90 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Ioven Limited, 3 Anglesea St., Clonmel Co. Tipperary, Ireland
Manufacturer: niche generics limited, Unit 5, 151 Ballydoyle Industrial Estate, Dublin 13, Ireland.

This leaflet was last revised in August 2011.
Module 4
Labelling

2.5 mg carton:
Blister:

BLISTER OUTLINES DO NOT PRINT

Batch number and expiry date to be added at the time of manufacture.
5 mg carton:
**Bisoprolol Fumarate 5mg Tablets**

**MA Holder:** Ivoven Limited

**Batch number and expiry date to be added at the time of manufacture.**
Blister:

**Batch number and expiry date to be added at the time of manufacture.**
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Bisoprolol Fumarate 2.5 mg, 5 mg and 10 mg Tablets (PL 20154/0017-9; UK/H/4301/001-3/DC) could be approved. These applications were submitted by the Decentralised Procedure, with the UK as Reference Member State (RMS), and France and Italy as Concerned Member States (CMS).

Bisoprolol Fumarate 2.5 mg, 5 mg and 10 mg Tablets are prescription-only medicines (POM) indicated 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 (for additional information see section 5.1 of SmPC).

These are applications made according to Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of the reference products Emcor 5 mg and 10 mg Tablets (Merck BV, Netherlands) which were first licensed in the EU in October 1987. The corresponding reference products in the UK are Cardicor 2.5mg, 5mg and 10mg film-coated tablets (PL 00493/0180, 0183 & 0184) first authorised to E.Merck Limited on 24 December 1999. The product used in the bioequivalence study was Concor 10 mg tablets, taken from the German market. It has been confirmed that this can be considered equivalent to the same product from the UK market.

Bisoprolol is a highly beta\textsubscript{1}-selective-adrenoceptor blocking agent, lacking intrinsic stimulating activity and without relevant membrane stabilising activity. It only shows low affinity to the beta\textsubscript{2}-receptor of the smooth muscles of bronchi and vessels as well as to the beta\textsubscript{2}-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta\textsubscript{2}-mediated metabolic effects. Its beta\textsubscript{1}-selectivity extends beyond the therapeutic dose range.

No new non-clinical studies were conducted, which is acceptable given that the applications were for products that are being considered as generic medicinal products of an originator product that have been licensed for over 10 years.

One single-dose, bioequivalence study was submitted to support these applications, comparing the test product Bisoprolol Fumarate 10 mg Tablets with the reference product Concor 10 mg tablets (Merck Pharma GmbH, Germany). No other new clinical studies were conducted, which is acceptable given that the applications were for products that are being considered as generic medicinal products of an originator product that have been licensed for over 10 years. 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, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved, with the end of procedure (Day 210) on 27 July 2011. After a subsequent national phase, the licences were granted in the UK on 25 August 2011.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Bisoprolol Fumarate 2.5 mg Tablets  
| Bisoprolol Fumarate 5 mg Tablets  
| Bisoprolol Fumarate 10 mg 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) | 2.5 mg, 5 mg and 10 mg tablets |
| Reference numbers for the Mutual Recognition Procedure | UK/H/4301/001-3/DC |
| Reference Member State | United Kingdom |
| Member States concerned | UK/H/4301/001/DC: France and Italy  
| UK/H/4301/002-3/DC: France |
| Marketing Authorisation Number(s) | PL 20154/0017-9 |
| Name and address of the authorisation holder | Ivowen Limited, 3 Anglesea Street, Clonmel, Co. Tipperary, Ireland. |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Bisoprolol fumarate

Chemical name: 

\[
\text{INN: 1-[4-[[2-(1-Methyl ethoxy) ethoxy methyl] phenoxy]-3-[1-methylethylamino]-2-propanol fumarate (2:1) (salt)
or}
\]

\[
(±)-1-\text{[α-(2-Isopropoxyethoxy)-p-toly]oxy} \text{-3-(isopropylamino)-2-propanol fumarate (2:1) (salt)
or}
\]

\[
(±)-1-\text{[p-(Isopropoxyethoxymethyl)phenoxy]3-(isopropylamino)-2-propanol fumarate (2:1) (salt).
}\]

Structure:

\[
\begin{array}{c}
\text{OH} \\
\text{OCH}_{2}\text{CH}_{2}\text{CH}_{2}\text{NHCH} \\
\text{CH}_{3} \\
\text{CH}_{2}\text{OCH}_{2}\text{CH}_{2}\text{OCH} \\
\text{CH}_{3} \\
\end{array}
\begin{array}{c}
\text{CH} \\
\text{HOOC} \\
\text{CH} \\
\text{COOH}
\end{array}
\]

Molecular formula: \((C_{18}H_{31}NO_{4})_2C_4H_4O_4\)

Molecular weight: 766.96

Appearance: Bisoprolol fumarate is a white to almost white powder. It is soluble in water and methanol

Bisoprolol fumarate was the subject of a European Pharmacopoeia monograph.

The manufacture and control of bisoprolol fumarate is covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the following pharmaceutical excipients microcrystalline cellulose, lactose monohydrate, magnesium stearate and crospovidone. In addition:

- the 5 mg strength also contains Yellow PB 22812 [consisting of iron oxide yellow (E172) and lactose monohydrate]
- the 10 mg strength also contains Beige PB 27215 [consisting of iron oxide yellow (E172), iron oxide red (E172) and lactose monohydrate]

All excipients comply with their respective European Pharmacopoeia monograph with the exception of Yellow PB 22812 and Beige PB 27215 which are controlled to suitable in-house specifications and are in compliance with current EEC directives concerning the use of colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients.
With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption. Magnesium stearate may be sourced from animal or vegetable origin. The supplier of magnesium stearate sourced from animal origins has provided certificates of suitability from the European Directorate for the Quality of Medicines (EDQM) to show that it is manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE). No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**

The objective of the development programme was to formulate robust, stable tablets containing 2.5 mg, 5 mg and 10 mg bisoprolol fumarate that could be considered as generic medicinal products of Concor 2.5 mg, 5 mg and 10 mg tablets (Merck Pharma GmbH, Germany). A satisfactory account of the pharmaceutical development has been provided.

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

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished Product Specification**

The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and these comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Container-Closure System**

All strengths of the finished product are packaged polyvinylchloride/polyvinylidene chloride/aluminium foil blisters and are available in pack sizes of 28, 30 and 90 tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the Product**

Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years, with the storage conditions ‘Do not store above 30°C‘.
**Bioequivalence/bioavailability**
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labels are acceptable.

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, as amended. The leaflet conforms to the requirements. The test shows that the patients/users are able to act upon the information that the leaflet contains.

**MAA Forms**
The MAA forms are 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**
There are no objections to the approval of these applications from a pharmaceutical viewpoint.

**III.2 NON-CLINICAL ASPECTS**
As the pharmacodynamic, pharmacokinetic and toxicological properties of bisoprolol fumarate are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a non-clinical viewpoint.

**III.3 CLINICAL ASPECTS**

**Pharmacokinetics**
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

**A two-way, randomised, single dose, crossover study to compare the pharmacokinetics of the test product Bisoprolol Fumarate 10 mg Tablets (Ivoven Limited) versus the reference product Concor 10 mg tablets (Merck Pharma GmbH, Germany) in healthy adult volunteers under fasted conditions.**
All volunteers received a single oral dose of either the test or reference product under fasting conditions. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 72 hours post dose. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for bisoprolol presented below (geometric Least Squares Mean, ratios and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-t}$ (ng/ml/h)</th>
<th>AUC$_{0-\infty}$ (ng/ml/h)</th>
<th>C$_{\text{max}}$ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>418.38</td>
<td>511.84</td>
<td>40.84</td>
</tr>
<tr>
<td>Reference (mean)</td>
<td>388.68</td>
<td>494.19</td>
<td>40.04</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>107.64% (100.87-114.87%)</td>
<td>103.57% (98.30-109.13%)</td>
<td>102.00% (95.90-108.48%)</td>
</tr>
</tbody>
</table>

AUC$_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity  
AUC$_{0-t}$ area under the plasma concentration-time curve from time zero to t hours  
C$_{\text{max}}$ maximum plasma concentration  

*ln-transformed values

The 90% confidence intervals for AUC and C$_{\text{max}}$ for test versus reference product for bisoprolol are within predefined acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1). Thus, the data support the claim that the test product is bioequivalent to the reference product.

As the 2.5 mg, 5 mg and 10 mg strengths of the product meet the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev1), the results and conclusions of the bioequivalence study on the 10 mg strength can be extrapolated to the other strengths.

Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for these applications.

Efficacy
No new efficacy data were submitted and none were required for these applications.

Safety
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were raised by the bioequivalence data.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the SmPC and in-line with current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.
Pharmacovigilance System and Risk Management Plan
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.

A suitable justification has been provided for not submitting a Risk Management Plan for these products.

Conclusion
There are no objections to the approval of these applications from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The quality characteristics of Bisoprolol Fumarate 2.5 mg, 5 mg and 10 mg 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type. The pharmacodynamic, pharmacokinetic and toxicological properties of bisoprolol fumarate are well-known.

Efficacy
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Bisoprolol Fumarate 10 mg Tablets and its respective reference product (Concor 10 mg tablets). As the 2.5 mg, 5 mg and 10 mg strength of the product meet the biowaiver criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), the results and conclusions of the bioequivalence study on the 10 mg strength can be extrapolated to the other strength tablets.

SAFETY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of bisoprolol fumarate is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference product, where appropriate.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s product and the originator product are interchangeable. Extensive clinical experience with bisoprolol fumarate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

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