SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bisoprololfumaraat 5 mg, filmomhulde tabletten
Bisoprololfumaraat 10 mg, filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg of bisoprolol fumarate.

Excipient with known effect
Each film-coated tablet contains 1.2 mg of lactose (as monohydrate).

Each film-coated tablet contains 10 mg of bisoprolol fumarate.

Excipient with known effect
Each film-coated tablet contains 2.4 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

5 mg film-coated tablets:
Yellow coloured, round, scored film-coated tablets with a one-sided embossment „BIS 5".
The tablet can be divided into four equal doses.

10mg film-coated tablets:
Apricot coloured, round, scored film-coated tablet with a one-sided embossment „BIS 10".
The tablet can be divided into four equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

Angina pectoris

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

4.2 Posology and method of administration

Posology

Hypertension/Angina pectoris

Adults
The dosage should be individually adjusted, in particular according to the pulse rate and therapeutic success.
It is recommended to start with 5 mg per day. The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg once daily.

Elderly
It is recommended to start with the lowest possible dose.

Renal or hepatic impairment
In patients with liver or kidney function disorders of mild to moderate severity, no dosage adjustment is normally required. In patients with severe renal impairment (creatinine clearance < 20 ml/min) and in patients with severe liver function disorders it is recommended that a daily dose of 10 mg is not exceeded.

Experience with the use of bisoprolol in renal dialysis patients is limited. However, there is no evidence that the dosage regime needs to be altered.

Discontinuation of treatment
Treatment must not be stopped abruptly (see section 4.4). The dosage should be diminished slowly by a weekly halving of the dose.

Stable chronic heart failure

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

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

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.

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

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.

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

The treatment with bisoprolol must not be stopped abruptly since this might lead to a transitory worsening of condition. Especially in patients with ischaemic heart disease, treatment must not be discontinued suddenly. Gradual reduction of the daily dose is recommended.

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.

All indications

Elderly
No dosage adjustment is required.

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

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

4.3 Contraindications

Bisoprolol is contraindicated in:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock
- AV block of second or third degree
- sick sinus syndrome
- sinoatrial block
- symptomatic bradycardia
- symptomatic hypotension

- severe bronchial asthma or severe chronic obstructive pulmonary disease
- severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome
- untreated phaeochromocytoma (see section 4.4)
- metabolic acidosis

4.4 Special warnings and precautions for use

Special warnings

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

Applies to all indications:
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:

Applies only to hypertension or angina pectoris:
Bisoprolol must be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.

Applies only to chronic heart failure:
The initiation and cessation 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 diseases and conditions:

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

Applies to all indications:
There is a risk of myocardial infarction and sudden death if the treatment is suddenly discontinued in patients with coronary heart disease (see section 4.2).
Bisoprolol must be used with caution in:

- bronchospasm (bronchial asthma, chronic obstructive pulmonary disease (COPD))

Although cardioselective ($beta_1$) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, this medicinal product may be used with caution. In patients with obstructive airways diseases, the treatment with bisoprolol should be started at the lowest possible dose and patients should be carefully monitored for new symptoms (e.g. dyspnea, exercise intolerance, cough). 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 $beta_2$-stimulants may have to be increased.

- 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.
- AV block of first degree
- Prinzmetal's angina. Cases of coronary vasospasm have been observed. Despite its high $beta_1$-selectivity, angina attacks cannot be completely excluded when bisoprolol is administered to patients with Prinzmetal's angina.
- peripheral arterial occlusive disease. Aggravation of symptoms may occur especially when starting therapy.
- general anaesthesia.
  In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischaemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance of beta-blockade should be continued peri-operatively. The anaesthetist must be aware of beta-blockade because of the potential for interactions with other medicinal products, resulting in bradyarrhythmias, attenuation of the reflex tachycardia and the decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocking agent therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

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

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

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

Combination of bisoprolol with calcium antagonists of the verapamil or diltiazem type, with Class I antiarrhythmic medicinal products and with centrally acting antihypertensive medicinal products is generally not recommended (see section 4.5).

[Nationally completed name] contains lactose and sodium
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations not recommended
Chronic heart failure only
Class I antiarrhythmic medicinal products (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide, propafenone): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

All indications
Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type: Negative influence on contractility and atrio-ventricular conduction. Intravenous administration of

verapamil in patients on β-blocker treatment may lead to profound hypotension and atrioventricular block.

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-blocking agent discontinuation, may increase the risk of "rebound hypertension".

Combinations to be used with caution
Hypertension/Angina pectoris only
Class I antiarrhythmic medicinal products (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide, propafenone): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

All indications
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 product (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: 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.

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

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

Concomitant use with antihypertensive agents as well as with other medicinal products 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-blocking agents, 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 foetus/newborn. In general, beta-adrenoceptor blocking agents reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the foetus and newborn infant. If treatment with beta-adrenoceptor blocking agents is necessary, $beta_1$-selective adrenoceptor blocking agents are preferable.

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

Breast-feeding
It is not known whether this medicinal product is excreted in human milk. Therefore, breastfeeding is not recommended during administration of bisoprolol.

4.7 Effects on ability to drive and use machines

In a study with coronary heart disease patients bisoprolol did not impair driving performance. Depending on the individual patient's response the ability to drive a vehicle or to use machines may be impaired. 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 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

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

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

Cardiac disorders
Very common: bradycardia in patients with chronic heart failure
Common: worsening of pre-existing heart failure in patients with chronic heart failure
Uncommon: AV-conduction disturbances. Worsening of pre-existing heart failure (in patients with hypertension or angina pectoris); bradycardia (in patients with hypertension or angina pectoris)

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

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

Hepatobiliary disorders
Rare: hepatitis

Skin and subcutaneous tissue disorders
Rare: hypersensitivity reactions such as itching, flush, rash and angioedema
Very rare: beta-blocking agents may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia

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

Reproductive system and breast disorders
Rare: erectile dysfunction

General disorders and administration site conditions
Common: fatigue*, asthenia (patients with chronic heart failure)
Uncommon: asthenia (in patients with hypertension or angina pectoris)

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

* These symptoms especially occur at the beginning of the therapy in patients with hypertension or angina pectoris. They are generally mild and usually disappear within 1–2 weeks.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

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 inter-individual 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.

Management

In general, if overdose occurs, bisoprolol 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: Administer intravenous atropine. If the response is inadequate, isoprenaline or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.

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

AV block (second or third degree): Patients should be carefully monitored and treated with isoprenaline infusion or transvenous cardiac pacemaker insertion.
Acute worsening of heart failure: Administer i.v. diuretics, inotropic agents, vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, $beta_2$-sympathomimetic medicinal products and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective. ATC Code: C07AB07

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

Bisoprolol is used for the treatment of hypertension, angina pectoris and heart failure. As with other beta-1-blocking agents, the method of acting in hypertension is unclear. However, it is known that bisoprolol reduces plasma renin activity markedly.
Antianginal mechanism: Bisoprolol by inhibiting the cardiac beta receptors inhibits the response given to sympathetic activation. That results in the decrease of heart rate and contractility this way decreasing the oxygen demand of the cardiac muscle.

The indication heart failure was investigated in the CIBIS II trial. In total 2647 patients were included, 83% (N = 2202) were in NYHA class III and 17% (N = 445) were in NYHA class IV. They had stable symptomatic systolic heart failure (ejection fraction ≤35%, based on echocardiography). Total mortality was reduced from 17.3% to 11.8% (relative reduction 34%). A decrease in sudden death (3.6% vs 6.3%, relative reduction 44%) and a reduced number of heart failure episodes requiring hospital admission (12% vs 17.6%, relative reduction 36%) was observed. Finally, a significant improvement of the functional status according to NYHA classification has been shown. During the initiation and titration of bisoprolol hospital admission due to bradycardia (0.53%), hypotension (0.23%), and acute decompensation (4.97%) were observed, but they were not more frequent than in the placebo-group (0%, 0.3% and 6.74%). The numbers of fatal and disabling strokes during the total study period were 20 in the bisoprolol group and 15 in the placebo group.
The CIBIS III trial investigated 1010 patients aged ≥65 years with mild to moderate chronic heart failure (CHF; NYHA class II or III) and left ventricular ejection fraction ≤35%, who had not been treated previously with ACE inhibitors, beta-blocking agents, or angiotensin receptor blockers. Patients were treated with a combination of bisoprolol and enalapril for 6 to 24 months after an initial 6 months treatment with either bisoprolol or enalapril.
There was a trend toward a 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.

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

Absorption
Bisoprolol is absorbed and has a biological availability of about 90% after oral administration.

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

Biotransformation and elimination
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.

Linearity/non-linearity
The kinetics of bisoprolol are linear and independent of age.

Special population

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. 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity. Like other beta-blocking agents, bisoprolol caused maternal (decreased food intake and decreased body weight) and embryo/foetal 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

5 mg film-coated tablets:

Tablet core:
Calcium hydrogen phosphate, anhydrous
Cellulose, microcrystalline
Maize starch, pregelatinised
Croscarmellose sodium
Silica, colloidal anhydrous
Magnesium stearate

Tablet coating:
Lactose monohydrate
Hypromellose
Macrogol 4000
Titanium dioxide (E 171)
Iron oxide, yellow (E 172)

10 mg film-coated tablets:

Tablet core:
Calcium hydrogen phosphate, anhydrous
Cellulose, microcrystalline
Maize starch, pregelatinised
Croscarmellose sodium
Silica, colloidal anhydrous
Magnesium stearate

Tablet coating:
Lactose monohydrate
Hypromellose
Macrogol 4000
Titanium dioxide (E 171)
Iron oxide, yellow (E 172)
Iron oxide, red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

NL/H/0597-0673:
60 months

NL/H/0684:
Blisters: 60 months
Bottles: 36 months

Shelf life after first opening:
Bottles: 6 months

6.4 Special precautions for storage

Blister:
This medicinal product does not require any special storage conditions.

Bottle:
This medicinal product does not require any special storage conditions.

Storage conditions after first opening of the bottle:
Do not store above 25°C.

6.5 Nature and contents of container

NL/H/0597-0673:

The film-coated tablets are packed in OPA/Alu/PVC/Alu blisters and inserted in a carton.

Pack sizes:
7, 10, 14, 20, 28, 30, 50, 56, 60, 100, 10x30 film-coated tablets

NL/H/0684:

The film-coated tablets are packed in OPA/Alu/PVC/Alu blisters and inserted in a carton, or are packed in a HDPE tablet bottle with PE cap.

Pack sizes:
Blister: 7, 10, 14, 20, 28, 30, 50, 56, 60, 90, 98, 100, 10x30, 500 film-coated tablets

Bottle: 10, 20, 30, 50, 60, 100, 250, 500 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The film-coated tablet can be divided by placing it on a solid surface with the score pointing upward. The film-coated tablet is divided by exerting a slight pressure with the thumb.
No special requirements.

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

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Hexal AG
Industriestrasse 25
83607 Holzkirchen
Duitsland

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 33091 (Bisoprololfumaraat 5 mg)
RVG 33093 (Bisoprololfumaraat 10 mg)

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 09 maart 2006
Datum van laatste verlenging 30 mei 2011

10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft rubriek 4.8: 24 maart 2022