Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bisoprololhemifumaraat Genthon 5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg bisoprolol hemifumarate, equivalent to 4.24mg of bisoprolol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

The tablet is light pink, round, biconvex, scored on both sides and embossed with BSL5 on one side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Hypertension.
- Chronic stable angina pectoris.

4.2 Posology and method of administration

Posology
Renal or hepatic impairment
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 bisoprolol hemifumarate is not exceeded

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

Paediatric population:
There is no experience with bisoprolol in children, therefore itsuse cannot be recommended.

Method of administration
Bisoprolol 5 mg film-coated tablets are for oral administration.

The dosage should be individually adjusted. It is recommended to start with the lowest possible dose. In some patients, 5 mg per day may be adequate. The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day.

The tablets should be taken in the morning. They should be swallowed with liquid and should not be chewed.

Discontinuation of treatment
Treatment should not be stopped abruptly (see section 4.4 Special warnings and precautions for use). The dosage should be diminished slowly by a weekly halving of the dose**.**

4.3 Contraindications

· 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 (without a pacemaker)
· sick sinus syndrome
· sinoatrial block
· bradycardia with less than 60 beats/min before start of therapy
· hypotension (systolic blood pressure less than 100 mm Hg)
· severe bronchial asthma or severe chronic obstructive pulmonary disease
· late stages of peripheral arterial occlusive disease and Raynaud's syndrome
· metabolic acidosis
· untreated phaeochromocytoma (see also section 4.4)
· combinations with floctafenine and sultopride (see also section 4.5)

4.4 Special warnings and precautions for use

Bisoprolol should be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.

Other formulations of bisoprolol containing medicinal products are used in the treatment of chronic heart failure. The use of β-blocking agents in this indication needs a very cautious approach and should be started with a very strict titration phase. In this phase increments are necessary all of which are not possible with the current medicinal product. This product should therefore not be used in the treatment of chronic heart failure.

The combination with amiodarone (see also section 4.5) should be used with caution considering the risk of contractility automatism and conduction disorders (suppression of compensatory sympathetic reactions).

Combination of bisoprolol with calcium antagonists of the verapamil and diltiazem type, with class I antiarrhytmic drugs and with centrally-acting antihypertensive drugs is generally not recommended (see also section 4.5).

Bisoprolol must be used with caution in:

· bronchospasm (bronchial asthma, obstructive airways disease): In bronchial asthma or other chronic obstructive airway 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 β_2-stimulants may have to be increased. It is recommended to have a functional respiratory test done before the initiation of treatment.
· concomitant treatment with anticholinesterastic drugs (including tacrine): AV conduction time and/or bradycardia may be increased (see also section 4.5).
· concomitant treatment with anaesthetics: Attenuation of the reflex tachycardia and increase of the risk of hypotension (see also section 4.5). Continuation of β-blockade reduces the risk of arrhythmia during induction and intubation. In patients undergoing general anaesthesia the anaesthetist must be aware of beta-blockade. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.
· Iodated contrast products: Beta-blockers may impede the compensatory cardiovascular reactions associated with hypotension or shock induced by iodated contrast products.
· diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia can be masked. Blood glucose levels should be monitored during treatment with bisoprolol.
· thyrotoxicosis, adrenergic symptoms may be masked.
· strict fasting.
· ongoing desensitisation therapy.
· As with other β-blocking agents bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Adrenaline treatment does not always give the expected therapeutic effect. Higher doses of epinephrine (adrenaline) may be necessary.
· AV block of first degree.
· Printzmetal's angina: β-blocking agents may increase the number and duration of anginal attacks in patients with Printzmetal's angina. The use of β-1 selective adrenoceptor blocking agents is possible in cases of mild forms and only in combination with a vasodilating agent.
· peripheral circulatory disorders, such as Raynaud's phenomena and intermittentclaudication: intensification of complaints might happen especially during start of therapy.
· In patients with phaeochromocytoma (see section 4.3), bisoprolol must not be administered until after α-receptor blockade has been successfully established.
· pre-existing or existing psoriasis, bisoprolol should only be given after careful balancing of benefits against risks.

The initiation of treatment with bisoprolol necessitates regular monitoring, especially when treating elderly patients. The cessation of therapy with bisoprolol should not be done abruptly unless clearly indicated. There is a risk of myocardial infarction and sudden death if the treatment is suddenly discontinued in patients with ischaemic heart disease. For more information please refer to section 4.2 Posology and method of administration.

This medicinal product contains an active substance, which results in a positive test during antidoping controls.

4.5 Interaction with other medicinal products and other forms of interactions

Combinations contra-indicated
· Floctafenine: β-blockers may impede the compensatory cardiovascular reactions associated with hypotension or shock that may be induced by floctafenine.
· Sultopride: bisoprolol should not be concomitantly administered with sultopride since there is an increase risk of ventricular arrhythmia.

Combinations not recommended
· Calcium antagonists of the verapamil, type and to a lesser extent of the diltiazemtype: negative influence on contractility, atrio-ventricular conduction and blood pressure (see also section 4.4).
· Clonidine and other centrally-acting antihypertensive drugs, i.e. methyldopa, guanfacin, moxonidine, rilmenidine: Increased risk of rebound hypertension as well as exaggerated decrease in heart rate and cardiac conduction, including worsening the cardiac insufficiency.
· Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the beta-blockers but also risk for hypertensive crisis.

Combinations to be used with caution
· Class I antiarrhythmic drugs (e.g. disopyramide, quinidine): effect on atrio-venticular conduction time may be potentiated and negative inotropic effect may be increased.(Strict clinical and ECG monitoring is required).
· Class III antiarrhythmic drugs (e.g. amiodarone): effect on atrio-ventricular conduction time may be potentiated (see section 4.4).
· Calcium antagonists of the dihydropyridinetype: increased risk of hypotension. In patients with latent heart failure concomitant use of β-blocking agents can lead to heart failure.
· Anticholinesterastic drugs (including tacrine): atrio-ventricular conduction time and/or bradycardia may be increased (see also section 4.4).
· Other β-blocking agents, including eye-drops for the treatment of glaucoma, have additive effects
· Insulin and oral anti-diabetic drugs: intensification of blood sugar lowering effect. Blockade of β-adrenoreceptor may mask symptoms of hypoglycaemia.
· Digitalis glycosides: reduction of heart rate, increase of atrio-ventricular conduction time.
· Anaesthetic agents: attenuation of the reflex tachycardia and increased risk of hypotension (for further information on anaesthesia see also section 4.4).
· NSAIDs: decrease of the antihypertensive effect (inhibition of vasodilatative prostaglandin by NSAID and water and sodium retention with pyrazolone NSAID).
· Ergotamine derivatives: exacerbation of peripheral circulatory disturbances.
· Beta-sympathomimetic agents (eg. Isoprenaline, dobutamine): combination with bisoprolol may reduce effects 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.
· Tricyclic antidepressants, barbiturates, phenothiazines as well as other antihypertensive agent: increased blood pressure lowering effect.
· Baclofene: increased antihypertensive activity.
· Amifostine: increased hypotensive activity.
· Parasympathomimetic drug: Concomitant use may increase atrioventricular conduction time and the risk of bradycardia.
· Concomitant use with antihypertensive agents as well as other drugs with blood pressure lowering potential may increase the risk of hypotension

Combinations to be considered
· Mefloquine: increased risk of bradycardia..
· Corticosteroids: decrease of antihypertensive effect due to water and sodium retention.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Bisoprolol causes harmful pharmacological effects during pregnancy and/or on the fetus/newborn. In general, β-adrenoceptor blocking agents reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse reactions (e.g. hypoglycaemia, bradycardia) may occur in the fetus and newborn infant. If treatment with β-adrenoceptor blocking agents is necessary, β1-adrenoceptor blocking agents are preferable.
Bisoprolol is recommended during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, the uteroplancental blood flow and 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.

Breastfeeding:
It is unknown whether bisoprolol/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

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, due to individual variations in reactions to the medicinal product, the ability to drive a vehicle or to operate machinery may be impaired. This should be considered particularly at start of the treatment and upon change of medication as well as in conjunction with alcohol.

4.8 Undesirable effects

The reported undesirable effects are generally attributable to the pharmacological properties of β-blocking agents.
The following undesirable effects have been observed during treatment with bisoprolol with the following frequencies:
Common (≥1/100, < 1/10)
Uncommon (≥1/1,000, < 1/100)
Rare (≥1/10,000, < 1/1,000)
Very rare (<1/10,000)

Immune system disorders
Rare: the appearance of antinuclear antibodies with exceptional clinical symptoms such as lupus syndrome, which disappear upon cessation of treatment, allergic rhinitis
Metabolism and nutrition disorders
Rare: hypoglycaemia
Very Rare: hypoglycaemic shock

Psychiatric disorders
Uncommon: sleep disturbances, depression
Rare: Nightmare, hallucinations

Nervous system disorders
Common:dizziness, headache (especially at the beginning of the therapy, they are generally mild and often disappear within 1-2 weeks)
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
Uncommon: bradycardia, AV-stimulus disturbances (slowed AV-conduction or increase of existing AV-block), worsening of pre-existing heart failure

Vascular disorders
Common: feeling of coldness or numbness of the extremities, Raynaud's disease, increase of existing intermittent claudication (orthostatic) hypotension

Respiratory, thoracic and mediastinal disorders
Uncommon: bronchospasm in patients with bronchial asthma or a history of obstructive airway disease
Rare: allergic rhinitis

Gastrointestinal disorders
Common: gastrointestinal complaints such as nausea, vomiting, diarrhoea, abdominal pain and constipation

Hepatobiliary disorders
Rare: hepatitis

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

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

Reproductive system and breast disorders
Rare: potency disorders

General disorders
Common: fatigue (especially at the beginning of the therapy, they are generally mild and often disappear within 1-2 weeks)
Uncommon: asthenia

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

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:

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

Symptoms
The most common expected symptoms with overdosage of bisoprolol are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency, conduction disorders and hypoglycaemia. 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.

Management
In the case of overdosage, bisoprolol treatment should be stopped and supportive and symptomatic treatment should be provided. Resorption of bisoprolol in the gastrointestinal tract must be avoided; gastric lavage, or administration of adsorbents (i.e. activated charcoal), and a laxative agent (i.e. sodium sulphate) may be used. Respiration must be monitored and if necessary, artificial respiration should be initiated. Bronchospasm should be counteracted with bronchodilator therapy such as

isoprenaline or $ß_2$-sympathomimetic drugs. Cardiovascular complications should be treated symptomatically: AV-block (second or third degree) needs careful monitoring and be treated with isoprenaline infusion or transvenous cardiac pacemaker insertion. Bradycardia should be treated with intravenous atropine (or M-methyl-atropine). Fall in blood pressure or shock should be treated with plasma substituting agents and vasopressors.
Hypoglycaemia can be treated with i.v.-glucose.

Limited data suggest that bisoprolol is hardly dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Selective $ß_1$-blocking agents, ATC code: C07 AB07

Mechanism of action
Bisoprolol is a potent, highly $ß_1$-selective-adrenoceptor blocking agent devoid of intrinsic sympathomimetic activity. As with other ß-blocking agents, the mode of action in hypertension is unclear. However, it is known that bisoprolol markedly depresses plasma renin activity.

In patients with angina, the blockade of ß-receptors reduces heart action and thus reduces oxygen demand.

Bisoprolol possesses similar local anaesthetic properties to propanolol.

5.2 Pharmacokinetic properties

Absorption
Bisoprolol is absorbed almost completely from the gastrointestinal tract.

Distribution
Together with the very small first pass effect in the liver, this results in a high bioavailability of approximately 90%. The plasma protein binding of bisoprolol is about 30%. The distribution volume is 3.5 l/kg. The total clearance is approximately 15 l/h.

Elimination
The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage.
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 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.

Linearity/non-linearity
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 β-blocking agents, 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

Core

Microcrystalline cellulose
Calcium hydrogen phosphate
Pregelatinised maize starch
Crospovidone
Colloidal anhydrous silica
Magnesium stearate

Coating
Hypromellose
Macrogol 400
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/PE/PVDC/Al blister in Al sachet: 2 years
PVC/PE/PVDC/Al blister: 3 years

6.4 Special precautions for storage

PVC/PE/PVDC/AL blister and PVC/PE/PVDC/AL blister in Al sachets:
Do not store above 25 °C.
Store in the original package to protect from moisture and light.

6.5 Nature and contents of container

Carton boxes with 2, 3, 5, 6 or 10 PVC/PE/PVDC/Al blister packaging of 10 tablets or PVC/PE/PVDC/Al blister packaging in Al sachets of 10 tablets each.
Carton boxes with 1, 2 of 4 PVC/PE/PVDC/Al blister packaging of 14 tablets or PVC/PE/PVDC/Al blister packaging in Al sachets of 14 tablets each.
Carton boxes with 50 tablets in EAV blister packaging (PVC/PE/PVDC/Al).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Genthon B.V.
Microweg 22
6545 CM, Nijmegen
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0740/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd November 2002
Date of last renewal: 20th February 2007

10 DATE OF REVISION OF THE TEXT

October 2016