# Part II

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Emvasc 5 mg Tablets.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains bisoprolol fumarate 5 mg.
Each tablet contains 0.015mg of E110.

For excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated Tablets.
Pink, round biconvex film coated tablets, embossed with BPL 5 on one face.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Hypertension
Chronic stable angina pectoris

### 4.2 Posology and method of administration

Bisoprolol 5mg 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.

Patients with kidney impairment
In patients with severe renal impairment (creatinine clearance < 20ml/min), the dose should not exceed 10 mg bisoprolol once daily. This dosage may eventually be halved to 5mg per day.

Patients with severe liver impairment
No dosage adjustment is required, however careful monitoring is advised.

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

Children under 12 years and adolescents:
There is no paediatric experience with this medicine, therefore its use cannot be recommended

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

- 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 (less than 45-50 beats per minute during therapy, or less than 60 beats per minute 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
- hypersensitivity to bisoprolol or to one of the excipients listed.
- untreated phaeochromocytoma *(see 4.4).*
- combinations with floctafenine and sultopride *(see also section 4.5)*
- with anaesthetics which depress myocardial activity (e.g. cyclopropane and trichlorethylene) *(see also section 4.5)*

## 4.4 Special warnings and precautions for use

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.

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

Bisoprolol must be used with caution in:

- concomitant treatment with amiodarone: risk of contractility automatism and conduction disorders (suppression of compensatory sympathetic reactions), *(see also Section 4.5)*
- 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 $\beta_2$-stimulants may have to be increased. It is recommended to have a functional respiratory test done before the initiation of treatment.
- concomitant treatment with anticholinesterase drugs (including tacrine): atrio-ventricular 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 sections 4.3 & 4.5).* Continuation of β-blockade reduces the risk of arrhythmia during induction and intubation. The anaesthesiologist should be informed when the patient is receiving bisoprolol.
- Iodinated 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 may be masked. Blood glucose levels should be monitored during treatment with bisoprolol
- thyrotoxicosis, symptoms and clinical signs of thyrotoxicosis 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.
- peripheral circulatory disorders, such as Raynaud's phenomena and intermittent claudication: 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 a thorough risk/ benefit assessment

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.
This medicinal product contains sunset yellow FCF (E110), which may cause allergic reactions.

## 4.5 Interaction with other medicinal products and other forms of interaction

*Combinations contra-indicated*
Floctafenine: beta 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 increased risk of ventricular arrhythmias.
Anaesthetics which depress myocardial activity.

*Combinations not recommended*
Calcium antagonists **(**verapamil, diltiazem, bepridil): negative influence on contractility, atrio-ventricular conduction and blood pressure *(see also section 4.4).*
Class I antiarrhythmic drugs (e.g. disopyramide, quinidine): effect on atrioventricular conduction time may be potentiated and negative inotropic effect may be increased. Strict clinical and ECG monitoring is required *(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 III antiarrhythmic drugs (e.g. amiodarone): effect on atrial conduction time may be potentiated *(see section 4.4).*
Calcium antagonists (, dihydropyridine derivatives): increased risk of hypotension. In some patients with latent heart failure concomitant use of β-blocking agents can lead to heart failure
Anticholinesterase drugs (including tacrine): atrio-ventricular conduction time and/or bradycardia may be increased *(see also section 4.4).*
Other β-blocking agents, including in eye-drops, have additional 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).*

Ergotamine derivatives: exacerbation of peripheral circulatory disturbances.
*NSAIDs: decrease of the antihypertensive effect (inhibition of vasodilatative prostaglandin by NSAI and water and sodium retention with pyrazolone NSAI).*
Beta-sympathomimetic agents (e.g. 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 non selective β-blockers.

Tricyclic antidepressants, barbiturates, phenothiazines as well as other antihypertensive agent: increased blood pressure lowering effect.
Baclofen: increased antihypertensive activity
Amifostine: increased hypotensive activity

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

## 4.6 Pregnancy and lactation

*Pregnancy:*
Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or 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, $\beta_1$-adrenoceptor blocking agents are preferred.

Bisoprolol should not be used during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, the uteroplacental 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.

*Lactation:*
It is not known whether bisoprolol 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 patient's 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 as bisoprolol can cause dizziness and fatigue. 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 side 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:
Very common (≥ 10%),
common (≥ 1% and < 10%),
uncommon (≥ 0.1% and < 1%),
rare (≥ 0.01% and < 0.1%),
very rare (< 0.01%) including isolated reports

Immune system disorders
Rare: Allergic rhinitis, the appearance of antinuclear antibodies with exceptional clinical symptoms such as lupus syndrome, which disappear upon cessation of treatment

Metabolism and nutrition disorders
Rare: Increased triglycerides, hypoglycaemia

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

Nervous system disorders
Common: Tiredness, exhaustion, dizziness, headache (especially at the beginning of the therapy, they are generally mild and often disappear within 1-2 weeks)

Eye disorders
Rare: Reduced tear flow (to be considered if the patient uses lenses)
Very rare: Conjunctivitis

Ear and labyrinth disorders
Rare: Hearing impairment

Cardiac disorders
Uncommon: Bradycardia, AV-stimulus disturbances (slowed AV-conduction or increase of existing AV-block), worsening of heart failure

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

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

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea, abdominal pain, and constipation

Hepato-biliary disorders
Rare: Increased liver enzymes (ALAT, ASAT), 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

## 4.9 Overdose

The most common signs expected with overdosage of bisoprolol are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia.

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 $\beta_2$-sympathicomimetic drugs. Cardiovascular complications should be treated symptomatically: AV-block (second or third degree) needs careful monitoring and should 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.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective $\beta_1$-blocking agents, ATC code: C07AB07

Bisoprolol is a potent, highly $\beta_1$-selective-adrenoceptor blocking agent devoid of intrinsic sympathomimetic activity. As with other $\beta_1$-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 β-receptors reduces heart action and thus reduces oxygen demand.

Bisoprolol possesses similar local anaesthetic properties to propranolol.

## 5.2 Pharmacokinetic properties

Bisoprolol is absorbed almost completely from the gastrointestinal tract. 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

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.

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 was not teratogenic.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Calcium Hydrogen Phosphate Dihydrate
Microcrystalline Cellulose
Pregelatinised Starch
Croscarmellose Sodium
Silica, Colloidal anhydrous
Magnesium Stearate

Film Coat

Hypromellose (HPMC, E464)
Titanium dioxide (E171)
Macrogol 400
FD&C Yellow (E110)
Carmine (E120)
Iron oxide Red (E172)

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf Life

2 years.

## 6.4 Special precautions for storage

Do not store above 25° C.
Store in the original package to protect from moisture.

## 6.5 Nature and contents of container

The tablets are placed in thermoformed PVC foil laminated with aluminium.
The blister pack is then placed in a printed boxboard carton with pack size of 7, 14, 21, 28, 30, 50, 56, 60, 84, 90, 98, 100, 112, 120, 250 and 500.

Not all pack sizes will be marketed.

## 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

## 7 MARKETING AUTHORISATION HOLDER

Norton Healthcare Limited
Albert Basin
Royal Docks
London E16 2QJ
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER

PA 0282/081/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 January 2003

Date of last renewal: 02 February 2006

## 10 DATE OF REVISION OF THE TEXT

September 2007