SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bisoprolol 2.5mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Bisoprolol 2.5mg: Each Film coated tablet contains 2.5mg Bisoprolol Fumarate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Bisoprolol 2.5mg: White and heart-shaped with a break-line on both sides

The tablets can be divided into equal doses.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations not recommended

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

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.

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

Combinations to be used with caution

Calcium antagonists 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.

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

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

Insulin and oral antidiabetic drugs: Intensification of blood sugar lowering effect. Blockade of beta-adrenoreceptors may mask symptoms of hypoglycaemia.

Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension (for further information on general anaesthesia see also section 4.4.).

Digitalis glycosides: Reduction of heart rate, increase of atrio-ventricular conduction time.

Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol.

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

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

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.

### 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 should not be used during pregnancy unless clearly necessary. If treatment with bisoprolol is considered necessary, the uteroplacental blood flow and the fetal growth should be monitored. In case of harmful effects on pregnancy or the fetus alternative treatment should be considered. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.
**Lactation:**
It is not known whether this drug is excreted in human milk. Therefore, breastfeeding is not recommended during administration of bisoprolol.

**Fertility:**
In reproduction toxicology studies Bisoprolol had no influence on fertility or on general reproduction performance (see section 5.3).

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

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

- Very common (≥ 1/10)
- Common (≥ 1/100, < 1/10)
- Uncommon (≥ 1/1,000, < 1/100)
- Rare (≥ 1/10,000, < 1/1,000)
- Very rare (< 1/10,000)
- Frequency not known (cannot be estimated from available data)

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

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

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

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

**Ear and labyrinth disorders:**
- Rare: hearing impairment.

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

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

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

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

General disorders:
Common: asthenia, fatigue.

Hepatobiliary disorders:
Rare: hepatitis.

Reproductive system and breast disorders:
Rare: potency disorders.

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

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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

4.4 Special warnings and precautions for use

Bisoprolol must be used with caution in:

- bronchospasm (bronchial asthma, obstructive airways diseases)
- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia can be masked
- strict fasting
- ongoing desensitisation therapy
- first degree AV block
- Prinzmetal’s angina
- peripheral arterial occlusive disease (intensification of complaints might happen especially during the start of therapy)
- general anaesthesia
In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The 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 the decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

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

Combination of bisoprolol with calcium antagonists of the verapamil or diltiazem type, with Class I antiarrhythmic drugs and with centrally acting antihypertensive drugs is generally not recommended, for details please refer to section 4.5.

In bronchial asthma or other chronic obstructive lung diseases, which may cause symptoms, bronchodilating therapy should be given concomitantly. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of beta2-stimulants may have to be increased.

As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Adrenaline treatment does not always give the expected therapeutic effect.

Patients with psoriasis or with a history of psoriasis should only be given beta-blockers (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 thyreotoxicosis may be masked.
The initiation of treatment with bisoprolol necessitates regular monitoring. For the posology and method of administration please refer to section 4.2.

The cessation of therapy with bisoprolol should not be done abruptly unless clearly indicated. For further information please refer to section 4.2.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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

Biotransformation and Elimination

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. 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.

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

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 (PH-112)
   Maize Starch
   Crospovidone (Type B)
   Colloidal Anhydrous Silica
   Magnesium Stearate
   Purified Water

Film coating (1.25mg tablets and 2.5mg tablets): Hypromellose, Macrogol 400 and Titanium dioxide (E171).
Film coating (3.75mg tablets, 5 mg tablets and 7.5mg tablets): Hypromellose, Macrogol 400, Titanium dioxide (E171) and Ferric oxide yellow (E172)
Film coating (10 mg tablets): Hypromellose, Macrogol 400, Titanium dioxide (E171), Ferric oxide yellow (E172), Ferric oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special requirements

6.5 Nature and contents of container

20, 28, 30, 50, 56, 60, 90, or 100 tablets
Not all pack sizes are marketed.
Tablets are packed in Aluminium (0.02mm thickness) and PVC (0.25mm)/ PVDC (120 gsm) blisters.
Blisters are packed in cartons.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER

Medreich Plc
Warwick House
Plane Tree Crescent
Feltham
TW13 7HF

8 MARKETING AUTHORISATION NUMBER(S)

PL 21880/0127-0132

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 August 2012

10 DATE OF REVISION OF THE TEXT

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7. Marketing Authorisation Holder

Medreich Plc
Warwick House
Plane Tree Crescent
Feltham
TW13 7HF

8 MARKETING AUTHORISATION NUMBER(S)

PL 21880/0128

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

06/08/2012

10 DATE OF REVISION OF THE TEXT

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